BINGE DRINKING IN THE ADOLESCENT AND YOUNG BRAIN

EDITED BY: Eduardo López-Caneda, Fernando Cadaveira and Salvatore Campanella
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frontiers Research Topics

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BINGE DRINKING IN THE ADOLESCENT AND YOUNG BRAIN

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Binge drinking (BD) is a highly prevalent pattern in most Western countries characterized by the intake of large amounts of alcohol in a short time followed by periods of abstinence. This abusive form of alcohol consumption is a regular practice in around a third of European and American youths. The high prevalence of BD at this age is of particular concern since adolescence and youth are in a period of special vulnerability to neurotoxic effects of alcohol, mainly due to the structural and functional changes going on in the brain throughout this key developmental stage. Evidence gathered during the last decade from animal and human studies seems to point to multiple brain anomalies associated with BD.

In this Research Topic, we have collated a compendium of articles that address multiple aspects of BD during adolescence and young adulthood such as identification, prevalence, gender differences and neurocognitive anomalies associated with this excessive alcohol consumption pattern. These articles collectively highlight the breadth of current research conducted in this field but also the need to join efforts to improve the screening of the BD pattern, the characterization of its consequences as well as the translation of knowledge acquired in the laboratory into clinical practice. We remain confident that this Research Topic will contribute significantly to the understanding of BD and its consequences and will further stimulate high-quality investigation in this relatively new research field.

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Editorial: Binge Drinking in the Adolescent and Young Brain

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Editorial on the Research Topic

Binge Drinking in the Adolescent and Young Brain

Alcohol is considered the world's third largest risk factor for disease and about 6% of all deaths worldwide are attributable to this substance (Rehm et al., 2009; World Health Organization, 2014). Excessive alcohol use is especially harmful for younger age groups, where alcohol has been (directly or indirectly) related to more than 30% of deaths among males aged 15–29 years in the American and European regions (World Health Organization, 2011).

Binge drinking (BD), an excessive but episodic alcohol consumption pattern, has become a major public health problem as it is held accountable for multiple adverse consequences, including poor quality of life, injuries, risky sexual behavior and neurocognitive deficits (White and Hingson, 2013; Carbia et al., 2018; Dormal et al., 2018). This pattern, defined as the consumption of 5 or more drinks (male) or 4 or more drinks (female) in about 2 h (National Institute of Alcohol Abuse Alcoholism, 2004), is a regular practice in about one third of European and American youths (Kraus et al., 2016 Substance Abuse and Mental Health Services Substance Abuse and Mental Health Services Administration, 2016). The high prevalence of BD at this age is of particular concern since adolescence and youth are in a period of special vulnerability to neurotoxic effects of alcohol, mainly due to the structural and functional changes going on in the brain throughout this key developmental stage (Jones et al., 2018).

Research on this topic has significantly increased in recent years. As such, the number of studies involving BD during adolescence and youth have almost quintupled during the period 2004–2014 (from 111 in 2004 to 510 in 2014), with a slight increase in the last few years (see **Figure 1**). The objective of this Research Topic was to produce and compile a highly informative collection of original research and reviews aiming at cover a comprehensive framework of aspects related to BD from different domains (animal and human), perspectives (cellular, behavioral, neuropsychological, neuroimaging, etc.), and methods (e.g., biochemical, behavioral, psychophysiological, neurostructural, and neurofunctional).

With regard to animal studies, two articles included in this Research Topic involved animal models of BD. Lee et al. provided novel evidence that BD during adolescence induces profound negative affect (anxiety- and depressive-like behaviors), excessive alcohol consumption and dysregulation within extended amygdala structures, which manifest during protracted withdrawal in adulthood. Nickell et al., in turn, studied hippocampal neurogenesis in adolescent male rats exposed to BD. They observed a marked increment in cell proliferation in hippocampus following 4-day alcohol exposure, although it is not clear whether this reactive neurogenesis is a beneficial repair mechanism (e.g., recovery of hippocampal structure and function) or a pathological phenomenon (e.g., reflecting ectopic new neurons as that observed in seizure models).

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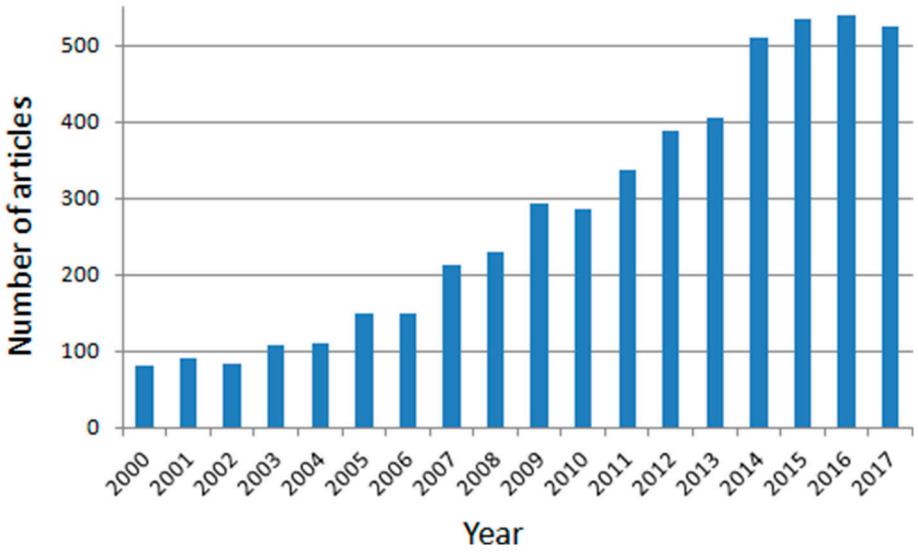

FIGURE 1 | Number of articles involving binge drinking during adolescence and youth for the period 2000–2017. The search strategy was conducted in PubMed with the following key terms: [("binge drinking" OR "binge drinkers" OR "heavy drinking" OR "heavy drinkers" OR "heavy episodic drinking" OR "college drinking" OR "college drinkers" OR "social drinkers") AND (adolescen* OR youth* OR teen* OR "young" OR "young adults" OR "college students" OR "university students"].

Within human studies, Cortés-Tomás et al. developed a new abbreviated version of the Alcohol Use Disorder Identification Test (AUDIT) which includes the combination of items 2 and 3 in a revised form. Their findings revealed that using of these two revised items lead to a more precise identification of BD in adolescents. Using the classical AUDIT questionnaire, Gómez et al. indentified five different profiles of Spanish university students based on their alcohol use over 9 years and reported a generalized reduction of the AUDIT scores over this period for all profiles, suggesting a common effect of "maturing out" of problematic alcohol use in their late twenties. Pilatti et al. observed, in a large sample of Argentinean college freshmen, a high prevalence of BD in this country (around 55% of college students between 18 and 30 years old reported BD in the last 6 months). In addition, alcohol was the entry-point for the consumption of tobacco and marijuana and an early drinking onset was associated with greater use of alcohol.

Adan et al. reviewed the findings on personality traits related to binge drinkers (BDs) and conclude that the main characteristics of personality related to the practice of BD were impulsivity and high sensation seeking, as well as anxiety sensitivity, neuroticism, extraversion and conscientiousness. Dir et al., in turn, provided an overview of potential gender differences in risk factors for adolescent BD. They showed that—presumably due to the sex-specific neurobiological changes that occur during adolescent development—there is a differential risk for BD between males and females. Thus, while the main factors contributing for BD in females were stress, depression, and other internalizing behaviors, the most significant contributions for risk of BD in males were driven by externalizing symptoms such as behavioral disinhibition, impulsivity and sensation seeking. In the same vein, in an online cross-sectional study with more than 1,800 French students, Rolland et al. revealed that severity of BD was associated with, among other factors, male gender, younger age and sensation seeking. In addition, they pointed out that BD score was correlated with severity of binge eating (BE), but not with other disordered eating symptoms, indicating that BD and BE may share common characteristics, including an impaired emotion regulation.

The studies by Lannoy et al. and Poncin et al. explored emotional processing and emotion regulation strategies in young BDs, respectively. Results of Lannoy et al. showed no significant differences between the control and BD groups in emotional processing abilities as measured by an emotional crossmodal task. Similarly, Poncin et al. did not find differences between BDs and controls in the overall scores of emotional distress induced by an insoluble anagrams task, though emotional distress was related to more self-blame, rumination, and maladaptive regulation strategies in BDs only.

Amid the neuropsychological studies that evaluated cognitive functions, Peeters et al. examined whether the imbalance between behavioral control and reward sensitivity might account for risky behaviors such as alcohol and cannabis use. They found that a weak effortful control in early adolescence (age 11) was a significant unique predictor of risk taking behavior in mid adolescence (age 16), particularly among adolescents who were more reward sensitive. In the same vein, Bø et al. reported that future severity of BD was associated with making risky decisions in the prospect of gain in the Information Sampling task, which was suggestive of reward hypersensitivity in young BDs. However, in a 4 years follow-up study conducted by Carbia et al., adolescents and young adults with a BD pattern did not show deficits in decision making under ambiguous conditions as measured by the Iowa gambling task, though there

were gender-related differences in task performance as females displayed a higher sensitivity to loss frequency than males.

Gil-Hernandez et al. in a study that covered a wide range of cognitive functions (e.g., working memory, inhibition, cognitive flexibility, self-control) and ages (13–15, 16–18, and 19–22 years), observed that control subjects obtained better results than BDs but only in the 19–22-year-old range, suggesting that several years of BD history are necessary to make cognitive impairments apparent through neuropsychological tests.

Also by means of neuropsychological tasks, Vinader-Caerols et al. assessed the effects of different blood alcohol concentrations (BAC) on memory in adolescents with a history of BD. Both immediate visual memory and working memory were susceptible of being impaired by high doses of alcohol, but only immediate visual memory was affected by moderate doses of alcohol, suggesting that immediate visual memory is more sensitive than working memory to the neurotoxic effects of alcohol in adolescent BDs. These results are in line with the mini-review conducted by Hermens and Lagopoulos, who compiled numerous studies on the detrimental effects of BD in learning and memory (and on its main structural support, the hippocampus) and, particularly, on the ability of this pattern of consumption to induced memory loss (blackouts) in the adolescent and young adult population.

Besides the neuropsychological studies, two articles of this Research Topic used electroencephalography (EEG) for exploring the relationship between BD and memory deficits. The Smith et al.'s study analyzed brain electrical activity by event-related potentials (ERPs) while participants (BDs, cannabis users and controls) completed a modified verbal learning task. The authors showed that BDs displayed larger P540 amplitude (an electrophysiological index of recollection) relative to controls, suggesting greater use of recollection-based recognition in the BD group. The study by Folgueira-Ares et al. used the ERP technique to explore potential differences between young BDs and controls during the memory encoding process in a face-name associative memory task. While the control group displayed larger ERP amplitudes during memory encoding for subsequently remembered face-name pairs than for subsequently forgotten pairs, BDs exhibited similar neural activity for successful and unsuccessful encoding, presumably reflecting a neural signature of BD-induced impairment on this memory stage.

Cservenka and Brumback reviewed neuroimaging research involving the effects of BD on adolescent and young adult brain structure and function. In their mini-review, authors highlighted that most of the neurostructural studies seem to point to reduced prefrontal cortex (PFC) and cerebellar volume as well as to attenuated white matter development in young people with a BD pattern. Additionally, they also report that BDs usually show greater reliance on fronto-parietal regions while performing cognitive tasks linked to working memory, verbal learning, and inhibitory control processes. However, and in line with the authors' assertion that additional replication studies are needed in order to verify the direction of BD-induced brain abnormalities, two studies of the present Research Topic suggest a different profile of such anomalies. Indeed, Sousa et al.'s study reported increased gray matter densities in the left middle frontal gyrus in BDs, when compared with alcohol abstinent controls. Similarly, the study by Cohen-Gilbert et al. showed that a higher recent incidence of BD was associated with decreased activation of PFC regions during negative relative to neutral inhibitory trials in an emotional Go/NoGo task. These apparently inconsistent results should encourage researchers to perform greater efforts in terms of homogenization of sample selected (e.g., age, inclusionary criteria for BD and control groups), tasks chosen (e.g., identical tasks for replication of neurofunctional findings) and type of analysis conducted (e.g., volume, thickness or density when analyzing brain morphology).

Collectively, this Research Topic contains a compendium of articles that address multiple aspects of BD during adolescence and young adulthood (such as identification, prevalence, gender differences, neurocognitive consequences, etc.). We hope that this collection exhorts researchers to extend and refine the studies conducted to date as well as to address still unanswered questions. In this regard, attention should be paid to the impact of particularly high levels of alcohol consumption, namely high-intensity drinking (Patrick and Azar, 2018). Likewise, follow-up studies should be carried out to shed light on the causes and consequences of BD and on the course of problems/improvements observed with the maintenance/cessation of this pattern (Maurage et al., 2009; López-Caneda et al., 2014; Winward et al., 2014; Carbia et al., 2017). It is also important to assess the role of possible interactions with other substances—illegal or prescription drugs—(Blazer and Wu, 2009; Keith et al., 2015) as well as to clarify whether there are gender differences and how they may be related to the different neuromaturational pace that occurs during this developmental period (Medina et al., 2008; Squeglia et al., 2015). Finally, further research should also extend studies—which at present are almost entirely limited to university students—to the general population.

In short, these, among many other issues, should raise awareness of the importance of addressing pending challenges in this—still relatively new—research field and, therefore, encourage the growth of a strong and more comprehensive body of knowledge that can be translated into measurable societal impact.

AUTHOR CONTRIBUTIONS

EL-C conceptualized the proposal and wrote the first draft of the manuscript. All authors read, revised, and approved the final manuscript.

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Negative Affect and Excessive Alcohol Intake Incubate during Protracted Withdrawal from Binge-Drinking in Adolescent, But Not Adult, Mice

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Binge-drinking is common in underage alcohol users, yet we know little regarding the biopsychological impact of binge-drinking during early periods of development. Prior work indicated that adolescent male C57BL6/J mice with a 2-week history of binge-drinking (PND28-41) are resilient to the anxiogenic effects of early alcohol withdrawal. Herein, we employed a comparable Drinking-in-the-Dark model to determine how a prior history of binge-drinking during adolescence ($EtOH^{adolescents}$) influences emotionality (assayed with the light-dark box, marble burying test, and the forced swim test) and the propensity to consume alcohol in later life, compared to animals without prior drinking experience. For additional comparison, adult mice ($EtOH^{adults}$) with comparable drinking history (PND56-69) were subdivided into groups tested for anxiety/drinking either on PND70 (24 h withdrawal) or PND98 (28 days withdrawal). Tissue from the nucleus accumbens shell (AcbSh) and central nucleus of the amygdala (CeA) was examined by immunoblotting for changes in the expression of glutamate-related proteins. $EtOH^{adults}$ exhibited some signs of hyperanxiety during early withdrawal (PND70), but not during protracted withdrawal (PND98). In contrast, $EtOH^{adolescents}$ exhibited robust signs of anxiety-l and depressive-like behaviors when tested as adults on PND70. While all alcohol-experienced animals subsequently consumed more alcohol than mice drinking for the first time, alcohol intake was greatest in $EtOH^{adolescents}$. Independent of drinking age, the manifestation of withdrawal-induced hyperanxiety was accompanied by reduced Homer2b expression within the CeA and increased Group1 mGlu receptor expression within the AcbSh. The present data provide novel evidence that binge-drinking during adolescence produces a state characterized by profound negative affect and excessive alcohol consumption that incubates with the passage of time in withdrawal. These data extend our prior studies on the effects of subchronic binge-drinking during adulthood by demonstrating that the increase in alcoholism-related behaviors and glutamate-related proteins observed in early withdrawal dissipate with the passage of time. Our results to date highlight

a critical interaction between the age of binge-drinking onset and the duration of alcohol withdrawal in glutamate-related neuroplasticity within the extended amygdala of relevance to the etiology of psychopathology, including pathological drinking, in later life.

Keywords: binge drinking, adolescence, Group 1 metabotropic glutamate receptors, receptors, anxiety, depression, alcoholism

INTRODUCTION

Adolescence is a critical period of accelerated neurodevelopment, which occurs between the ages of approximately 11–21 years in humans and conservative estimates of adolescence in rodents range from postnatal days (PNDs) 28–42 (Spear, 2000, 2010; Laviola et al., 2003). During adolescence, there is a dramatic reduction of gray matter as the cortex undergoes synaptic pruning, and a proliferation of white matter from ongoing myelination of axons, leading to extensive remodeling of the structure and function of the brain (e.g., Sowell et al., 2003; Gogtay et al., 2004). These processes are essential for refining excitatory and inhibitory connectivity and stabilizing synapses within corticofugal projections that exert control over subcortical hyperactivation (Casey et al., 2011; Sturman and Moghaddam, 2011; Arain et al., 2013). Thus, adolescents typically exhibit increased impulsivity, sensation/novelty seeking, risk-taking, and mood swings, compared to adults (Casey et al., 2008; Sturman and Moghaddam, 2011; Spear and Swartzwelder, 2014). Drug experimentation is also common during the adolescent stage of development, with alcohol being the most commonly used substance among adolescents (Kelley et al., 2004; Lopez et al., 2008). Indeed, underage alcohol-drinking is a serious public health concern, with 7.7 million individuals between the ages of 12–20 reporting drinking alcohol within the past month (published by the Center for Behavioral Health Statistics and Quality, 2016). Over 90% of alcohol consumed by underage drinkers is in the form of binge-drinking episodes (National Institute on Alcohol Abuse, and Alcoholism [NIAAA], 2017), i.e., consumption sufficient to achieve a blood alcohol concentration (BACs) $\geq$80 mg/dL (approximately 4–5 drinks) in a 2-h period (National Institute on Alcohol Abuse, and Alcoholism [NIAAA], 2004). Additionally, research has consistently shown that adolescent drinking is one of the strongest predictors of substance abuse problems and addiction later in life (Grant and Dawson, 1997; Chassin et al., 2002; Tapert and Schweinsburg, 2005).

In both humans and animal models, adolescents typically consume larger quantities of alcohol than adults per drinking episode and adolescents also respond differently to alcohol than their adult counterparts (White et al., 2002; Spear and Varlinskaya, 2005; Novier et al., 2015). Adult drinkers often show pronounced signs of acute withdrawal following a binge episode, including headaches, anxiety, agitation, lethargy, gastrointestinal distress, in severe cases even withdrawal-induced seizures (Knapp et al., 1998). In contrast, both clinical and preclinical data show that adolescents tend to be less sensitive than adults both to the negative properties of acute intoxication such as sedation, motor impairment, and hypothermia, as well as the 'hangover' symptoms seen in adults during withdrawal (Little et al., 1996; White et al., 2002; Doremus et al., 2003; Varlinskaya and Spear, 2004; Anderson et al., 2010; Schramm-Sapyta et al., 2010). At the same time, adolescents show increased sensitivity to the pleasurable, reinforcing properties of alcohol such as positive reward and social facilitation (Pautassi et al., 2008; Ristuccia and Spear, 2008; Doremus-Fitzwater et al., 2010). Blunting of the aversive consequences that typically serve as negative feedback to inhibit excessive consumption, along with enhancement of the positive incentive properties of alcohol, are theorized to promote high alcohol consumption in both human and animal adolescents (Spear and Varlinskaya, 2005).

Binge-drinking is the most toxic pattern of excessive alcohol consumption and has been shown to produce a 'kindling' effect (Ballenger and Post, 1978; Becker, 1998), whereby repeated cycles of acute intoxication followed by periods of abstinence intensify withdrawal-induced neurotoxicity (Begleiter and Porjesz, 1979; Overstreet et al., 2002; Duka et al., 2004). Frequent binge-drinkers can rapidly develop tolerance to the subjective intoxicating effects of alcohol, leading to an escalation of intake and brain exposure to harmful concentrations of alcohol (Tabakoff et al., 1986; Hoffman and Tabakoff, 1989; Gruber et al., 1996). This is particularly concerning, as research suggests that adolescents are uniquely susceptible to neurotoxic insult resulting from chronic alcohol exposure and can suffer potentially life-long dysfunction resulting from perturbed maturation of prefrontal control over subcortical circuitry, particularly within regions involved in emotionality (Casey and Jones, 2010; Crews et al., 2016).

Studies have revealed persistent alcohol-induced neurobiological changes within the extended amygdala – the subcortical macrostructure integrally involved in governing diverse emotional states (Alheid, 2003; Jennings et al., 2013; Shackman and Fox, 2016). The extended amygdala consists of the central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), and shell subregion of the nucleus accumbens (AcbSh). These structures are highly vulnerable to drug-induced plasticity and dysregulation within the extended amygdala circuitry is known to underlie many of the negative reinforcing properties of withdrawal that fuel the cycle of addiction (reviewed in Koob, 2003; Baker et al., 2004). Mood disorders such as anxiety and depression, are also thought to be related to abnormal corticofugal development resulting in insufficient regulatory control over subcortical regions involved in emotion and motivation, for example the AchSh and CeA (Andersen and Teicher, 2008).

Common underlying neuropathology could account for the high comorbidity between alcohol abuse and mood disorder, which is especially prominent amongst those with a history of drinking during adolescence. In fact, adolescent alcohol use disorder is one of the strongest predictors of major depressive disorder in adulthood (Grant and Dawson, 1997; Briere et al., 2014).

Consistent with existing human and animal research, previous work from our lab has demonstrated that adolescent mice exhibit minimal signs of negative affect during early (24 h) withdrawal, and are also resistant to changes in protein expression within the Acb (Lee et al., 2016) using the Drinking-in-the-Dark (DID) animal model of voluntary binge-drinking (Rhodes et al., 2005, 2007; Thiele and Navarro, 2014). For example, we demonstrated recently that, in contrast to adult binge-drinking mice that exhibit robust anxiety-like behavior during early (24 h) withdrawal across several conventional behavioral tests of negative affect (e.g., light-dark shuttle box, novel object encounter, Porsolt swim test, elevated plus-maze), adolescent binge-drinking mice resemble water-drinking controls (Lee et al., 2015, 2016). In the present study, we sought to expand these findings to assess the adult consequences of adolescent binge-drinking on negative affect and subsequent alcohol-drinking. Based on the human literature (Grant and Dawson, 1997; Chassin et al., 2002; Briere et al., 2014), we predicted that when tested during adulthood (i.e., in protracted withdrawal), adolescent drinkers would show signs of alcohol-induced negative affect and increased alcohol consumption. Other studies of this nature have typically employed alcohol-naïve animals as the control group; however, we also wanted to compare adolescent drinkers to animals with equivalent drinking experience during adulthood, in order to specifically isolate the unique effects of alcohol during adolescence from the non-age-dependent effects of alcohol, more generally. Based on the high-risk nature of adolescent binge-drinking reported clinically, we speculated that the withdrawal-induced hyper-anxiety manifested in adulthood would be more pronounced in animals with a prior history of binge-drinking during adolescence, than in animals with a prior history of drinking during adulthood. To complement the behavioral data, we also collected brain tissue samples from the AcbSh and CeA for immunoblotting, as these extended amygdala structures exhibit hyperactivity in adult mice during withdrawal from binge-drinking (Lee et al., 2015), as well as increases in protein indices of glutamate transmission that promote binge-alcohol intake (e.g., Cozzoli et al., 2009, 2012, 2014, 2015). We sampled tissue also from the adjacent nucleus accumbens core (AcbC) and the basolateral amygdala (BLA) to examine the subregional specificity of any observed protein effects. These adjacent subregions share connectivity and proximity with the extended amygdala but are not considered parts of this macrosystem, thus enabling us to determine whether or not any observed changes in protein expression were specific to the extended amygdala. If adult and adolescent drinkers do indeed show distinct withdrawal phenotypes, these differences could be reflected in divergent alcohol-induced protein changes within extended amygdala structures.

MATERIALS AND METHODS

Experimental procedures were similar to those in our previous studies (Lee et al., 2015, 2016) and are briefly summarized below. All experiments were conducted in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (NIH Publication No. 80–23, revised 2014) and approved by the IACUC of the University of California, Santa Barbara.

Subjects

The animals used in this study were male C57BL/6J mice (Jackson Laboratories, Sacramento, CA, United States). Animals were housed in groups of 4 in standard Plexiglas cages, in a temperature-controlled vivarium (23°C), under a 12 h reverse light/dark cycle (lights off at 10 am). Food and water were available *ad libitum*, except during the 2 h alcohol-drinking period. Adolescent drinkers ($EtOH^{adolescents}$) began drinking at PND28, spanning the approximate period of early-mid adolescence in mice (Spear, 2000; Brust et al., 2015), and underwent behavioral testing in adulthood on PND70, after 28 days withdrawal (i.e., protracted withdrawal). Adult drinkers ($EtOH^{adults}$) were PND56 at drinking onset and consisted of two subgroups: one group was behaviorally tested at PND70, after 1 day withdrawal ($wd1EtOH^{adults}$), to match the age of the aforementioned $EtOH^{adolescents}$ mice and control for known age-related differences in basal behavior and protein expression (Spear, 2010). In a follow-up experiment, an additional group of adult mice was added to the study and tested for behavior on PND98 (i.e., after 28-days withdrawal; $wd28EtOH^{adults}$), to control for the effects of a 28-days withdrawal period upon behavior/protein expression. All control animals (PND70 and PND98) received only water prior to behavioral testing. Sample sizes were $n = 9$ for all groups. The experimental timeline for behaviorally tested animals is summarized in **Figure 1**.

A separate cohort of animals ($n = 12$/group) was used to generate brain tissue for immunoblotting, as a previous study from our laboratory showed that behavioral testing procedures induced cellular activation within Acb subregions (Lee et al., 2015). These animals were subjected to the same drinking procedures as the animals in the behavioral experiment, but were sacrificed on PND70 or PND98 to obtain brain tissue, in lieu of behavioral testing.

Drinking-in-the-Dark (DID) Procedures

Initial Alcohol Exposure

All alcohol-experienced animals were exposed to 14 consecutive days of binge-drinking under our 4-bottle DID procedures (Lee et al., 2016). Alcohol-access was restricted to 14 days in order to correspond with the estimated length of early-mid adolescence in mice (Spear, 2000), when developmental changes are most prolific (Spear, 2010). The DID protocol is a widely accepted model of binge-drinking that has been shown to elicit high voluntary alcohol consumption in laboratory animals (Rhodes et al., 2005; Crabbe et al., 2009). Each day prior to the drinking period, animals were separated into individual cages and allowed to acclimate for approximately 45 min. Beginning

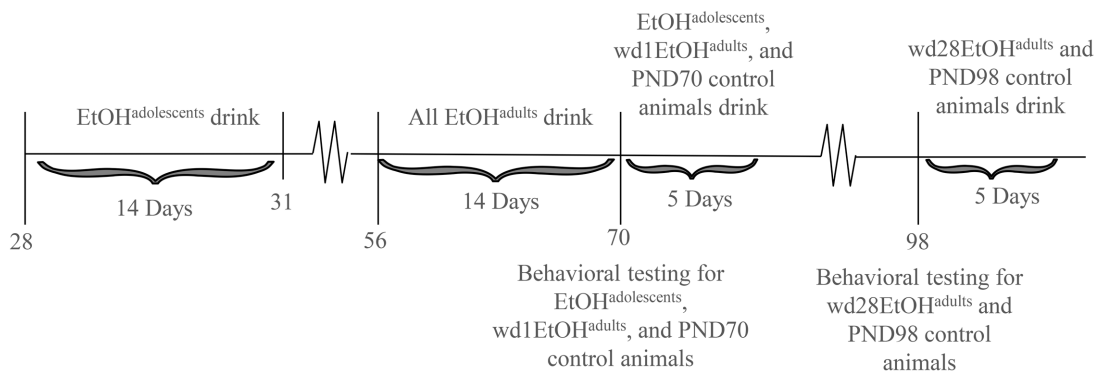

FIGURE 1 | Procedural time-line of the experiments. Summary of the timing of the binge-drinking and testing procedures for comparing the protracted effects of a history of binge-drinking during adolescence ($EtOH^{adolescents}$) or adulthood ($EtOH^{adults}$) upon behavioral measure of negative affect and subsequent alcohol intake. wd1 and wd28 denote, respectively, 1 and 28 days withdrawal.

3 h into the dark phase of the circadian cycle, the peak time of daily fluid intake (Rhodes et al., 2005), animals were given simultaneous access to 5, 10, 20, and 40% (v/v) unsweetened ethanol solutions for 2 h. The positioning of the bottles on the cage was randomized each day. Expanding the traditional 1-bottle DID protocol to include 4 bottles of differing concentration has been shown to elicit even higher voluntary intakes (Henniger et al., 2002; Tordoff and Bachmanov, 2003; Gustafsson and Nylander, 2006; Cozzoli et al., 2014), as animals are able to sample from all the bottles and consume whichever concentration they find most palatable. This being said, the immunoblotting results for the CeA that ensued from our study of mice drinking under the 4-bottle procedure (see below) prompted us to conduct a follow-up immunoblotting study in which mice were presented with a single bottle containing 20% (v/v) alcohol for 2 h/day for 14 days. In either case, the amount of alcohol consumed each day was calculated by bottle weight immediately before and after the drinking period.

Blood Alcohol Sampling

Submandibular blood samples were collected on drinking day 10, immediately following the 2-h drinking period. The scheduling of the blood sampling was selected to ensure that the animals' intakes had stabilized, while also allowing ample time for recovery prior to behavioral testing. BACs were determined using an Analox alcohol analyzer (model AM1, Analox Instruments United States, Lunenburg, MA, United States).

Subsequent Drinking in Adulthood

Beginning approximately 24 h following behavioral testing, all animals, including previously alcohol-naïve water drinkers, were subjected to 5 additional days of DID procedures in order to relate prior alcohol experience, age of first exposure, and affective state to alcohol consumption in adulthood.

Behavioral Testing

Behavioral testing consisted of the marble burying test, which was followed by the Porsolt forced swim test (FST). Both of these procedures were demonstrated to be particularly sensitive to the effects of alcohol withdrawal in our previous studies of mice (Lee et al., 2015, 2016). The order of testing was based on recommendations from our IACUC discouraging additional testing following the FST to allow animals to fully recover.

Marble Burying

The marble-burying test was used as a measure of anxiety-induced defensive burying, as an increase in burying-related behavior serves as an index of anxiety (Young et al., 2006; Umathe et al., 2008) In our paradigm, 12 square glass pieces (2.5 $cm^2 \times 1.25$ cm tall) were placed in the animals' home cage, six at each end. Animals were then left undisturbed for 15 min and video recorded for later analysis. At the end of the trial, a blind observer recorded the number of marbles at least 75% buried. Later, a blind observer reviewed the video footage and the latency to begin burying and the total time spent burying was recorded using a stopwatch.

Porsolt Forced Swim Test

The FST is a common measure of depression-like behaviors in laboratory animals, based on changes in active swimming (Porsolt et al., 1977a,b, 2001). Each animal was placed into an 11-cm diameter cylindrical container filled with room-temperature water such that animals were unable to touch the bottom. The latency to first exhibit immobility (defined as no horizontal or vertical displacement of the animal's center of gravity for 5^{++}s), total time spent immobile, and the numbers of immobile episodes were monitored during a 6-min period using AnyMaze^{TM} tracking software (Stoelting Co., Wood Dale, IL, United States).

Sucrose Preference Test

The sucrose preference test is a common assay of anhedonia (e.g., Serchov et al., 2016), used to model depression in laboratory animals (Katz, 1982; Willner et al., 1992). Upon conclusion of the marble burying and FST, animals were returned to the colony room and presented with overnight access to 2 identical sipper tubes, one containing 5% sucrose and the other containing plain water. Bottles were weighed prior to being placed on the home

cage at approximately 16:00 h and again after removal at 09:00 h the following day. Change in bottle weight was used to determine the volume consumed and a relative sucrose preference was calculated as the volume of sucrose consumed/total fluid volume consumed.

Brain Tissue Collection

Animals in the immunoblotting study were rapidly decapitated approximately 24 h following the final alcohol presentation to mirror the time-frame of the behavioral testing. Brains were removed and cooled on ice, then sectioned in 1 mm-thick coronal slice at the level of the striatum and amygdala. The AcbSh and CeA were bilaterally sampled from the slice located approximately 1.18 mm and −1.22 mm relative to Bregma, respectively, as shown in the mouse brain atlas of Paxinos and Franklin (2004), using a 18-gauge biopsy needle (depicted in **Figures 6**, **7**).

Immunoblotting

Western blotting was performed on whole tissue homogenates from the AcbSh and AcbC (AP +1.18 mm), and CeA and BLA (AP −1.34 mm) (location relative to bregma, as depicted in Paxinos and Franklin, 2004) following procedures identical to those described in Lee et al. (2016). The following primary antibodies and concentrations were used: mGlu1 (Synaptic Systems, Göttingen, Germany; 1:1000 dilution), mGlu5 (Millipore, Temecula, CA, United States; 1:1000 dilution), Homer2b (Millipore, Temecula, CA, United States; 1:1000 dilution), and calnexin (Enzo Life Sciences, Farmingdale, NY, United States; 1:1000 dilution) for standardization. Homer2b is a postsynaptic density scaffolding protein that regulates signaling of Group 1 metabotropic glutamate receptors (mGluRs) (Szumlinski et al., 2005). Together, these proteins were selected for study based on our laboratory's prior work identifying them as relevant to alcohol-induced neuroplasticity (Szumlinski et al., 2005, 2007, 2008; Cozzoli et al., 2009, 2012, 2014, 2015; Obara et al., 2009; Goulding et al., 2011; Lum et al., 2014; Lee et al., 2015; Quadir et al., 2016).

Statistical Analysis

Alcohol intake data from the 14-day drinking period were analyzed with a repeated measures analysis of variance (ANOVA), with drinking age ($EtOH^{adolescents}$ or $wd1EtOH^{adults}$) as the between-subjects factor and day (14 days) as the within-subjects repeated measure to screen for potential group differences in alcohol consumption, which could confound alcohol-induced behavioral and neurobiological changes. The 5-day intake data was similarly analyzed with a drinking age ($EtOH^{adolescents}$, $wd1EtOH^{adults}$, or no prior experience) X day (5) repeated-measures ANOVA. A repeated measures ANOVA was also used determine if there was an effect of age/prior alcohol experience on the preference for a particular alcohol concentration, with drinking age ($EtOH^{adolescents}$, $wd1EtOH^{adults}$, or no prior experience) as the between-subjects factor and both day (14 or 5 levels) and concentration (5, 10, 20, or 40%) as the within-subjects factors.

Behavioral data for animals tested at PND70 were analyzed using between-subjects ANOVAs, with drinking ($EtOH^{adolescents}$ or $wd1EtOH^{adults}$) as the between-subjects factor, and Tukey's *post hoc* comparisons when appropriate; $\alpha = 0.05$. All comparisons between $wd28EtOH^{adults}$ and age-matched control animals were conducted using independent samples *t*-tests with Bonferroni corrections for multiple comparisons, as these animals were run as a separate follow-up to the animals tested at PND70. Paired-samples *t*-tests were used to compare the average consumption during the first and second rounds of drinking in alcohol-experienced animals.

The immunoblotting data for the animals subjected to our 4-bottle-choice drinking procedures were analyzed using a drinking age ($EtOH^{adolescents}$, $wd1EtOH^{adults}$, or no prior experience) univariate ANOVA, while that for the animals subjected to our single-bottle procedure were analyzed using unpaired-samples *t*-tests. For all analyses, statistical outliers were identified using the $\pm 1.5^{*}$IQR rule and omitted from analyses. There were no statistical outliers excluded from the behavioral data. Outlier exclusion resulted in n's of 10–12 per group for the immunoblotting data (the specific n's for individual analyses are reported in the figure legends). All statistics and calculations were performed using SPSS v.21 statistical software.

RESULTS

14-Day Alcohol Consumption

Although the repeated measures ANOVA showed no between-subjects differences in the total amount of alcohol consumed by $EtOH^{adolescents}$, $wd1EtOH^{adults}$, and $wd28EtOH^{adults}$ across the initial 14-day drinking period [$F(2,24) = 0.14$, $p = 0.87$], there was a significant age × day within-subjects interaction [$F(78,845) = 6.11$, $p < 0.001$]. Further analysis revealed that over days 1–7, $wd1EtOH^{adults}$ drank more alcohol than $EtOH^{adolescents}$ ($p = 0.001$) but the converse occurred over days 8–14 ($p < 0.001$). This shift was reflected by a similar drinking-age × concentration × day interaction [$F(39,624) = 4.62$, $p < 0.001$] for concentration preference, with $EtOH^{adolescents}$ exhibiting greater preference for lower concentration during the first week and a shift to a preference for higher concentration during the second week compared to $wd1EtOH^{adults}$ (**Table 1**). The repeated measures ANOVA also showed a significant drinking-age × concentration interaction [$F(3,48) = 3.317$, $p = 0.028$] and *post hoc* analysis revealed that $wd1EtOH^{adults}$ had a lower preference for the 5% concentration and a higher preference for the 20% concentration compared to $EtOH^{adolescents}$ ($p = 0.03$ and $p = 0.049$, respectively). There was a trend toward higher preference for the 40% in adolescents compared to adults ($p = 0.078$). During the subsequent 5-day drinking period, there were no significant main effects or interactions between age/prior alcohol experience or concentration (p's > 0.10).

There were no differences in alcohol intake amongst the animals used for tissue collection [$F(2,32) = 0.39$, $p = 0.68$] and an overall analysis of all alcohol-drinking animals revealed no

differences between cohorts used for behavioral testing or tissue collection [$F(5,56) = 0.69$, $p = 0.63$; summarized in **Table 2**].

Blood Alcohol Concentrations

As the ANOVA revealed no significant differences in alcohol consumption between behavioral testing and immunoblotting animals, day 10 intakes and BACs were collapsed across both cohorts within each drinking group (**Figure 2A**). On day 10 of drinking, $EtOH^{adolescents}$ consumed an average 4.96 ± 0.21 g/kg of alcohol with a resulting BAC of 94.18 ± 9.25 mg/dL; $wd1EtOH^{adults}$ consumed an average of 3.93 ± 0.22 g/kg with a resulting BAC of 77.73 ± 8.46, and $wd28EtOH^{adults}$ consumed an average of 4.72 ± 0.25 g/kg with a resulting BAC of 79.47 ± 9.05 mg/dL. BAC was significantly correlated with alcohol consumption when sampled on day 10 of drinking ($r = 0.62$, $p = 0.001$, $n = 63$; **Figure 2B**).

TABLE 1 | Summary of group differences in the preference for different alcohol concentrations during the 2-week drinking period.

Day 1	$EtOH^{adolescents}$ had a higher 5% and lower 40% preference, compared to $wd1EtOH^{adults}$ ($p < 0.001$ and $p = 0.014$, respectively)
Day 2	$EtOH^{adolescents}$ had a higher 10% and a lower 20% preference, compared to $wd1EtOH^{adults}$ ($p = 0.047$ and $p = 0.003$, respectively)
Day 3	$EtOH^{adolescents}$ had a higher 40% preference, compared to $wd1EtOH^{adults}$ ($p = 0.037$)
Day 4	No differences
Day 5	$EtOH^{adolescents}$ had a higher 5 and 10% ($p = 0.009$ and $p = 0.007$, respectively), but lower 20 and 40% preference, compared to $wd1EtOH^{adults}$ ($p = 0.005$ and $p < 0.001$, respectively)
Day 6	No differences
Day 7	$EtOH^{adolescents}$ had a higher 5%, but lower 20%, preference, compared to $wd1EtOH^{adults}$ ($p = 0.002$ and $p = 0.014$, respectively)
Day 8	No differences
Day 9	$EtOH^{adolescents}$ had a higher 5%, but lower 10%, preference, compared to $wd1EtOH^{adults}$ ($p = 0.005$ and $p = 0.022$, respectively)
Day 10	$EtOH^{adolescents}$ had a higher 5% preference, compared to $wd1EtOH^{adults}$ ($p = 0.001$)
Day 11	$EtOH^{adolescents}$ had a lower 10%, but higher 40%, preference, compared to $wd1EtOH^{adults}$ ($p = 0.002$ and $p = 0.037$, respectively).
Day 12	$EtOH^{adolescents}$ had a higher 40% preference, compared to $wd1EtOH^{adults}$ ($p < 0.001$)
Day 13	$EtOH^{adolescents}$ had a higher 10%, lower 20%, higher 40% ($p = 0.048$, $p = 0.002$, and $p = 0.014$), compared to $wd1EtOH^{adults}$
Day 14	$EtOH^{adolescents}$ had a lower 10 and 20%, but higher 40%, preference, compared to $wd1EtOH^{adults}$ ($p = 0.04$, $p = 0.031$, $p < 0.001$)

Results of post hoc analysis of the day × age × concentration interaction [$F(39,624) = 4.62$, $p < 0.001$] in $EtOH^{adolescents}$ and $wd1EtOH^{adults}$; n = 9/group.

TABLE 2 | Summary of the average total alcohol intake exhibited by mice with a 14-day history of binge-drinking during adolescence ($EtOH^{adolescents}$), or during adulthood (wd1 or $wd28EtOH^{adults}$).

	Behavioral testing animals	Immunoblotting animals
$EtOH^{adolescents}$	4.16 ± 0.10	4.48 ± 0.15
$wd1EtOH^{adults}$	4.05 ± 0.14	4.46 ± 0.08
$wd28EtOH^{adults}$	4.12 ± 0.10	4.40 ± 0.12

Note that there were no significant group differences in alcohol intake across the 14-day drinking period.

Sucrose Preference

The ANOVA showed significant group differences in sucrose preference [$F(2,24) = 20.01$, $p < 0.001$; **Figure 3**] and *post hoc* analysis revealed that while $wd1EtOH^{adults}$ showed increased sucrose preference ($p = 0.003$ compared to alcohol-naïve control animals), $EtOH^{adolescents}$ showed decreased preference ($p = 0.04$).

Marble Burying

In the marble burying test, there were significant group differences in total time spent burying [$F(2,24) = 11.82$, $p < 0.001$; **Figure 4A**], the latency to start burying [$F(2,24) = 4.15$, $p = 0.028$; **Figure 4B**], and total number of marbles buried [$F(2,24) = 9.76$, $p = 0.001$; **Figure 4C**]. Both $wd1EtOH^{adults}$ and $EtOH^{adolescents}$ spent more time burying compared to water controls ($p = 0.04$ and $p < 0.001$, respectively). $EtOH^{adolescents}$ also had a shorter latency to start burying ($p = 0.022$) and buried more marbles overall ($p = 0.001$). However, $wd1EtOH^{adults}$ did not differ significantly from controls on these factors (p's > 0.1). There were no differences between $wd28EtOH^{adults}$ and age-matched control animals on any behavioral factor tested (p's > 0.10, non-significant results are summarized in **Table 3**).

Forced Swim Test

In the FST, there were group differences found for the number of immobile episodes [$F(2,24) = 3.94$, $p = 0.033$; **Figure 5A**], total time spent immobile [$F(2,24) = 17.49$, $p < 0.001$; **Figure 5B**], and the latency to first immobility [$F(2,24) = 38.81$, $p < 0.001$; **Figure 5C**]. Both $wd1EtOH^{adults}$ and $EtOH^{adolescents}$ had significantly fewer immobile episodes ($p = 0.04$ and $p = 0.02$, respectively) compared to control animals, but $EtOH^{adolescents}$ spent significantly more time immobile ($p = 0.008$), while adults spent less ($p = 0.04$). $EtOH^{adolescents}$ also had a shorter latency to first immobility ($p < 0.001$) but $wd1EtOH^{adults}$ did not ($p > 0.20$). Despite having fewer immobile episodes, $EtOH^{adolescents}$ spent more time immobile, compared to control animals, thus reflecting an overall increase in immobility with longer time spent immobile per episode.

Re-exposure Drinking

During the subsequent 5-day drinking period following behavioral testing, the repeated measures ANOVA showed a significant effect of prior alcohol experience [$F(2,24) = 20.92$, $p < 0.001$; **Figures 6A,B**]. *Post hoc* tests showed that both $wd1EtOH^{adults}$ and $EtOH^{adolescents}$ consumed more alcohol than first-time drinkers [$wd1EtOH^{adults}$ $p = 0.034$, $EtOH^{adolescents}$ $p < 0.001$]. Additionally, $EtOH^{adolescents}$ drank more than $wd1EtOH^{adults}$ ($p = 0.003$). Both $wd1EtOH^{adults}$

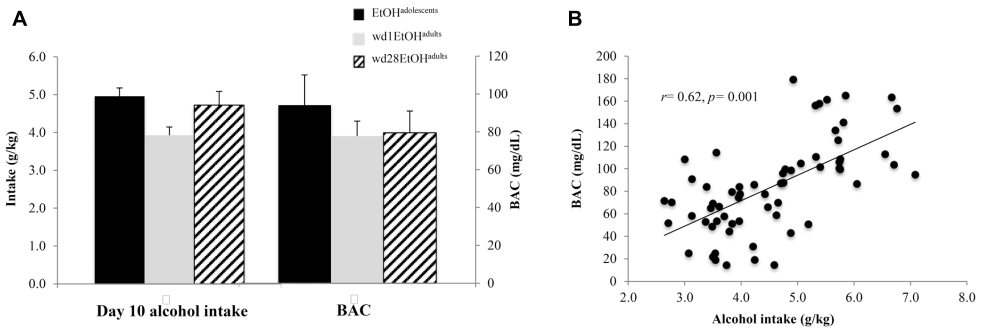

FIGURE 2 | Day 10 BAC sampling. **(A)** Average alcohol intake and BAC by group, averaged across both behavioral testing and immunoblotting animals (n = 21/group). **(B)** Alcohol intake was significant correlated with BAC. Data depict all alcohol-drinking animals (n = 63).

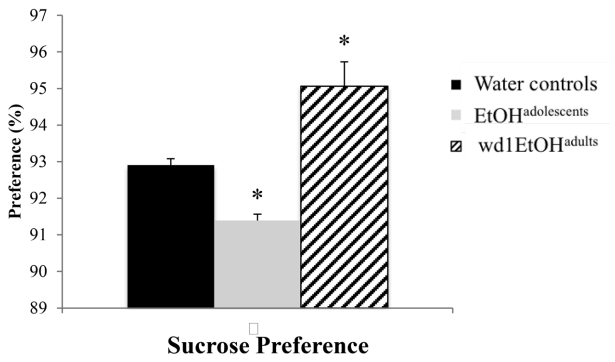

FIGURE 3 | Altered sucrose preference following alcohol drinking. EtOH^{adolescents} showed significantly reduced sucrose preference compared to water control animals while wd1EtOH^{adults} showed increased preference. *$p < 0.05$ vs. water controls. Data represent mean + SEM, n = 9/group.

and EtOH^{adolescents} also exhibited higher average alcohol consumption overall compared to their previous 14-day average [EtOH^{adolescents} $t(8) = 3.53$, $p = 0.001$, wd1EtOH^{adults} $t(8) = 7.12$, $p < 0.001$; Bonferroni $\alpha = 0.025$]. There was no difference in intake between wd28EtOH^{adults} and PND98 water control animals [wd28EtOH^{adults}: $M = 3.63$, SEM = 0.14; PND98 water controls: $M = 3.09$, SEM = 0.11; $t(16) = 1.73$, $p = 0.10$] and no increase in intake between the 14- and 5-day drinking period in wd28EtOH^{adults} [$t(8) = 1.85$, $p > 0.10$].

Immunoblotting

In the AcbSh, there were significant group differences in mGlu1 expression [$F(2,31) = 3.71$, $p = 0.03$; **Figure 7A**] and mGlu5 [$F(2,32) = 4.15$, $p = 0.02$; **Figure 7B**]. *Post hoc* analysis showed that EtOH^{adolescents} had increased mGlu1 expression relative to water controls ($p = 0.04$), with a similar trend seen in wd1EtOH^{adults} ($p = 0.09$). wd1EtOH^{adults}, but not EtOH^{adolescents}, showed a significant increase in mGlu5 expression ($p = 0.02$ and $p > 0.10$, respectively). There were no group differences in Homer2b expression within the AcbSh (non-significant immunoblotting results are from the AcbSh and CeA are summarized in **Table 4**).

There were significant group differences in mGlu1 expression within the CeA [$F(2,33) = 6.32$, $p = 0.005$; **Figure 8A**] and Homer 2b [$F(2,30) = 5.97$, $p = 0.007$; **Figure 8B**]. *Post hoc* testing showed that both EtOH^{adolescents} and wd1EtOH^{adults} had decreased Homer2b expression relative to water controls ($p = 0.007$ and $p = 0.04$, respectively). EtOH^{adolescents}, but not wd1EtOH^{adults}, showed a significant decrease in mGlu1 relative to water controls ($p = 0.04$ and $p = 0.53$, respectively). There were no group differences found in mGlu5 expression (**Table 4**). There were no significant differences in mGlu1, mGlu5, or Homer2 within the AcbC or BLA (**Table 4**; all p's > 0.10).

Finally, when the immunoblotting data for the adult mice drinking under our single-bottle paradigm were compared, we replicated the reduction in CeA expression of mGlu1 (**Figure 9A**) [$t(18) = 3.05$, $p = 0.006$] in alcohol-experienced animals versus water-drinking controls (**Figure 9A**) and also observed a trend toward reduced CeA Homer2 expression (**Figure 9B**) [$t(18) = 1.86$, $p = 0.079$].

DISCUSSION

Drinking-Age-Dependent Behavioral Differences during Withdrawal

In prior work, we showed that adult mice with a binge-drinking history exhibit robust negative affect in the light-dark box, marble burying test, and FST during early (24 h) withdrawal that are not apparent in adolescent drinkers (Lee et al., 2016). In the present study, we assayed the behavior of adolescent drinkers during protracted withdrawal and uncovered distinct age-related differences in the time-course and presentation of withdrawal-induced negative affect in adolescent versus adult drinkers. Replicating our previous findings, wd1EtOH^{adults} showed signs of hyperanxiety during early withdrawal, as indicated by increased marble burying and decreased immobility in the FST. We have consistently observed decreased immobility in adult drinkers during early withdrawal, which we have interpreted as anxiety-related hyperactivity in response to an acute stressor (Lee et al., 2015, 2016, 2017). wd1EtOH^{adults} also showed increased sucrose preference compared to water control animals, which is not surprising given that studies have shown increased preference

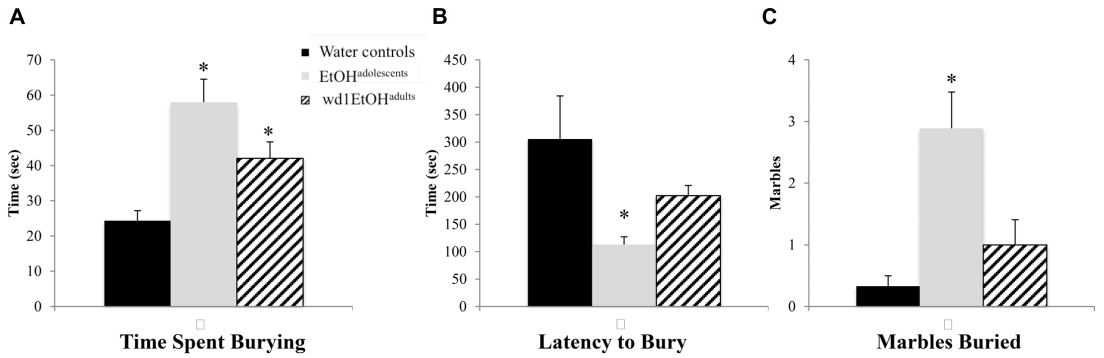

FIGURE 4 | Increased marble burying following alcohol drinking. **(A)** Both EtOH^{adolescents} and wd1EtOH^{adlits} spent significantly more time burying marbles compared to control animals. **(B)** EtOH^{adolescent} also had a shorter latency to start burying and **(C)** buried more marbles overall compared to both control animals and wd1EtOH^{adults}. *$p < 0.05$ vs. water controls. Data represent mean + SEM, n = 9/group.

TABLE 3 | Behavioral results from adult drinkers during protracted withdrawal.

	PND98 water controls	wd28EtOH^{adults}
Marbles buried	1.44 ± 0.60	2.00 ± 0.40
Time spent burying (s)	32.67 ± 4.56	40.51 ± 5.32
Latency to bury (s)	119.44 ± 16.19	105.78 ± 14.26
FST immobile episodes	20.77 ± 1.19	19.77 ± 0.92
Time spent immobile (s)	111.86 ± 6.13	110.35 ± 11.34
Latency to first immobility (s)	51.53 ± 7.09	54.68 ± 3.70
Sucrose preference	93.87 ± 0.21	93.44 ± 0.25
5-day drinking average (g/kg)	3.09 ± 0.17	3.63 ± 0.25

When tested 3 weeks following the end of their 14-day drinking session, no significant differences in behavior was observed between mice with a history of binge alcohol-drinking during adulthood (wd28EtOH^{adults}) and their age-matched water controls. Data represent mean ± SEM, n = 9/group.

for sweet/sugary drinks amongst both humans (Kampov-Polevoy et al., 1997; Kranzler et al., 2001) and animals (Katz, 1982; Gosnell and Krahn, 1992; Stewart et al., 1994) with a history of chronic alcohol consumption. These results support the presence of hyperanxiety, but not depression, in wd1EtOH^{adults}. However, these alcohol-induced behavioral differences dissipated during the course of withdrawal and by day 28, wd28EtOH^{adults} showed no significant differences compared to PND98 water control animals. This latter finding is particularly interesting as we reported previously that a 30-day history of binge-drinking during adulthood produces a persistent increase in negative affect across a large number of assays and behavioral measures (Lee et al., 2015). As the drinking period employed in this study was only 14 days, our collection of work indicates that not only the severity (Lee et al., 2016), but also the persistence, of alcohol withdrawal-induced hyper-anxiety varies as a function of the chronicity of binge alcohol-drinking in adults, with more chronic drinking experience eliciting more robust and enduring pharmacodynamic changes that drive the elevated negative affective state.

In contrast to adults with a 2-week binge-drinking history, EtOH^{adolescents} exhibited signs of both hyperanxiety and depression during protracted withdrawal. In fact, EtOH^{adolescents} demonstrated increased burying behavior across all measures in the marble-burying test and exhibited greater immobility in the FST, relative to wd1EtOH^{adults}. Although general locomotion was not assessed in this study, it is unlikely that the FST results are attributable to suppressed locomotor activity, given the vigorous burying behavior exhibited in the marble-burying test. Based on conventional interpretations of the FST, this increased immobility is indicative of depressive-like behavior. Consistent with this interpretation, EtOH^{adolescents} also showed significantly lower sucrose preference relative to both wd1EtOH^{adults} and water control animals, supporting the presence of an anhedonic state. Interestingly, the difference in sucrose preference between EtOH^{adolescents} and wd1EtOH^{adults} suggests that an alcohol-induced preference for sweet liquids is either absent in EtOH^{adolescents} or is masked by the manifestation of anhedonia.

All alcohol-experienced animals consumed significantly more alcohol during the subsequent 5-day drinking period compared to their 14-day baseline average. Interestingly, EtOH^{adolescents} consumed significantly more than wd1EtOH^{adults}, despite the fact that wd1EtOH^{adults} were earlier in withdrawal, when the presence of an alcohol deprivation effect is typically more pronounced (Melendez et al., 2006; Vengeliene et al., 2014). These data provide additional evidence that early alcohol experience predisposes individuals to higher alcohol consumption in adulthood and may thus accelerate the transition to chronic alcohol abuse and addiction.

The present data, combined with our prior work (Lee et al., 2016), argue that a history of binge-drinking during adolescence *does* elicit a robust negative affective state, but that the manifestation of this state is dependent upon an incubation period during withdrawal. These results are consistent with others reported in the preclinical literature. For example, Pandey et al. (2015) showed increased anxiety-like behavior in the light-dark box and elevated-plus maze and excessive alcohol consumption in rats at approximately 50 days withdrawal following adolescent alcohol exposure. In contrast to our previous findings, this prior study also showed evidence of increased anxiety at 24 h withdrawal in adolescent animals. However, given that alcohol was administered via IP injection,

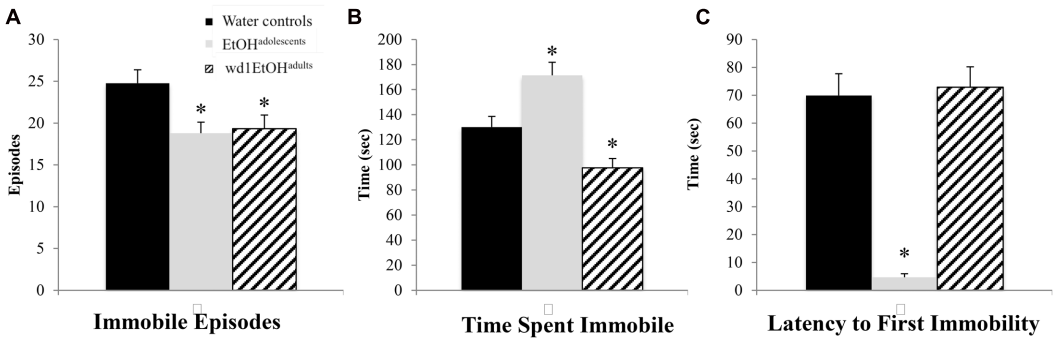

FIGURE 5 | Altered FST behavior following alcohol drinking. **(A)** Both EtOH^{adolescents} and wd1EtOH^{adilts} had fewer immobile episodes than water controls. **(B)** EtOH^{adolescents} spent more time immobile compared to control animals, while wd1EtOH^{adults} spent less time immobile. **(C)** EtOH^{adolescents} had a shorter latency to first immobility, although wd1EtOH^{adults} did not differ significantly from control animals. *$p < 0.05$ vs. water controls. Data represent mean + SEM, $n = 9$/group.

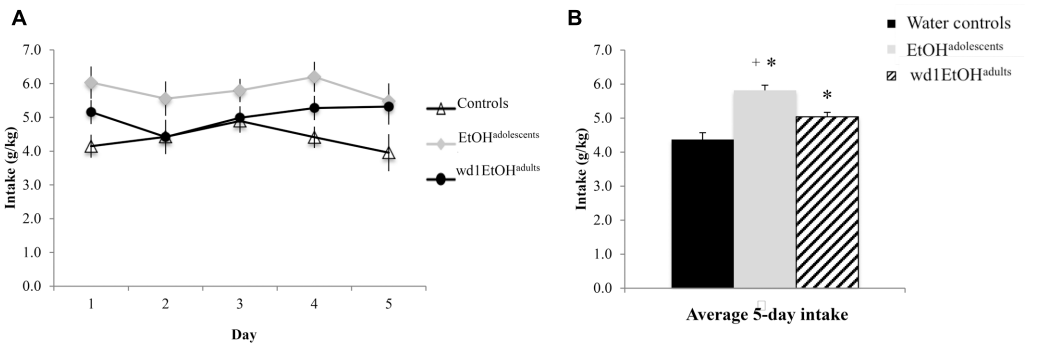

FIGURE 6 | Increased consumption in alcohol-experienced animals. **(A)** Across the 5-day drinking period following behavioral testing, all alcohol-experienced animals consumed more alcohol than first-time drinkers. **(B)** When averaged across day, EtOH^{adolescent} consumed significantly more than wd1EtOH^{adults}. *$p < 0.05$ vs. water controls, $^{+}p < 0.05$ vs. wd1EtOH^{adults}. Data represent mean ± SEM, $n = 9$/group.

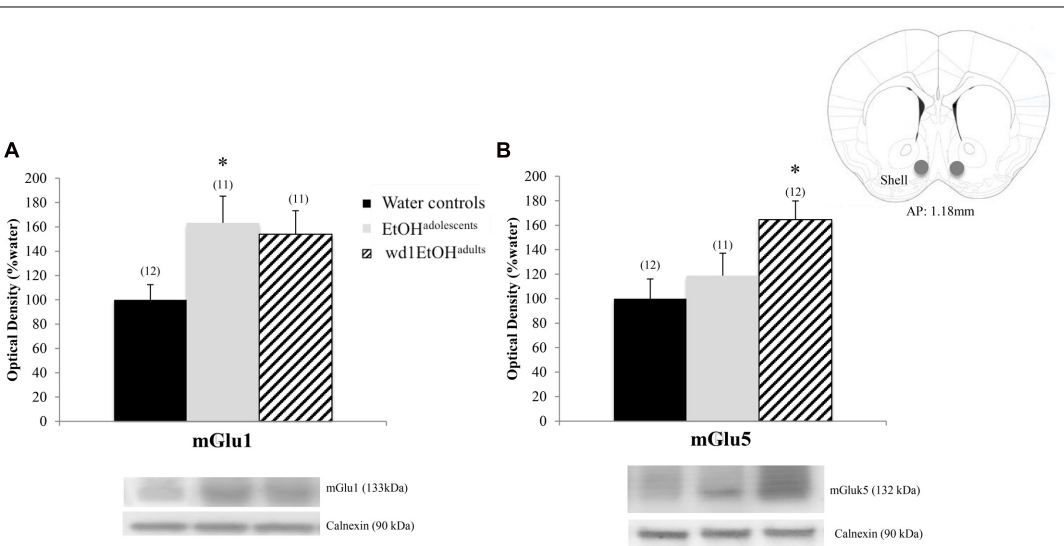

FIGURE 7 | Alcohol-induced increases in mGluR expression within the AcbSh. **(A)** EtOH^{adolescents} showed a significant increase in mGlu1 expression within the AcbSh, with a similar trend in wd1EtOH^{adults}. **(B)** wd1EtOH^{adults} showed a significant increase in mGlu5, with no change observed in EtOH^{adolescents}. *$p < 0.05$ vs. water controls. Data represent mean + SEM of the number of animals indicated in parentheses.

TABLE 4 | Summary of non-significant immunoblotting results.

	PND70 water controls	EtOH^{adolescents}	wd1EtOH^{adults}	PND98 water controls	wd28EtOH^{adults}
AcbSh: mGlu1				100 ± 16.33	97.33 ± 16.59
AcbSh: mGlu5				100 ± 21.07	117.34 ± 25.34
AcbSh: Homer2	100 ± 24.36	66.62 ± 8.07	126.86 ± 21.00	100 ± 16.94	73.78 ± 9.97
CeA: mGlu1				100 ± 32.63	76.48 ± 17.69
CeA: mGlu5	100 ± 12.12	198.81 ± 18.27	185.46 ± 14.76	100 ± 26.03	108.69 ± 22.60
CeA: Homer2				100 ± 24.78	71.31 ± 17.98
AcbC: mGlu1	100 ± 15.63	105.86 ± 15.90	92.05 ± 12.24	100 ± 18.14	80.39 ± 20.88
AcbC: mGlu5	100 ± 18.53	108.31 ± 24.17	113.36 ± 31.79	100 ± 11.30	115.52 ± 12.96
AcbC: Homer2	100 ± 19.42	116.98 ± 24.87	107.71 ± 18.91	100 ± 24.12	93.65 ± 13.10
BLA: mGlu1	100 ± 19.38	85.35 ± 17.36	116.25 ± 20.89	100 ± 15.88	81.98 ± 17.36
BLA: mGlu5	100 ± 14.07	75.80 ± 17.45	92.44 ± 17.37	100 ± 14.15	128.47 ± 26.05
BLA: Homer2	100 ± 13.28	86.09 ± 14.85	94.76 ± 16.15	100 ± 14.02	84.39 ± 15.06

There were no significant differences in protein expression in adult drinkers following 28-days withdrawal (wd28EtOH^{adults}) compared to age-matched water control animals. Data represent mean ± SEM, n = 10–11/group.

it is possible that there was an alcohol × stress interaction due to the stress related to the route of alcohol delivery.

Although the dissipation of withdrawal signs in wd28EtOH^{adults} during protracted withdrawal could be attributed to the relatively short 14-day drinking history, as our lab and others have shown persistent dysfunction following more prolonged alcohol exposure (Valdez et al., 2003; Santucci et al., 2008; Lee et al., 2015). However, this difference nonetheless demonstrates that, compared to adults, adolescent drinkers are hypersensitive to persistent dysfunction following even brief periods of binge-drinking. Such findings suggest that the neural dysfunction underpinning the emotional hyper-reactivity observed in adult mice with a prior adolescent drinking history undergoes an incubation- or sensitization-like process, which likely relates to alterations in the developmental trajectory of corticofugal afferents governing emotional control.

Changes in Glutamate-Related Protein Expression within the AcbSh and CeA

Consistent with previous immunoblotting studies, wd1EtOH^{adults} showed increased mGlu5 expression in the AcbSh at 24 h withdrawal, with a similar positive trend in mGlu1 (Obara et al., 2009; Cozzoli et al., 2014; Lee et al., 2016). Although adolescent binge-drinkers do not exhibit increased Group 1 mGluR expression in early withdrawal (Lee et al., 2015), adolescent drinkers in the present study showed a significant increase in mGlu1, but not mGlu5, during protracted withdrawal. These results are consistent with evidence implicating the importance of Group 1 mGluRs within the AcbSh

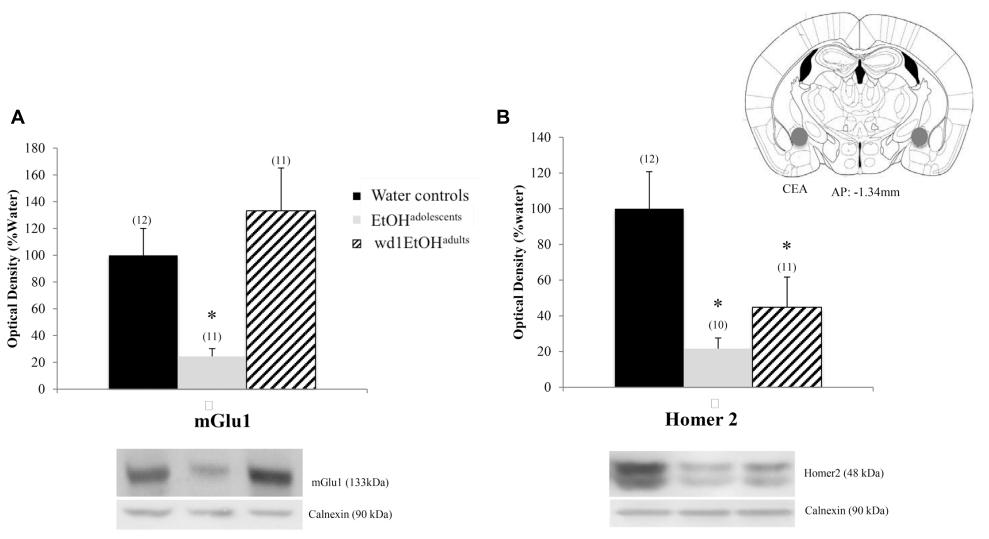

FIGURE 8 | Alcohol-induced decreases in glutamate-related protein expression within the CeA. **(A)** EtOH^{adolescents}, but not wd1EtOH^{adults}, showed a significant decrease in mGlu1 expression within the CeA. **(B)** Both EtOH^{adolescent} and wd1EtOH^{adults} showed a significant decrease in homer 2 expression $^{*}p < 0.05$ vs. water controls. Data represent mean + SEM of the number of animals indicated in parentheses.

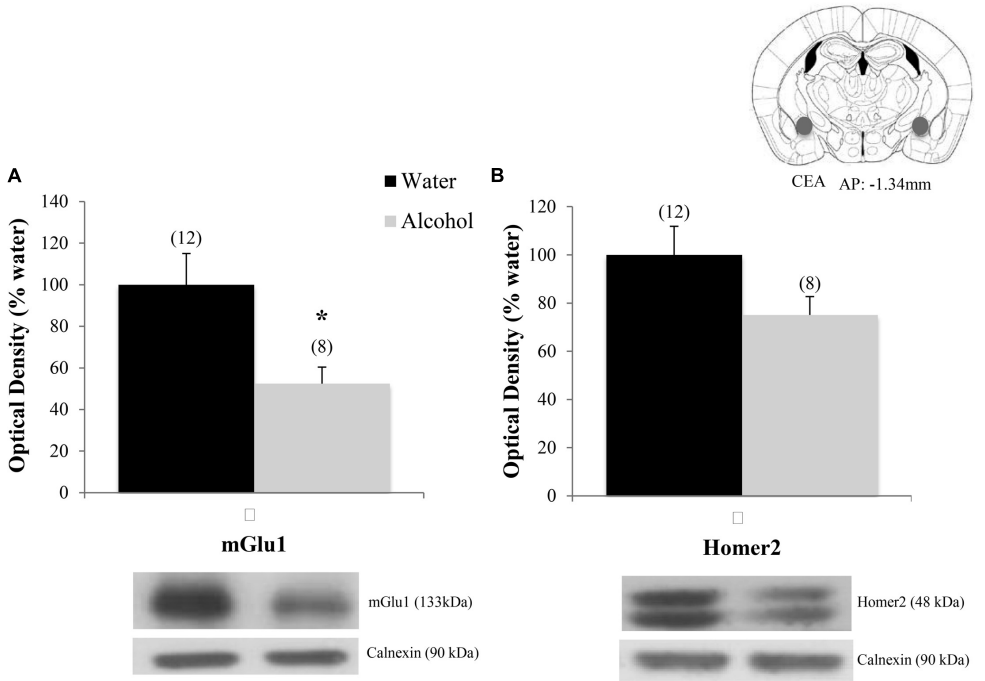

FIGURE 9 | Decreases in glutamate-related protein expression within the CeA following single-bottle drinking. In a 14-day pilot study of single-bottle (20% EtOH) drinking in adults, animals consumed an average of 3.12 ± 0.18 g/kg. **(A)** Alcohol drinkers showed a significant decrease in mGlu1 expression within the CeA at 24 h withdrawal. **(B)** A similar negative trend was observed in Homer 2 expression. *$p < 0.05$ vs. water controls. Data represent mean + SEM of the number of animals indicated in parentheses. Unequal sample sizes due to sample availability, not outlier exclusion.

in drug-taking, including the positive reinforcing properties of alcohol (Gass and Olive, 2008), as well as the initiation, maintenance, and escalation of intake (Cozzoli et al., 2009, 2012, 2015; Kalivas et al., 2009; Griffin et al., 2014; Lum et al., 2014). Therefore, these changes could underlie the increased alcohol consumption seen during the subsequent 5-day drinking period. However, given that these protein changes coincided with the emergence of behavioral dysfunction, increased group 1 mGluR expression could also be relevant to withdrawal-induced negative affect. Additionally, the lack of differences in the AcbC and BLA demonstrate that these changes in protein expression are specific to extended amygdala subregions implicated in emotion.

The AcbSh receives significant glutamatergic input from the amygdala, which is known to mediate many of the negative reinforcing properties of alcohol withdrawal (Christian et al., 2012; Gilpin et al., 2015). Additionally, the Acb itself also has a role in negative affective states (Salamone, 1994; Shirayama and Chaki, 2006; Lim et al., 2012). There has been increased interest in the role of glutamatergic signaling within the Acb in aversive states such as anxiety, depression, and withdrawal-induced negative affect. For example, it has also been shown that an intra-AcbSh glutamate microinjection increases signs of depression in the FST, while inhibiting glutamate is antidepressant (Rada et al., 2003). Glutamatergic antagonism also alleviates the depressive, hypo-dopaminergic state during alcohol withdrawal (Rossetti et al., 1991). Therefore, the alcohol-induced increase in mGluR protein expression shown in the present study could render the AcbSh hypersensitive to glutamate-induced perturbation.

Within the CeA, $EtOH^{adolescents}$ exhibited decreased mGlu1 expression and both $EtOH^{adolescents}$ and $wd1EtOH^{adults}$ showed decreased Homer2b expression during withdrawal. While these results are consistent with post-mortem studies in human alcoholics demonstrating reduced glutamate receptor isoform expression within the CeA (Jin et al., 2014), they contrast with published data from our group (Obara et al., 2009; Cozzoli et al., 2014) and others (e.g., Rossetti and Carboni, 1995; Roberto et al., 2004; Zhu et al., 2007) indicating an increase in glutamate-related signaling within the CeA during alcohol withdrawal. Comparable to our findings in the Acb, there were no significant changes in the BLA control region. This is consistent with previous studies from our lab (Obara et al., 2009; Cozzoli et al., 2014) and further substantiates the regional specificity of the changes observed herein. At the present time, it remains to be determined whether or not our inability to replicate our prior results from the CeA of binge-drinking C57BL/6J mice (i.e., Cozzoli et al., 2014) reflected procedural differences related to the total duration of alcohol-access (14 days vs. 30 days) or to the number of bottles presented during alcohol-access (4 vs. 1). However, the results of a pilot immunoblotting study in our laboratory suggest the former, as a 2-week history of access to a single 20% alcohol bottle also reduced mGlu1 within the CeA of $wd1EtOH^{adults}$ at 24 h withdrawal, with a similar negative trend in Homer2 (**Figure 9**).

The functional relevance of the observed reduction in CeA mGlu1/Homer2 expression remains to be determined, particularly considering that negative affect is classically associated with amygdalar hyperactivation (Davis and Whalen, 2001; Shackman and Fox, 2016). However, optogenetic evidence supports a causal relationship between reduced glutamatergic signaling within the CeA and negative affective states (Tye et al., 2011). Under basal conditions, glutamatergic inputs from the BLA excite GABAergic medium spiny neurons within the lateral subdivision of the CeA, which in turn exerts feed-forward inhibition onto the adjacent medial subdivision of the CeA, the output region which mediates autonomic and behavioral responses associated with anxiety and fear through projections to the brainstem (Hilton and Zbrozyna, 1963; LeDoux et al., 1988; Davis and Whalen, 2001; Gilpin et al., 2015). Inhibition of this BLA projection reduces glutamatergic input to the CeA and increases anxiety-related behaviors, whereas stimulation of this projection is anxiolytic (Tye et al., 2011). Additionally, low glutamatergic input produces asynchronous firing of GABAergic neural networks within the amygdala (Zhang et al., 2012). This asynchronous firing is associated hyper-anxious behaviors that can be reversed by treatment with a group 1 mGluR agonist, which restores both neuronal synchronicity within the CeA and emotionality.

As the present study assayed protein expression in whole-cell homogenates, the site-specificity of these changes (i.e., subcellular location or cell phenotype) remains to be determined. Nevertheless, the work of Tye et al. (2011) and Zhang et al. (2012) support the possibility that reduced glutamate-related protein expression within the CeA, induced by a 2-week history of binge-drinking, may contribute to the manifestation of a hyper-anxious state in adult mice during early withdrawal. Furthermore, such a cause-effect relationship suggests that a time-dependent reduction in mGlu1/Homer2b-signaling within this region contributes to the apparent incubation of negative affect in mice with a prior history of binge-drinking during adolescence. In support of this possibility, no changes in glutamate receptor expression were observed within either the AcbSh or CeA in binge-experienced adult mice during protracted withdrawal (i.e., at a time when affective responding has normalized). As such, neuropharmacological and site-directed transgene delivery studies are currently on-going in our laboratory to directly assess the functional relationship between reduced glutamate signaling within the CeA and alcohol withdrawal-induced hyper-emotionality within the context of short-term binge-drinking.

CONCLUSION

This study provides further basic science evidence to support a causal relationship between adolescent binge-drinking and negative outcomes manifested during protracted withdrawal in adulthood. Despite apparent insensitivity to the negative affective consequences of drinking during acute withdrawal, this study indicates that adolescent binge-drinkers are uniquely vulnerable to the latent maladaptive effects of alcohol upon emotionality that manifest in later withdrawal and shows that even a 2-week history of binge-drinking during the adolescent phase of neurodevelopment can have profound and enduring effects upon negative affect and subsequent drinking behavior, which are temporally related to molecular anomalies within brain regions regulating emotionality and negative reinforcement. This combination of negative affect and increased drinking likely contributes to the predisposition toward alcohol abuse and alcoholism later in life. Alcohol-induced dysregulation within extended amygdala structures regions offers a potential neurobiological correlate for the high comorbidity between substance abuse and mood disturbances. Additional research is necessary to characterize the progression and duration of these changes throughout the course of withdrawal in order to further our understanding of the ontogenetic differences in the etiology of alcoholism and its high rate of comorbidity with affective disorders.

ETHICS STATEMENT

All of the research described in this report was approved by the Institutional Animal Care and Use Committee of the University of California, Santa Barbara.

AUTHOR CONTRIBUTIONS

KL, MC, NS, and KS conducted the experiments. KL and KS analyzed the data. KL composed the manuscript. MC, NS, and KS edited the manuscript.

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Type 2 Neural Progenitor Cell Activation Drives Reactive Neurogenesis after Binge-Like Alcohol Exposure in Adolescent Male Rats

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Excessive alcohol consumption during adolescence remains a significant health concern as alcohol drinking during adolescence increases the likelihood of an alcohol use disorder in adulthood by fourfold. Binge drinking in adolescence is a particular problem as binge-pattern consumption is the biggest predictor of neurodegeneration from alcohol and adolescents are particularly susceptible to the damaging effects of alcohol. The adolescent hippocampus, in particular, is highly susceptible to alcohol-induced structural and functional effects, including volume and neuron loss. However, hippocampal structure and function may recover with abstinence and, like in adults, a reactive burst in hippocampal neurogenesis in abstinence may contribute to that recovery. As the mechanism of this reactive neurogenesis is not known, the current study investigated potential mechanisms of reactive neurogenesis in binge alcohol exposure in adolescent, male rats. In a screen for cell cycle perturbation, a dramatic increase in the number of cells in all phases of the cycle was observed at 7 days following binge ethanol exposure as compared to controls. However, the proportion of cells in each phase was not different between ethanol-exposed rats and controls, indicating that cell cycle dynamics are not responsible for the reactive burst in neurogenesis. Instead, the marked increase in hippocampal proliferation was shown to be due to a twofold increase in proliferating progenitor cells, specifically an increase in cells colabeled with the progenitor cell marker Sox2 and S-phase (proliferation) marker, BrdU, in ethanol-exposed rats. To further characterize the individual subtypes of neural progenitor cells (NPCs) affected by adolescent binge ethanol exposure, a fluorescent quadruple labeling technique was utilized to differentiate type 1, 2a, 2b, and 3 progenitor cells simultaneously. At one week into abstinence, animals in the ethanol exposure groups had an increase in proliferating type 2 (intermediate progenitors) and type 3 (neuroblast) progenitors but not type 1 neural stem cells. These results together suggest that activation of type 2 NPCs out of quiescence is likely the primary mechanism for reactive hippocampal neurogenesis following adolescent alcohol exposure.

Keywords: neurogenesis, neural stem cell, ethanol, adolescence, alcohol use disorders

INTRODUCTION

Alcohol use disorders (AUDs) remain a significant public health problem. Nearly 14% of the USA population meet the DSM-V diagnostic criteria for an AUD in any given year which translates into a life-time prevalence of 29% (1). AUDs often originate with experimentation with alcohol in adolescence, defined as ages 10–19 (2, 3). Indeed, DSM-IV based rates of AUDs in adolescence (~6%) were remarkably similar to that in adults [8.5% (4–7)]. Although rates of adolescent drinking have steadily declined over the last two decades (8), they are still high. For example, over 60% of adolescents report having consumed alcohol by 12th grade and more critically 5.7% (8th graders) to 37.3% (12th graders) have been drunk in the last year (8). Of those adolescents who drink alcohol, over half of them drink in a binge pattern, defined as greater than four (females) or five (males) drinks in a 2 h period (9, 10). Unfortunately, binge pattern drinking is associated with damage to the CNS (11) and adolescents show more degenerating neurons in corticolimbic regions than adults following binge/bender-like alcohol exposure in animal models (12). The adolescent's greater susceptibility to alcohol-induced neurodegeneration may explain why hippocampal pathology has been observed in human adolescents with AUDs despite only a few years of drinking (13–16).

Drinking in young adolescence increases the risk of developing an AUD fourfold versus drinking onset at age 18 and older (17), which suggests that there are significant developmental differences in the effects of alcohol on the brain (16, 18–21). This heightened risk is due to a combination of several factors. Adolescence is a dynamic time for brain development, especially in frontal, cortical, and limbic behavioral control centers (22–24). Neurological immaturity coincides with increased risk taking, novelty seeking, and a reduced responsiveness to the sedative and motor impairing effects of alcohol intoxication [e.g., (25, 26)] that essentially create the "perfect storm" to drive excessive alcohol intake during adolescence (19, 21). The adolescent hippocampus, in particular, shows greater susceptibility to a host of negative effects resulting from excessive alcohol consumption including those from the intoxicating effects of alcohol as well as from the consequences of prior alcohol exposure (27–31). Human adolescents who meet criteria for an AUD demonstrate impairments on hippocampal-dependent tasks (32–34), which is in agreement with observations of reduced hippocampal volumes [(13–15); see also (35) for review]. Animal models of the consequences of adolescent alcohol consumption also demonstrate behavioral impairments on hippocampal-dependent tasks (36, 37), and have helped elucidate the underlying neurobiology, likely impairments in hippocampal structure and function (12, 27, 31, 38–40). However, others have seen only transient [e.g., (41)] or no effect (42) of prior alcohol exposure on hippocampal-dependent learning and memory behavior in adolescents.

The hippocampus is one of the few regions of the brain that contains a pool of neural stem cells (NSCs) that produce new neurons throughout the life of the organism (43–45). NSCs, located along the subgranular zone (SGZ), are now well accepted to produce granule cell neurons that contribute to hippocampal structure and function (45–50). The birth of new neurons is comprised of four main processes: cell proliferation, differentiation, migration, and survival/integration. Newly born neurons originate from a population of radial glia-like NSCs [type 1; (44)]. Type 1 NSCs self-renew by dividing asymmetrically to give rise to a daughter NSC and a daughter intermediate progenitor cell with glial (type 2a) or neuronal (type 2b) phenotypes, that then become a more lineage-committed neuroblast [type 3; reviewed in Ref. (45)]. Neuroblasts then migrate into the granule cell layer, extend axons and dendrites and become integrated as part of the hippocampal circuitry as they mature (45). Alcohol affects each of these processes depending on the timing (age), dose, duration, and pattern of exposure (51–53).

In animal models of AUDs, alcohol-induced neurodegeneration and recovery of hippocampal structure and function corresponds to a similar pattern in alcohol-induced effects on NSCs and adult neurogenesis [reviewed in Refs. (52–54)]. Specifically, alcohol intoxication inhibits NSC proliferation and adult neurogenesis in a duration-dependent and blood ethanol concentration (BEC)-dependent manner (55–63) while a rebound or compensatory effect on adult neurogenesis is observed during withdrawal and abstinence (64–68). Indeed, within the first several days of abstinence there is a striking burst in cell proliferation along the SGZ that results in a significant increase in newborn neurons in both adult and adolescent models of AUDs (64, 66–69). This reactive neurogenesis has been observed in other acutely damaging events such as traumatic brain injury (70), ischemia (71–73), and seizure (74, 75). Recent work describes that reactive NSC proliferation is due to stem cell activation in rodent models of traumatic brain injury (76) and alcohol dependence in adults.[1] Specifically, an increase in the number of neural progenitor cells (NPCs) and proliferating NPCs was observed, suggesting an expansion of the stem cell pool (see text footnote 1). This expansion appears to be due, in part, to more type 1 NSCs recruited out of quiescence at 7 days of abstinence to help drive this reactive neurogenesis effect in adult rats (see text footnote 1). However, findings in adults or adult models do not necessarily generalize to adolescents. For example, the adolescent brain shows more profound and aberrant effects of alcohol on this reactive, adult neurogenesis phenomenon (67). In adolescent rats after alcohol dependence (the 4-day binge model), newborn neurons are observed in ectopic locations (67) and increases in the NSC pool have been observed immediately following the last dose of alcohol in adolescent rats but not adults (77). Therefore, due to these significant age differences in alcohol-induced reactive neurogenesis, we investigated the mechanism of reactive hippocampal neurogenesis in adolescent male rats after the 4-day binge model of alcohol dependence. Specifically, as the mechanism of increased proliferation would be either a shortened (accelerated) cell cycle or activation of a larger number of NPCs out of quiescence, we screened for cell cycle effects and examined which subtype of progenitor cells were proliferating at 7 days of abstinence.

[1] Hayes DM, Geil Nickell CR, Chen KY, McClain JA, Heath MM, Nixon K. Activation of neural stem cells from quiescence drives reactive hippocampal neurogenesis after alcohol dependence. *Neuropharmacology*. (In Review).

MATERIALS AND METHODS

Animal Model

Sixty-two adolescent male Sprague-Dawley rats (Charles River Laboratories; $n = 32$ controls; $n = 30$ ethanols) were used in this study. A timeline of experimental events is shown in **Figure 1A**. Upon arrival, postnatal day (PND) 30, rats were individually housed and allowed 5 days to acclimate to an AALAC accredited vivarium at the University of Kentucky with a 12 h light (0700)/dark (1900) cycle. All procedures were approved by the University of Kentucky's Institutional Animal Care and Use Committee and conformed to the Guide for the Care and Use of Laboratory Animals (78).

The 4-day binge model, based on that originated by Majchrowicz (79) was chosen as it uses the common route of consumption in humans, it mimics a binge-bender typical of the truly problematic portion of the AUD population and has high BECs typical of binge-pattern drinking within the range of that reported in adolescents (80). Starting on PND 35, mid adolescence (81), rats were orally gavaged every 8 h for 4 days with either 25% w/v ethanol or isocaloric dextrose in Vanilla Ensure Plus™ that followed a procedure modified from Majchrowicz (79) as described previously (82). Rats received an initial 5 g/kg dose of ethanol with subsequent doses titrated based on the following behavioral intoxication scale: 0-normal rat (5 g/kg), 1-hypoactive (4 g/kg), 2-ataxic (3 g/kg), 3-delayed righting reflex (2 g/kg), 4-loss of righting reflex (1 g/kg), and 5-loss of eye blink reflex (0 g/kg). Control rats were given the average volume of isocaloric diet administered to the ethanol group. Three ethanol rats and one control died as a result of gavage error and/or treatment (not included in the $n = 62$), leading to unequal group numbers. Tail blood was collected 90 min after the seventh dose of ethanol diet, which is midway of the 12 total doses as well as when the peak BECs occur (82). BECs were analyzed using an AM1 Alcohol Analyser (Analox Instruments LTD., London, UK) with a 300 mg/dl standard.

Ten hours after the last dose of ethanol, animals underwent monitored withdrawal. Rats were observed for behavioral signs of alcohol withdrawal for 30 min of every hour, for 17 h exactly as reported previously (82). Animals were scored according to an established rubric of behavioral signs of withdrawal modified from Majchrowicz (79) as described previously (82, 83). Each hour the highest observed score was recorded and was then

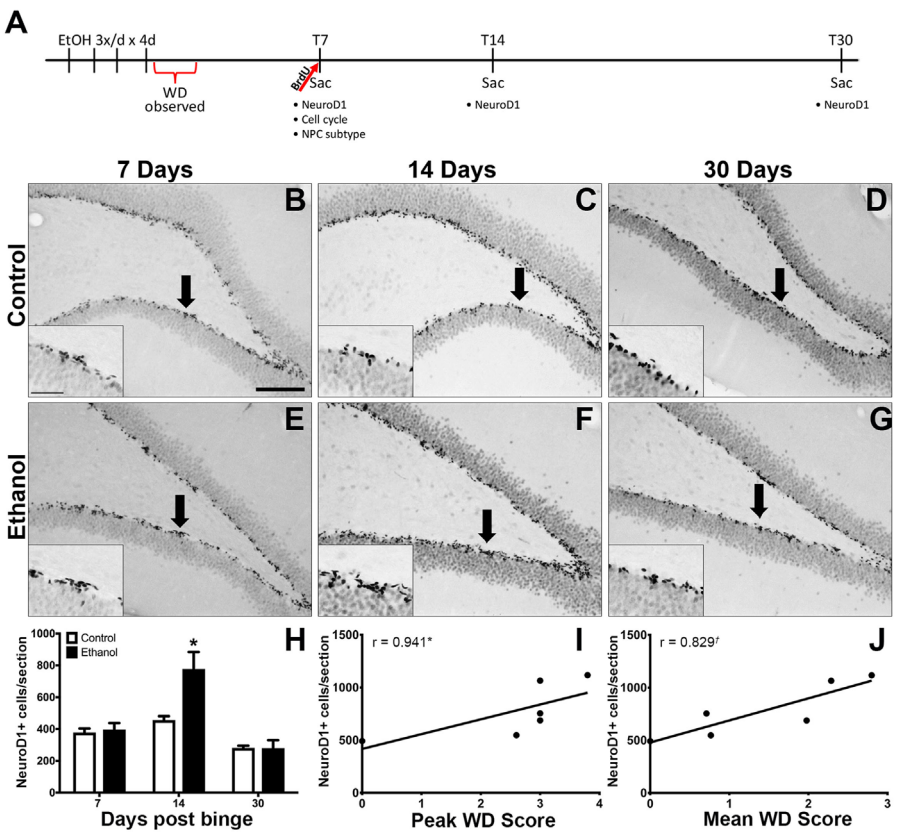

FIGURE 1 | Reactive Neurogenesis confirmed with NeuroD1. **(A)** Experimental timeline is shown. Increased proliferation along the subgranular zone (SGZ) at T7 (67) is followed by enhanced NeuroD1 expression. **(B–G)** Representative images show NeuroD1 immunoreactivity present along the inner side of the granule cell layer in control **(B–D)** and ethanol **(E–G)** rats after 7, 14, and 30 days post the final dose of alcohol. Arrows point to areas represented in insets. Scale bars = 100 μm. **(H)** Profile counts revealed that the number of NeuroD1$^+$ cells located in the SGZ increased significantly 14 days after binge ethanol exposure. **(I,J)** Spearman's correlation shows a positive relationship between 14-day NeuroD1$^+$ cell counts and peak withdrawal score **(I)** and mean withdrawal score **(J)**. $^*p < 0.05$. $^†p = 0.058$.

averaged across all 17 h of withdrawal ("mean WD"). For each animal, the maximum withdrawal score each rat achieved was reported as "peak WD" score.

Tissue Collection

Based on our previous studies on reactive cell proliferation (64, 67, see text footnote 1) and important timelines in adult neurogenesis, the thymidine analog, 5-Bromo-2′-deoxyuridine (BrdU, 300 mg/kg;Roche) was injected at 2 h prior to sacrifice at 7 (T7), 14 (T14), or 30 (T30) days after their last dose of ethanol to detect changes in cell proliferation. The dose of BrdU and 2 h exposure was chosen to maximally label cells in S-phase in adolescent rats based on estimates of its half-life at around 30 min (46, 84). Rats were overdosed with sodium pentobarbital (Nembutal®; MWI Veterinary Supply, Nampa, ID, USA, or Fatal-Plus®; Vortech Pharmaceuticals, Dearborn, MI, USA) followed by transcardial perfusion using 0.1 M phosphate-buffered saline (PBS; pH 7.4) and 4% paraformaldehyde. Brains were extracted, postfixed in paraformaldehyde for 24 h and then stored in PBS at 4°C. Brains were sliced coronally into 40 µm sections with a vibrating microtome (Leica Microsystems, Wetzlar, Germany) using unbiased tissue collection methodologies. Twelve equally spaced series of sections (every 12th section) were collected beginning at a random starting point around Bregma 1.6 through approximately Bregma 6.3. Sections were stored in a cryoprotectant at −20°C until immunohistochemistry (IHC) was performed. Brains were coded so that the experimenter was blind to treatment conditions at all times.

Immunohistochemistry

3,3′-Diaminobenzidine Tetrahydrochloride (DAB) Labeled IHC

For antibodies to the neurogenesis-related and cell cycle-related markers, adjacent sections of every 12th (Ki67, pHisH_3, and NeuroD1) or 6th (BrdU) tissue section were processed for free-floating IHC. To examine the number of cells in each phase of the cell cycle and calculate the percentage of cells in G_1, S, and G_2/M phases of the cell cycle, the following combination of cell cycle markers was measured: (1) Ki67, expressed during all stages of the cell cycle, was used to determine the number of actively dividing cells in the SGZ (85, 86); (2) BrdU, which is incorporated into the DNA during DNA synthesis [S-phase; (87)], was used to quantify cells in S-phase; (3) pHis-H_3 was used to quantify the number of cells in G_2 and M [G_2/M-phase; (88)]; (4) the population of dividing cells in G_1 phase was estimated by subtracting the total number of pHis-H_3^+ and $BrdU^+$ cells from the number of $Ki67^+$ cells. Minichromosome maintenance 2, typically used to identify G_1 phase cells, was not specific for G_1 phase in our hands (not shown). Thus, sections were rinsed in Tris-buffered saline (TBS) to remove traces of the cryoprotectant and incubated in 0.6% H_2O_2 for 30 min to quench endogenous peroxidase activity. An antigen retrieval step in Citra® buffer (BioGenex, Freemont, CA) at 65°C (1 h for Ki67 or 20 min for NeuroD1 and pHisH_3) was followed by washes in TBS then sections were blocked in 3–10% normal serum for 30 min. For BrdU, DNA-denaturing steps were included as previously described (55, 64, 77). Sections were then incubated in primary antibody for 1–2 nights at 4°C (refer to **Table 1**). Tissue was then washed in blocking buffer, incubated for 1 h in secondary antibody (1:200; **Table 1**), incubated in avidin-biotin-peroxidase complex (Vector Laboratories, Burlingame, CA, USA) for 1 h, and colorized with nickel enhanced DAB (Polysciences, Waltham, MA, USA) as previously described (55, 64, 77). Sections were mounted onto glass slides and BrdU and Ki67 were counterstained with cresyl violet and neutral red, respectively. Slides were coverslipped using Cytoseal® mounting media (Richard Allen Scientific, Kalamazoo, MI, USA).

Fluorescent IHC

In order to examine the number of proliferating NPCs or differentiate type 1, 2a, 2b versus 3 progenitor cells, a series of every 12th section of T7 tissue was processed for double ($Sox2^+$/$BrdU^+$) or quadruple (Ki67, GFAP, Sox2, and NeuroD1) fluorescent IHC as described (see text footnote 1). Briefly, tissue was washed in TBS, followed by antigen retrieval steps [BrdU: DNA denaturing as in Ref. (64), Quad label: sodium citrate buffer at 65°C for 1 h]. Sections were washed, blocked in 3% or 10% normal serum, and incubated in primary antibodies (**Table 1**) for 48 h (double) or 96 h (quad). Sections were then rinsed in blocking buffer and incubated in fluorescent secondary antibody for 1 h (double) or overnight (quad) in the dark (**Table 1**). Following

TABLE 1 | Antibodies.

Primary antibody	Antibody concentration; source, product number	Incubation period (h)	Secondary antibody
DAB (individual)			
Mouse α-Ki67	1:200; Vector, VP-K452	48	Horse α-mouse, Vector
Rabbit α-pHisH3	1:1,000; Millipore, 06-570	16	Goat α-rabbit, Vector
Mouse α-BrdU	1:5,000; Millipore, MAB3424	16	Horse α-mouse, Vector
Goat α-NeuroD1	1:1,000; Santa Cruz, sc-1054	48	Rabbit α-goat, Vector
Fluorescent			
Double			
Sox2	1:200; Millipore, AB5603	48	AlexaFluor goat α-rabbit 488, Invitrogen
BrdU	1:400; Accurate; OBT0030	48	AlexaFluor goat α-rabbit rat 546, Invitrogen
Quad			
Mouse α-Ki67	1:100; Vector, VP-K452	96	Donkey α-mouse 405, Jackson ImmunoResearch
Chicken α-GFAP	1:1,000; Abcam, ab467m	96	Donkey α-chicken 488, Jackson ImmunoResearch
Goat α-NeuroD1	1:500; Santa Cruz, sc-1054	96	Donkey α-goat 633, Invitrogen
Rabbit α-Sox2	1:200; Millipore, AB5603	96	Donkey α-rabbit 546, Invitrogen

additional washes in TBS, sections were mounted onto glass slides, dried, and coverslipped with ProLong® Gold anti-fade reagent (Life Technologies, Eugene, OR, USA).

Quantification of IHC

DAB-Based IHC

The number of immunoreactive cell profiles (BrdU, Ki67, NeuroD1, and $pHisH_3$) within hippocampal SGZ were quantified using a 100x objective and an Olympus BX-41 microscope (Olympus, Center Valley, PA). A profile counting approach was chosen over stereology for several reasons besides expediency: (a) the question of interest is relative difference versus controls which we have previously shown to be identical for profile counts versus stereology for proliferation markers (89), (b) stereology is not appropriate for proliferation markers as they are heterogeneously scattered along the SGZ and relatively few in number (90), and (c) the volume of the hippocampus is not different between ethanol and controls (91). The SGZ was defined as a ~50 µm thick ribbon of tissue between the granule cell layer and hilus of the dentate gyrus. As tissue is collected in an unbiased procedure, immunopositive profiles were counted across 6–8 sections (every 12th) or 8–10 sections (every 6th) per brain and presented as mean number of immunopositive profiles ± SEM.

Double Fluorescent-Labeled IHC

Colabeled $BrdU^+$ and $Sox2^+$ cells were quantified along the SGZ using a 100x objective lens with an Olympus BX51 microscope (Olympus, Center Valley, PA, USA) with epifluorescence and bandpass filter cubes to visualize red (546 nm) and green (488 nm). Similar to above, as tissue was collected in an unbiased procedure, colabeled cells were counted across six to eight sections per brain as follows: Analysis started with $BrdU^+$ cells, which were then evaluated for the presence or absence of Sox2 expression and reported as the mean number of colabeled cells per section ± SEM.

Quadruple Fluorescent-Labeled IHC

Sox2 labels multiple types of progenitor cells and the subtypes respond differently to neurogenic stimuli (92, 93). To determine the subtypes of NPCs responding during the proliferation burst at T7, a quadruple fluorescent IHC scheme was devised to differentiate proliferating type 1, 2a, 2b, and 3 cells simultaneously in tissue (see text footnote 1). To identify type 1, 2a, 2b, and 3 progenitor cells, a Leica TCS SP5 confocal microscope (Wetzlar, Germany) was used to collect z-stack images of 40 cells across five to six sections per brain under a 63.4x lens at 0.8 µm thickness, similar to previous (60, see text footnote 1). Proliferating cells ($Ki67^+$) were defined as type 1 ($GFAP^+/Sox2^+/NeuroD1^-$), type 2 (type 2a = $GFAP^-/Sox2^+/NeuroD1^-$; type 2b = $GFAP^-/Sox2^+/NeuroD1^+$), and type 3 ($GFAP^-/Sox2^-/NeuroD1^+$) according to published definitions identical to our previous work in adults (61, 92, see text footnote 1). Cells were evaluated for colabeling in z-stack images rendered into a 3D model by ImagePro Plus 3D software (6.3, Media Cybernetics, Silver Springs, MD, USA). Due to software limitations, only three channels could be compared simultaneously. Therefore, two separate 3D renderings were made for each z-stack. The first included NeuroD1, Sox2, and Ki67 and were used to quantify type 2a, 2b, and 3 NPCs (**Figure 4A**). The second included GFAP, Sox2, and Ki67 and were combined with data collected from the first rendering to differentiate type 1 from type 2a progenitors. Each channel's surface values were adjusted to minimize background signal while maintaining visibility of the fluorescent immunoreactivity. To ensure accuracy, the 3D renderings were compared side by side with the raw z-stack images during quantification. The percentage of cells of each subtype ± SEM is presented along with an estimate of the number of proliferating cells generated by multiplying the percentages obtained with actual counts of DAB-labeled $Ki67^+$ cells.

Statistics

All data were initially assembled in Microsoft Excel with statistical tests performed using either Prism (GraphPad, LaJolla, CA, USA) or SPSS (IBM, Version 22, Armonk, NY, USA) software. Data are graphed as mean ± SEM. BECs and mean ethanol dose per day were analyzed by one-way analysis of variance (ANOVA) followed by *post hoc* Tukey's tests. Intoxication and withdrawal behavior scores were analyzed by the non-parametric Kruskal-Wallis. Histological data were analyzed by appropriate ANOVA followed by Bonferroni *post hoc* tests. Correlation between histology and withdrawal behavior was assessed by the non-parametric, Spearman correlation. *p*-values were accepted as significantly different at $p < 0.05$.

RESULTS

Binge Data

Ethanol intoxication parameters including mean intoxication scores, daily ethanol dose, BECs, and mean and peak withdrawal scores for each cohort are presented in **Table 2**. While all binges

TABLE 2 | Binge intoxication parameters.

Time point (days post EtOH)	*n*	Intoxication score	EtOH dose (g/kg/day)	BEC (mg/dL)	Mean withdrawal	Peak withdrawal
T7 (1-Quad label)	8	1.0 ± 0.1	11.9 ± 0.4	372.5 ± 18.7	1.0 ± 0.3	3.1 ± 0.3
T7 (2—all other)	7	0.7 ± 0.1	13.0 ± 0.3	363.3 ± 21.7	1.2 ± 0.2	3.5 ± 0.1
T14	6	1.4 ± 0.1[a]	10.9 ± 0.3[a]	388.6 ± 22.0	1.4 ± 0.4	2.6 ± 0.5
T30	9	1.0 ± 0.1	12.3 ± 0.2[b]	309.7 ± 11.7[b]	0.3 ± 0.1[b]	2.1 ± 0.3

All controls n = 8.
[a]p < 0.05 vs. T7 group 2.
[b]p < 0.05 vs. T14.
EtOH, ethanol; BEC, blood ethanol concentration.

were conducted identically, groups occasionally differ in some parameters. **Table 2** illustrates that the mean BECs [$F_{(3,27)} = 4.17$; $p < 0.05$] and mean WD scores [$F_{(3,29)} = 3.09$; $p < 0.05$] were significantly lower in the animals at the T30 timepoint (30 days postbinge alcohol exposure) than those in the T14 group (14 days postbinge). Despite the T30 group having a lower BEC, the average daily dose of ethanol was significantly higher compared to T14 [$F_{(3,29)} = 4.73$; $p < 0.001$]. T14 animals also received a lower mean dose per day than T7 group 2 ($p < 0.05$), reflecting the increased intoxication scores of the T14 group [$F_{(3,29)} = 6.95$; $p < 0.005$]. Despite higher BEC's and mean WD scores in the T14 group, there was no difference between T14 and T30's intoxication score. The variable dosing in this model is to maintain high blood alcohol levels (>200 mg/dl) across the 4 days of alcohol exposure, which these measures confirmed did occur. Importantly, all values were within the range previously reported for this model (82).

Reactive Neurogenesis Confirmed with NeuroD1

Our prior report on reactive adult neurogenesis after 4-day binge ethanol exposure in adolescent rats utilized Doublecortin expression to identify immature neurons (67). As Doublecortin may not be specific for newborn neurons (94), NeuroD1 IHC was used to identify late stage progenitor cells committed to a neuronal fate (95). NeuroD1 immunoreactivity was observed in a distinct line along the dentate gyrus SGZ in all groups as expected (**Figures 1B–G**). In the T14 group, those ethanol-exposed rats with the most severe withdrawal scores also had ectopic expression of NeuroD1$^+$ cells in the hilus and molecular layer of the dentate gyrus (data not shown) as expected based on our prior report of ectopic Doublecortin and Prox-1 expression in high withdrawal severity adolescent rats only (67). The number of NeuroD1$^+$ cells was counted along the SGZ only at T7, T14, and T30 days following 4-day binge ethanol exposure and reported as mean cells per section (**Figure 1H**). A two-way ANOVA (diet x time point) revealed significant main effects of diet [$F_{(1,40)} = 11.35$, $p < 0.005$], time [$F_{(2,40)} = 34.29$, $p < 0.001$], and a significant diet × time interaction [$F_{(2,40)} = 9.24$, $p < 0.001$]. A *post hoc* Bonferroni test for multiple comparisons showed that the number of NeuroD1$^+$ cells was significantly increased in the ethanol-treated group at T14 versus its respective control [$F_{(1,12)} = 11.34$, $p < 0.01$]. There was no difference in the number of NeuroD1$^+$ cells between ethanol and control rats at 7 (T7) or 30 (T30) days postbinge. Next, we examined the relationship between NeuroD1 expression at T14 and ethanol withdrawal severity, similar to our previous report (67). The results showed a positive relationship between the number of NeuroD1$^+$ cells at T14 and peak withdrawal score ($r = 0.941$; $p = 0.017$, **Figure 1I**), and mean withdrawal score ($r = 0.829$; $p = 0.058$, **Figure 1J**).

Cell Cycle Distribution in Adolescent Rats during Early Abstinence

Alcohol-induced reactive neurogenesis originated, in part, from a striking burst in cell proliferation at T7 of abstinence in the adolescent rat (67). Such increases in proliferation are due to either an increase in the number of proliferating progenitor cells and/or an acceleration (shortening) of the cell cycle. As we previously identified that alcohol accelerates the cell cycle during intoxication with 4 days of binge alcohol exposure in adolescent male rats (77), we screened for cell cycle effects remaining 7 days later, though in abstinence. The screen is sensitive to changes in the cell cycle based on the expression of various cell cycle specific markers, but uses a much smaller number of animals than is required for the saturate and survive methods used to study cell cycle kinetics (96).

Representative photomicrographs show that clusters of Ki67$^+$, BrdU$^+$, and pHisH$_3^+$ cells were visible along the SGZ of the dentate gyrus (**Figures 2A–F**). Similar to previous work (67), ethanol animals showed a 2-fold increase in the number of Ki67$^+$ cells compared to controls [$F_{(1,14)} = 15.934$, $p = 0.001$], a 2.5-fold increase in the number of BrdU$^+$ cells compared to controls [$F_{(1,12)} = 15.382$, $p < 0.01$], and a 2.4-fold increase in the number of pHis-H$_3^+$ cells compared to controls [$F_{(1,14)} = 4.655$, $p < 0.05$]. The calculated number of cells in G_1 phase [i.e. G_1 = Ki67$^+$ – (BrdU$^+$ + pHisH$_3^+$)] was only slightly but not significantly higher in the ethanol rats versus controls [$F_{(1,14)} = 1.931$, $p = 0.186$; **Figure 2H**]. Next, to determine the effect of alcohol on the distribution of cells across each phase of the cycle (detailed in **Figure 2G**), the proportion of cells within G_1, S, and G_2/M of all actively cycling hippocampal NPCs was calculated (**Figure 2I**). The results show that 7 days after binge alcohol exposure there were no changes in the proportion of hippocampal NPCs in each cell cycle phase in adolescent rats (**Figure 2I**), which suggests that the cell cycle was not altered by prior ethanol exposure at this time point (T7), similar to that observed in adult rats (see text footnote 1).

Characterization of Proliferating Progenitors

The similar fold increase in the number of Ki67$^+$, BrdU$^+$, and pHis-H$_3^+$ cells supported that binge ethanol exposure in adolescent rats activates hippocampal NPCs and leads to NPC proliferation. This reactive proliferation may be due to an expansion of the proliferating progenitor pool. Therefore, to test this hypothesis, the number of proliferating progenitor cells was examined by exhaustively counting the number of BrdU$^+$/Sox2$^+$ colabeled cells in the SGZ. Sox2$^+$ and BrdU$^+$ cells lined the SGZ as expected and similar to past work [data not shown; see text footnote 1]. The number of BrdU$^+$ cells copositive for Sox2 was counted in each group and ethanol-exposed rats showed a significant twofold increase in the number of BrdU$^+$/Sox2$^+$ cells at T7 compared to controls [$F_{(1,12)} = 16.6$, $p < 0.005$; **Figure 3**]. The magnitude of this increase was similar to BrdU alone and confirmed that, at the T7 time point in male adolescent rats, the proliferating cells were NPCs.

As Sox2 labels multiple types of progenitor cells, a quadruple fluorescent IHC scheme was devised to differentiate proliferating type 1, 2a, 2b, and 3 cells simultaneously in tissue (**Figure 4A**; see text footnote 1). Thus, 40 Ki67$^+$ cells (cells in active cycle) for each rat hippocampus were examined for colabeling with GFAP, Sox2, and NeuroD1 in 3D renderings of Z-stacks obtained from a confocal microscope. Representative confocal images for each

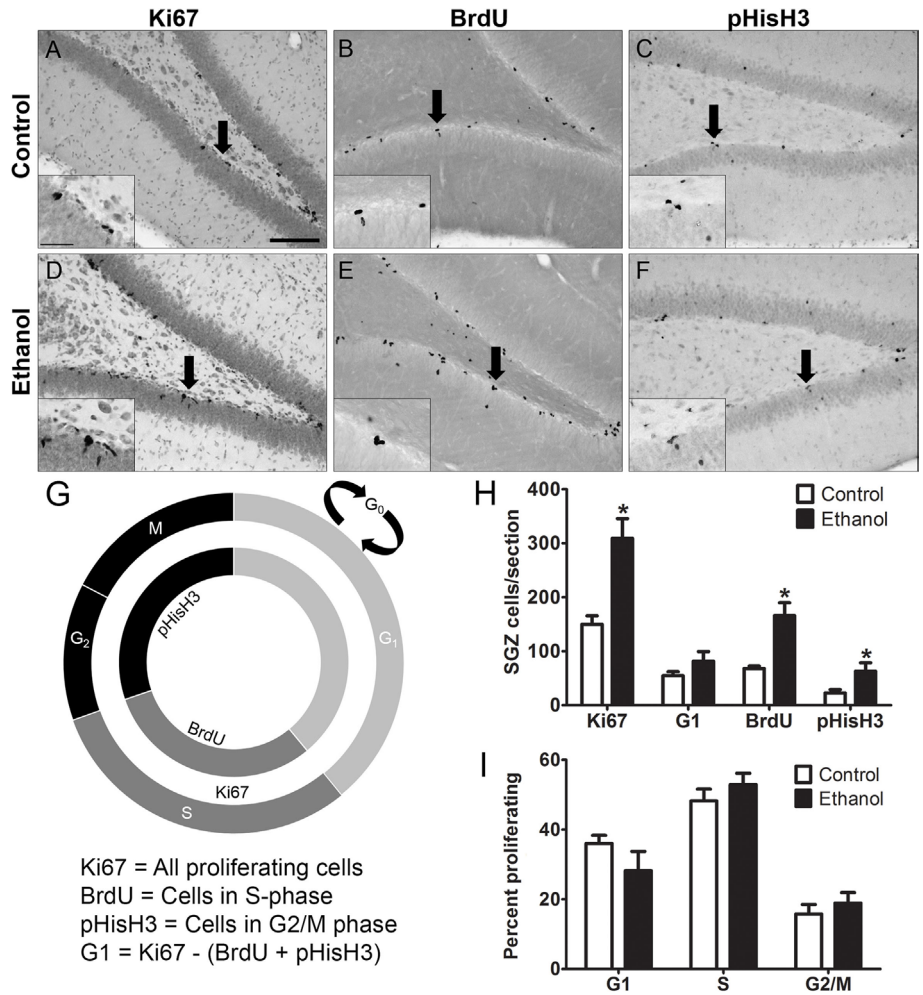

FIGURE 2 | Binge ethanol exposure during adolescence and cell cycle distribution of subgranular zone neural progenitor cells (NPCs) at day 7 of abstinence. **(A–F)** Representative images from sections stained for Ki67, BrdU, and pHis-H_3. Arrows denote area represented in the inset. **(G)** Cell cycle diagram showing the stages of the cell cycle labeled by Ki67, BrdU, and pHis-H_3. BrdU labels cells in S-phase, pHis-H_3 labels cells in G_2 and M phase, and Ki67 labels actively dividing cells of all stages. G_1 population is calculated by subtracting total $BrdU^+$ and pHis-H_{3+} cells from $Ki67^+$ cell numbers. **(H)** Quantification data of dividing cells in $Ki67^+$ (total), $BrdU^+$ (S phase), and $pHisH_3^+$ (G_2/M) cells. Calculated number of cells in G_1 was obtained by subtracting the number of $BrdU^+$ and $pHisH_3^+$ cells from the number of Ki67 cells. **(I)** Calculated distribution of dividing NPCs within each phase of the cell cycle based on total number of Ki67 cells.

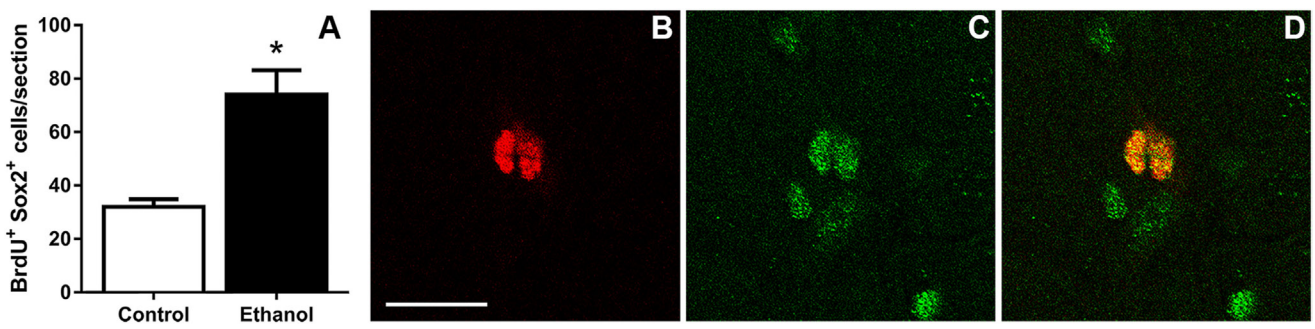

FIGURE 3 | Binge ethanol exposure during adolescence increases the number of subgranular zone neural progenitor cells at day 7 of abstinence. **(A)** Quantification data of $BrdU^+$ and $Sox2^+$ co-positive cells in control and alcohol rats. **(B–D)** Representative fluorescent images for BrdU [red **(B)**] and Sox2 [green **(C)**] and colabel **(D)**. Scale bars = 100 μm. *$p < 0.05$.

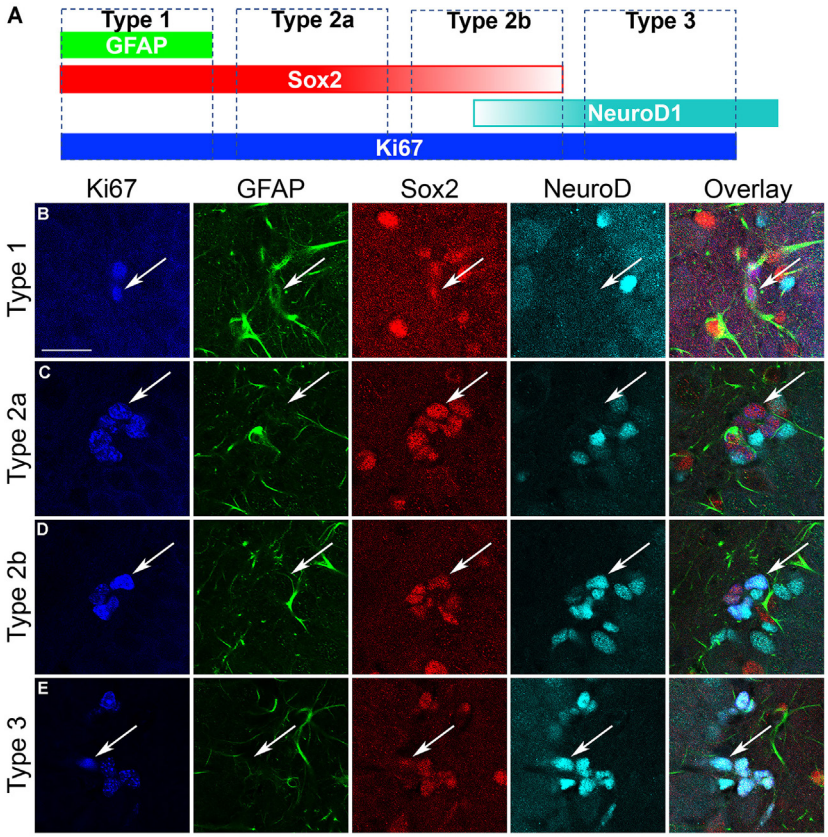

FIGURE 4 | Characterization of hippocampal neural progenitor cells. **(A)** Quadruple fluorescent immunohistochemistry was applied to identify each of the various progenitor cell subtypes as defined in the schematic as follows: GFAP$^+$/Sox2$^+$/NeuroD1$^-$ cells are considered as type 1; GFAP$^-$/Sox2$^+$/NeuroD1$^-$ cells are considered as type 2a; GFAP$^-$/Sox2$^+$/NeuroD1$^+$ cells are considered as type 2b; GFAP$^-$/Sox2$^-$/NeuroD1$^+$ cells are considered as type 3 cells. **(B–E)** Representative confocal images of each of the subtypes show Ki67$^+$ cells colabeled with GFAP, Sox2, and/or NeuroD1 according to that defined in **(A)**. Scale bars = 20 μm.

subtype is presented in **Figure 4**. Quadruple-label immunofluorescence for Ki67/GFAP/Sox2/NeuroD1 IHC demonstrated that the majority of cells were type 2 (type 2a = GFAP$^-$/Sox2$^+$/NeuroD1$^-$; type 2b = GFAP$^-$/Sox2$^+$/NeuroD1$^+$) with low percentages of type 1 cells (GFAP$^+$/Sox2$^+$/NeuroD1$^-$) and type 3 cells (GFAP$^-$/Sox2$^-$/NeuroD1$^+$) as expected (61, 92, see text footnote 1). No differences between control and ethanol groups were observed in the proportion of all four subtypes (type 1, 2a, 2b, 3; **Figure 5A**) as analyzed by one–way ANOVA. Next, the number of cells in each of the four subtypes was calculated: *n*, the number of Ki67$^+$ cells in the SGZ (**Figure 2H**) was multiplied by the cell subtype proportions (in 5 A). The twofold increase in the number of Ki67$^+$ cells resulted in similar significant increases in the numbers of type 2a, 2b, and 3 cells in ethanol-treated rats compared with controls according to one-way ANOVAs [type 2a: $F_{(1,15)} = 22.79$, $p < 0.001$; type 2b: $F_{(1,15)} = 13.79$, $p < 0.005$; and type 3: $F_{(1,15)} = 23.01$, $p < 0.001$]. There was no significant difference in the number of type 1 cells between control and ethanol-exposed rats (**Figure 5B**). Thus, type 2a cells were activated into the cell cycle as expected (92) but there were also significantly more proliferating type 2b and 3 cells that underlie reactive neurogenesis in abstinence.

DISCUSSION

In this study, we demonstrate that adolescent rats exhibit reactive hippocampal neurogenesis after 4-day binge ethanol exposure, confirmed by the enhanced expression of the immature neuronal marker, NeuroD1, 14 days after ethanol exposure (**Figure 1**). As previous work (67) demonstrated that reactive neurogenesis originated with an increase in hippocampal cell proliferation at 7 days following 4-day binge ethanol exposure, we examined two potential mechanisms of this increase: either *via* a shortened (accelerated) cell cycle or activating a larger number of NPCs out of quiescence and into the cell cycle. First, we investigated the effect of prior ethanol exposure on the number and distribution of hippocampal NPCs across the G_1, S, and G_2/M phases of the cell cycle. Prior binge alcohol exposure significantly increased NPC cell numbers in S and G_2/M phases (G_1 was increased, but not statistically) without changing the proportion of cells in each phase (**Figure 2I**). Therefore, the effects of alcohol on the number of cells in S and G_2/M phases was more likely due to an increase in the number of actively cycling cells. These data ruled out an accelerated (shortened) cell cycle underlying alcohol-induced reactive neurogenesis in adolescent rats. Next, we showed that

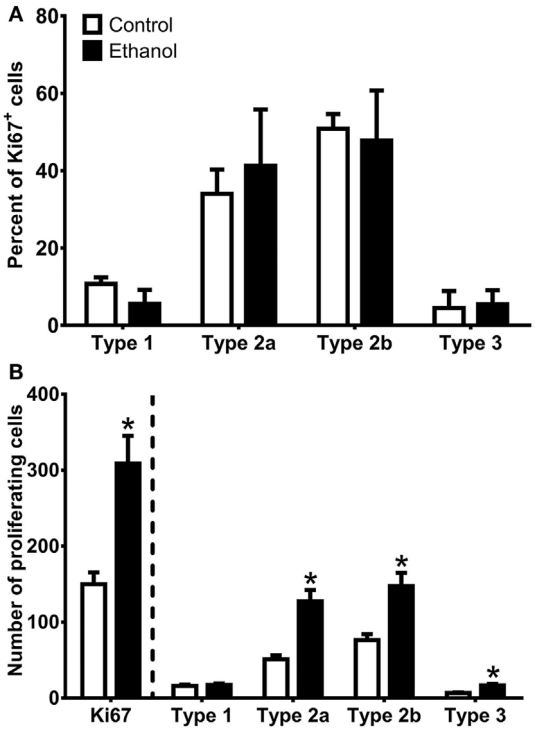

FIGURE 5 | Quantification of progenitor cell subtypes at day 7 of abstinence. **(A)** The graph shows the proportion of sampled Ki67$^+$ cells that were type 1 (GFAP$^+$/Sox2$^+$/NeuroD1$^-$), type 2a (GFAP$^-$/Sox2$^+$/NeuroD1$^-$), type 2b (GFAP$^-$/Sox2$^+$/NeuroD1$^+$), and type 3 (GFAP$^-$/Sox2$^-$/NeuroD1$^+$). **(B)** The graph shows calculated NPC subtypes based on the number of Ki67$^+$ cells present in the SGZ multiplied by the NPC subtype proportions. * indicates $p < 0.05$.

the reactive increase of cell proliferation seven days after alcohol exposure in adolescent rats was in actively proliferating NPCs, evidenced by a twofold increase in the number of BrdU$^+$/Sox2$^+$ colabeled cells (**Figure 3**). As Sox2 is expressed in multiples subtypes of progenitors (93) we probed further to examine whether prior alcohol affected any subtype of progenitor differentially. A quadruple fluorescent labeling scheme to differentiate proliferating type 1, 2a, 2b versus 3 cells revealed that prior alcohol exposure did not alter the percentage of cells classified as any of the four subtypes, but did increase the estimated numbers of proliferating type 2a, 2b, and 3 cells (**Figure 5**). These data support that alcohol-induced reactive neurogenesis is due to prior alcohol dependence, or its sequelae, activating NPCs out of quiescence and into active cycling at day 7 (T7) of abstinence.

The first experiment examined the number of NeuroD1$^+$ cells as our prior reports on reactive neurogenesis used Doublecortin, the former gold standard marker for neuroblasts, though recently observed in oligodendrocyte progenitors (94, 97, 98). NeuroD1, a basic helix-loop-helix transcription factor necessary normal neuronal development (95, 99–101), has an expression profile very similar to Doublecortin; it is expressed in mid- to late-stage NPCs committed to a neuronal cell fate (102). A further benefit of NeuroD1, as it is a transcription factor as opposed to the microtubule-associated protein, Doublecortin, NeuroD1 has a nuclear pattern of immunoreactivity and is therefore easier to quantify with profile cell counts or colabeling analysis of cell phenotype. At T14, the increased number of NeuroD1$^+$ cells along the SGZ in ethanol rats compared to control rats followed the increase in proliferation at T7, a pattern identical to that reported previously for Doublecortin immunoreactivity in both adult and adolescent rats exposed to the 4-day binge ethanol model (64, 67, see text footnote 1). Ectopic NeuroD1$^+$ cells were also observed as expected from our previous report of ectopic Doublecortin in the molecular and hilus layers (67). Ectopic NeuroD1 was not quantified for the current report as this work focuses on the progenitor cells of the SGZ. As adult born granule cells do not become fully integrated into existing hippocampal circuitry until 4–8 weeks following birth (103, 104) and the increased NeuroD1$^+$ cells were observed at only 2 weeks post ethanol, additional work should determine if these newly generated "reactive" neurons integrate properly into the existing hippocampal circuitry.

Next (**Figure 3**), we determined that cells proliferating in the SGZ, indicated by immunoreactivity for the S-phase marker, BrdU, were proliferating NPCs. We observed an increase in the number of cells colabeled for Sox2 and BrdU in the SGZ in the ethanol group as compared to controls, which supports that prior alcohol dependence results in an increase in the number of proliferating NPCs. As Sox2 labels multiple subtypes of proliferating NPCs (93) and each of these subtypes respond distinctly to neurogenic stimuli [e.g., (92)], we hypothesized that the type 2a progenitor would respond robustly. Our results show that increases in proliferation are largely seen in type 2 cells, in agreement with work that this cell type rapidly proliferates to neurogenic stimuli (92). Both the type 1 and type 3 cells generally accounted for less than 5% of the proliferating pool of cells, similar to our observations in adult rats (see text footnote 1). The lack of alcohol effect on the number of proliferating type 1 cells at T7 could be rooted in the low number of type 1 progenitors that actively proliferate coupled with our random sampling of 40 Ki67$^+$ cells. As such, a limitation in our approach is that only cells immuno-labeled with Ki67 are assessed and Ki67 may be undetectable during portions of early G_1 phase (86). Additionally, prior alcohol could theoretically affect the expression of Ki67. However, in adults, type 1 cells are recruited out of quiescence to a greater extent in 4-day binge alcohol rats as opposed to controls at this same time point (see text footnote 1), an observation that mirrors that seen in other brain insults (76, 105–107). Furthermore, only one time point in abstinence after alcohol dependence was assessed. In adults, NPC proliferation begins as early as T5 with only type 2 progenitors activated as predicted, though progressing to all four types by T7 (see text footnote 1). Therefore, different populations of NPCs could be activated into the cell cycle in a time line distinct from adults and should be assessed in future studies. Activation of different pools of progenitors has implications for mature neuronal phenotypes that arise from these progenitors (108).

A previous study from our laboratory in the same 4-day binge model demonstrated that ethanol intoxication specifically reduces the length of the S-phase in hippocampal NPCs

without altering the G_1 or G_2/M phases (77). Utilizing the same screening approach as employed above, it was clear that the cell cycle was affected ($BrdU^+$ cells reduced, while $Ki67^+$ cells were the same between adolescent alcohol and controls). Thus, the positive screen justified full study of cell cycle kinetics using the cumulative BrdU injection method (87). At T0, which is during intoxication, immediately after the last dose of alcohol in the 4-day binge, alcohol reduced NPC cell cycle duration by 36% and shortened S-phase by 62%, suggesting that binge alcohol exposure accelerates NPC cell cycle progression in adolescent rats (77). This acceleration resulted in an expansion of the NPC pool as indicated by a significant increase in the number of $Sox2^+$ NPCs in the hippocampal SGZ immediately following binge alcohol exposure. Therefore, 4-day binge ethanol intoxication in adolescent rats, specifically, shortens cell cycle length [at T0; (77)] which should increase the NPC pool, which is exactly what we then detected at T7 of abstinence (**Figures 3** and **5**). Interestingly, the cell cycle appears to return to control levels as cells were in similar proportions across the phases of the cell cycle for both prior ethanol exposed and control rats (**Figure 2**).

Neural progenitor cells along the SGZ of the hippocampus continuously generate new granule neurons throughout life, a phenomenon critical to hippocampal structure and function, namely, hippocampal-dependent learning and memory (45, 48, 109). Increases in adult neurogenesis are associated with improved hippocampal functions such as learning, memory, and mood (45, 49, 50, 110–112). Reactive neurogenesis and/or activation of NPCs after insult also contributes to recovery in other models of CNS insult (113–116). However, reactive neurogenesis in seizure appears to contribute to epileptogenesis (74, 75). Therefore, as alcohol dependence in adolescence results in withdrawal seizures in some animals (82), it is not known whether reactive neurogenesis after alcohol dependence is a beneficial repair mechanism or a pathological phenomenon (117). Data support both sides: reactive neurogenesis after alcohol dependence in adult rats correlates to recovery of dentate gyrus granule cell number (see text footnote 1) but reactive neurogenesis in adolescents can be ectopic if withdrawal is severe, similar to the ectopic new neurons observed in seizure models (67, 74). As speculated in Ref. (67), ectopic neurogenesis may be yet another aspect of the adolescent's susceptibility to alcohol-induced hippocampal dysfunction as ectopic neurogenesis is thought to contribute to hippocampal pathology in epilepsy (117). Fortunately, overt signs of alcohol withdrawal are less common in adolescents than adults (118), though behavioral symptoms of severity are identical between adult and adolescent rats in the model used (82). In sum, a critical future direction is to elucidate the role of reactive neurogenesis after alcohol dependence in adolescent rats specifically.

Another important question that arises from this body of work concerns the cause of reactive neurogenesis. That reactive neurogenesis is common to many forms of CNS insult suggests that cell death may be a common trigger of the phenomenon, especially since there is significant cell death in the 4-day binge model used here (12, 119–121). However, reactive neurogenesis has been observed in milder alcohol dependence models where there is less acute cell death than in this binge model (65, 66, 68). Seizure or excitatory activity in the hippocampus also results in reactive neurogenesis and seizure is observed in some animals in this model as discussed above. Intriguingly, in adults at least, eliminating overt seizures with diazepam did not prevent reactive cell proliferation from occurring (64). Diazepam does not suppress all behaviors that result from withdrawal-induced over-excitation though (122). Therefore, residual excitatory activity could continue to drive reactive neurogenesis through the recruitment of progenitors, as in other models (123–125). Indeed, the development of alcohol dependence is due, in part, to chronic inhibition of the N-methyl-D-aspartate (NMDA) receptor (126), while alcohol dependence-induced reactive neurogenesis mirrors NMDA receptor blockade effects on NPC proliferation and neurogenesis (127, 128). Thus, alcohol dependence and specifically, alcohol withdrawal-induced hyperexcitability, likely plays a major role in reactive neurogenesis in models of AUDs (64, 67, 68).

The resulting effect of increased neurogenesis detected in abstinence clearly requires further investigation in both adult and adolescent models of AUDs. It is worthy to note that the effects described occur with one 4-day exposure. Those with AUDs do not merely binge once or become dependent once. Therefore, future studies should consider models where there are cycles of dependence and withdrawal. That reported by Somkuwar et al. (68), however, highlights that long-term dependence facilitated by cycles of ethanol vapor inhalation, induces similar effects on reactive neurogenesis. Indeed, it is the similar results in these two models, besides the very different routes to dependence, that support our conclusion that an aspect of alcohol dependence is likely the major player in reactive neurogenesis.

ETHICS STATEMENT

All procedures were approved by the University of Kentucky's Institutional Animal Care and Use Committee and conformed to the Guide for the Care and Use of Laboratory Animals (78).

AUTHOR CONTRIBUTIONS

Conceived and designed experiments (CGN, KN, and DH), conducted experiments (CGN, JM, DH, KC, and KN), analyzed and/or interpreted data (CGN, HP, KC, and KN), and drafted and/or revised document (CGN, HP, DH, KC, JM, and KN).

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Revision of AUDIT Consumption Items to Improve the Screening of Youth Binge Drinking

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This study analyzes the appropriateness of an improved version of one of the most frequently used instruments for the screening of high-risk alcohol consumption. This adaptation was created in accordance with certain limitations recognized by other researchers and in an attempt to adjust the content and scales of some items to a more consensual definition of binge drinking. After revising items 2 and 3, the areas under the ROC curves of the AUDIT and of different abbreviated versions were calculated. A total of 906 minors (468 females) between the ages of 15 and 17 were evaluated. Stratified sampling was conducted on a population of high school students in the city of Valencia (Spain). One school was randomly chosen from each of the city's 16 school districts. Information was collected on sociodemographic aspects, consumption patterns and the AUDIT containing the improved items. The percentage of underage BD reached 36%, regardless of gender or age. BD groups have been differentiated by different intensity levels, both in males and females. Upon comparing the effectiveness of the distinct versions of the AUDIT, it is recommended that researchers and clinics use the combination of the revised items 2 and 3 to ensure a more precise identification of underage BD. A cut-off point of 5 for this test would permit identification of 94% of the underage BD and would notably reduce false positives.

Keywords: binge drinking, underage, AUDIT, alcohol screening, ROC

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INTRODUCTION

One of the most frequently used screening instruments for the identification of high-risk alcohol consumption in youth is the AUDIT and its abbreviated versions (Patton et al., 2014; Cortés et al., 2016; Hagman, 2016) which was designed to identify persons with hazardous and harmful patterns of alcohol consumption (Babor et al., 2001). Specifically, research on the young brain refers mainly to these tools to compile consumption data and classify youth as either binge drinking (BD) or no binge drinking (non-BD) (Mota et al., 2013; López-Caneda et al., 2014a,b). Other studies have used the AUDIT score for correlation with structural and functional aspects of certain brain areas (Wahlstrom et al., 2012; Howell et al., 2013; Smith and Mattick, 2013; Kvamme et al., 2015).

Of the three dimensions included in the AUDIT (quantity-frequency, symptoms of dependency, and consequences of consumption), the first of these dimensions is the most frequently used to determine consumption in youth (Chung et al., 2002; Thomas and McCambridge, 2008; Seguel et al., 2013). The three items making up this first dimension, AUDIT-C, obtain higher sensitivity and specificity values in the detection of high-risk consumption as compared to the overall scale (DeMartini and Carey, 2012; Barry et al., 2015; Cortés et al., 2016; García et al., 2016).

These results support the conclusions obtained in the revision conducted by Clark and Moss (2010) with regards to the abbreviated AUDIT versions appearing to be more useful for youth, even when limited to item 3. This item, used to classify underage BD, has revealed psychometric properties that are similar to those of the AUDIT-C (Bowring et al., 2013; Blank et al., 2015; Paiva et al., 2015).

Despite the fact that they are very frequently used instruments, limitations have been suggested with regards to their efficiency in identifying BD. On the one hand, reference has been made to the measurement scales used for the different items. Letourneau et al. (2017) warned that in item 3, a drinker who engaged in three BD days per week (e.g., Friday through Sunday) is forced to describe their drinking as either "*weekly*" or "*daily or almost daily*" on the AUDIT-C, even though said drinking took place only three times a week. For Question 2, the numerical amount for any respondent who reports consuming 10 or more drinks on a typical day, whether it is 12, 15, or 30 drinks, will be coded as 10.

On the other hand, in an attempt to better identify underage BD, an effort has been made to more precisely specify the cut-off points of the scales. In this regard, no consensus has been reached either, and there is still a very wide range for the AUDIT, varying between 2 and 10 points (Knight et al., 2003; Kelly et al., 2004; Clark and Moss, 2010). For minors, the most frequently used cut-off point is 4 (Chung et al., 2002; Santis et al., 2009; Cortés et al., 2016) and 3 in the AUDIT-C (Chung et al., 2002; Cortés et al., 2016).

Furthermore, some researchers have tried out new combinations of items in order to better predict the pattern of underage consumption. Again, in this case, consensus has yet to be reached. McCambridge and Thomas (2009) allude to the fact that the best combination would consist of items 3, 5, and 8. Bowring et al. (2013) suggest that the best combination is 3, 4, 8, and 9. More recently, Blank et al. (2015) referred to separately using items 2 and 3, increasing the number of response options to obtain more precise information on the consumption pattern. In this way, sensitivity and specificity of the items are improved until reaching 0.8 and 0.7, respectively. Furthermore, some studies have noted the low correlation of item 1 with the total of the scale (Gmel et al., 2001; McCambridge and Thomas, 2009), recommending its elimination.

All of this disagreement has led to an interest in making improvements in the wording of the consumption items (AUDIT-C) given that these are the most explanatory of the youth consumption pattern. Included in the suggested changes is the modification of item 3, reducing the number of drinks (five or more on one consumption occasion -Kokotailo et al., 2004-; four or more drinks for women and five or more drinks for men -Olthuis et al., 2011-); or transforming the number of drinks to standard drinking units (SDUs), according to the country of origin (García et al., 2016). Other proposals have narrowed the time limit to "one single consumption occasion" in item 2 (García et al., 2016), although it has also been suggested that grams of alcohol should be used instead of number of drinks to evaluate the quantity ingested for this item (Gmel et al., 2001).

None of the suggested improvements has been overwhelmingly accepted by researchers, perhaps because they do not comply with a consensual definition of BD. Recent revisions of the operationalization of this consumption pattern (Courtney and Polich, 2009; Parada et al., 2011; Cortés and Motos, 2016) coincide in identifying the National Institute on Alcohol Abuse, and Alcoholism [NIAAA] (2004) definition as being the most well-adjusted, although limiting it to consumption engaged in over the past 6 months – given that it is intermittent behavior- and adapting it to the SDU value of each country. In the case of Spain, BD is identified as the consumption, during a 2 h interval, of six or more SDUs for women and seven or more for men, at least once over the past 6 months. Furthermore, it is important to note that this definition only establishes a limit for a very heterogeneous group of consumers; therefore it is necessary to differentiate the most homogenous subgroups possible.

In this work, we have modified the content of the consumption items included in the AUDIT-C, adapting them both in terms of wording as well as in their measurement scales, to the proposed consensual definition of BD. This shall permit the identification of which of these items best classifies heavy youth drinkers, and therefore, shall optimize the selection of BD sample participants, thereby improving the precision of the obtained results.

MATERIALS AND METHODS

Participants

Nine hundred and six participants, 468 women and 438 men, took part in the study. Their ages ranged from 15 to 17, with mean age $M = 15.99$ years, $SD = 0.8$ years. All of the participants were high school students. **Table 1** shows the distribution of the participants based on gender, age and whether or not they engage in BD. Overall, 36.1% of these adolescents ($n = 327$) engaged in BD, 52.9% ($n = 173$) were female and 47.1% ($n = 154$) were male. Differences were not found based on gender [$F(1,904) = 0.191$; $p = 0.612$], or age [$F(1,904) = 3.929$; $p = 0.54$].

Procedure

Stratified sampling was carried out on a population of mandatory secondary school (grades 7–10), upper secondary (grades 11–12), and vocational training students in the city of Valencia (Spain). One school was randomly chosen from each of the 16 school districts in the city. Questionnaires were administered in classrooms during the school day. In all cases, participation was voluntary and anonymous.

A self-report diary was used, in which, for each day of the week, participants were to indicate the type and number of drinks consumed and the approximate time when the drinking took place. Each use was converted to grams of alcohol, based on the Spanish SDU (1 hard liquor = 20 g; 1 beer/wine = 10 g) (Rodríguez-Martos et al., 1999). This value was multiplied by the number of glasses of each type of alcoholic beverage that were consumed.

Based on the SDUs consumed and the number of hours in which this consumption took place, participants were classified as BD or non-BD. In all cases, there was compliance with the consumption proportion of seven or more SDUs in a 2 h interval

TABLE 1 | Demographic characteristics of sample.

	BD (*N* = 327 // 36.1%)			Non-BD (*N* = 579//63.9%)		
	Male *N* (%)	Female *N* (%)	Total *N* (%) [% of BD]	Male *N* (%)	Female *N* (%)	Total *N* (%) [% of Non-BD]
15 years old	42 (47.7%)	46 (52.3%)	88 (100%) [26.9%]	86 (44.3%)	108 (55.7%)	194 (100%) [33.5%]
16 years old	61 (45.9%)	72 (54.1%)	133 (100%) [40.7%]	112 (50.7%)	109 (49.3%)	221 (100%) [38.2%]
17 years old	51 (48.1%)	55 (51.9%)	106 (100%) [32.4%]	86 (52.4%)	78 (47.6%)	164 (100%) [28.3%]
Total *N* (%)	154 (47.1%)	173 (52.9%)	327 (100%)	284 (49.1%)	295 (50.9%)	579 (100%)

BD, binge drinkers.

for males and the consumption of six or more SDUs during the same time interval for females (National Institute on Alcohol Abuse, and Alcoholism [NIAAA], 2004).

Participants also filled out the 10 AUDIT items (Spanish version validated by Contel Guillamon et al., 1999). Three variables were extracted from this instrument: the sum of the 10 items (AUDIT), the sum of the first three items (AUDIT-C), and the score on the third question (AUDIT-3). In this study, the internal consistency of the AUDIT and the AUDIT-C was 0.74 and 0.83, respectively.

Next, the consensual definition of BD was used to improve item 3. It was worded as follows: *During the past 6 months, what is the average number of days per month with BD consumptions (seven or more Spanish SDUs for males and six or more SDUs for females over a 2 h period)*? The response scale was adapted based on the results obtained in prior studies conducted with minors and university students (Patrick et al., 2013; Cortés et al., 2016; Hagman, 2016). Following the revision of consumption quantity and frequency, it is considered more representative to use response alternatives that qualify normal situations, such as that some youth have engaged in BD once over the past 6 months, hence alternative 1 which considers this behavior to be sporadic and different from that of the other alternatives. The measurement scale definitively consists of the following: *(0) Never; (1) Sporadically -less than once a month-; (2) between 1 and 4 times; (3) between 5 and 8 times; (4) between 9 and 12 times; (5) 13 or more times.*

The wording of item 2 was also improved, changing number of drinks for number of Spanish SDUs consumed in 1 day. Finally, it is worded as follows: *How many SDUs do you tend to have on a day when you drink alcohol?* And maintaining its original response scale *(0) 1 or 2; (1) 3 or 4; (2) 5 or 6; (3) 7 to 9; and (4) 10 or more.*

Then, based on self-reports, these two new variables were generated. Later the value of the AUDIT-CR was calculated (A1+A2revised+A3revised), and the usefulness of the A3revised item was assessed. Finally, considering the recommendations from some prior studies, the A2revised+A3revised variable was also calculated.

Statistical Analyses

Four cluster analyses were also conducted with the BD and non-BD youth, based on the values of *number of grams consumed in a BD session* and *number of hours of consumption* for females and for males. In all cases, the extraction procedure consisted of two phases, which led to a natural classification of the subjects into different groups.

An analysis of variance (ANOVA) was performed, with its corresponding *a posteriori* tests, using the eight groups obtained in the clusters as independent variables (IVs) to determine whether there were differences in the grams consumed and the number of hours.

The area under the ROC (*Receiver Operating Characteristic*) curve was calculated using the method proposed by Hanley and McNeil (1983), which provides a graphic representation of a classifier's performance.

To determine the optimal AUDIT cut-off score, our goal was to minimize false negatives and thus improve, as much as possible, the detection of youth engaging in this activity. Therefore, cut-off scores that maximized sensitivity were used. This methodology is based on prior studies (Cortés et al., 2016; Cortés Tomás et al., 2017). In the absence of a gold standard, Zweig and Campbell (1993) suggest using a consensus or majority expert opinion. As described in the introduction, the gold standard used in this study was consumption during a 2 h interval of ≥6 SDUs for women and ≥7 SDUs for men at least once over the past 6 months.

It is possible to compare the discriminatory capacity of the different versions of this screening tool based on their respective ROC curves, given that they were measured simultaneously, were applied to the same subjects and were contrasted with the same consensual definition of the revisions of BD operationalization.

RESULTS

The cluster analysis among BD females produced two differentiated groups (BD1F/BD2F) (**Table 2**). In the case of the BD males, two groups were produced (BD1M/BD2M). Of the non-BD, two female (NONBD1F/NONBD2F) and two male (NONBD1M/NONBD2M) groups were produced.

The ANOVA performed among the eight groups (four BD and four non-BD) indicated that there were significant differences in the number of grams consumed [$F(7,898) = 326.905$; $p < 0.0001$] and in the number of consumption hours [$F(7,898) = 203.304$; $p < 0.0001$].

Upon comparison of the four BD groups (**Table 3**), it was found that the subgroups consuming the larger number of grams (BD1F and BD2M) took twice the amount of time in drinking this quantity. Furthermore, both are similar in terms of quantity consumed, as well as in time spent drinking.

TABLE 2 | Binge drinking (BD) and non-binge drinking (non-BD) groups differentiated by sex resulting from the clusters analyses.

	Cluster	*n* (%)	Mean grams (*SD*)	Mean consumption hours (*SD*)
BD				
Female	BD1F	52 (30.0)	186.1 (65.3)	4.94 (1.6)
	BD2F	121 (70.0)	82.97 (24.1)	2.14 (0.8)
Male	BD1M	104 (67.5)	97.98 (22.9)	2.29 (0.8)
	BD2M	50 (32.5)	212.6 (71.3)	4.68 (1.3)
Non-BD				
Female	NONBD1F	233 (79.0)	37.45 (15.6)	1.83 (0.9)
	NONBD2F	62 (21.0)	91.92 (31.6)	4.90 (1.4)
Male	NONBD1M	213 (75.0)	40.43 (18.3)	1.92 (0.97)
	NONBD2M	71 (25.0)	115 (45.2)	5.8 (1.96)

BD, binge drinkers; SD, standard deviation; BD1F, group one females of binge drinkers; BD2F, group two of females binge drinkers; BD1M, group one of males binge drinkers; BD2M, group two of males binge drinkers; NONBD1F, group one of NON females binge drinkers; NONBD2F, group two of NON females binge drinkers; NONBD1M, group one of NON mles binge drinkers; NONBD2M, group two of NON males binge drinkers.

Of the non-BD females, it is noteworthy that the NONBD2F group consumes a similar quantity of grams as the BD2F and BD1M groups, but it does so over a much longer time period, equivalent to that of groups BD1F and BD2M.

As for the non-BD males, the NONBD2M group is similar to BD1F in terms of quantity of grams consumed but it takes a greater number of hours to do so, therefore this is not considered BD.

When considering all of the interviewees, differentiated according to the eight resulting groups of the BD/non-BD clusters, the three classic versions of the AUDIT yielded lower values in the area under the ROC curve as compared to the results obtained for the modified versions of this instrument (**Table 4**). This area ranges from 0.741 in the case of the AUDIT to 0.801 in the case of the AUDIT-C.

The adjustment of the AUDIT questions to the definition of what is considered BD allows for the significant increase in the area under the ROC curve. Both when considering the AUDIT-CR, which includes the revision of the two items as well as when considering the A3R, the ROC area reaches 0.88.

But the most parsimonious combination that also permits a slight increase in the explained area is the one that includes the sum of the A2R and A3R (**Figure 1**).

Using the score of 5 on the A2R+A3R, 94% of the BD young people were detected (sensitivity) and 75% of the non-BD (specificity). When the cut-off score was established at 4, the sensitivity increased slightly, but the specificity was much worse.

DISCUSSION

This study analyzes the appropriateness of an improved version of the AUDIT. The adaptation has been carried out based on the limitations recognized by other researchers (McCambridge and Thomas, 2009; Olthuis et al., 2011; Bowring et al., 2013; Blank et al., 2015; Cortés et al., 2016; García et al., 2016; Letourneau et al., 2017) and by attempting to adjust the content and the scales of some items to a more consensual definition of BD.

Within the group of heavy drinkers, the underage population warrants special attention due to the potential repercussions on its bio-psycho-social development and maturity (Squeglia et al., 2011; Pascual et al., 2014). In Spain, 4 out of every 10 minors have access to this substance which is not legally authorized until the

TABLE 3 | A posteriori Games-Howell test.

(I) Clusters_only_BD	(J) Clusters_only_BD	Difference in means (I–J)	Std. error	Significant	95% confidence interval (lower bound – upper bound)	
Alcohol grams						
BD1F	BD2F	103.187(*)	9.322	0.000	73.86	132.52
	BD1M	88.173(*)	9.336	0.000	58.81	117.54
	BD2M	−26.446	13.562	0.521	−68.45	15.56
BD2F	BD1M	−15.014(*)	3.133	0.000	−24.60	−5.43
	BD2M	−129.633(*)	10.325	0.000	−162.19	−97.07
BD1M	BD2M	−114.619(*)	10.337	0.000	−147.21	−82.03
Hours						
BD1F	BD2F	2.802(*)	0.238	0.000	2.05	3.55
	BD1M	2.654(*)	0.240	0.000	1.90	3.41
	BD2M	0.262	0.295	0.986	−0.65	1.18
BD2F	BD1M	−0.148	0.105	0.853	−0.47	0.17
	BD2M	−2.540(*)	0.201	0.000	−3.17	−1.91
BD1M	BD2M	−2.392(*)	0.203	0.000	−3.03	−1.75

(*) The difference in means is significant at the 0.05 level.

BD, binge drinking; Std. error, standard error; BD1F, group one of females binge drinkers; BD2F, group two of females binge drinkers; BD1M, group one of males binge drinker; BD2M, group two of males binge drinkers.

TABLE 4 | Performance of the three versions of the AUDIT in detecting binge drinking for the entire sample.

	Cut-off	Sensitivity	Specificity	ROC (95% confidence interval)
AUDIT	≥5	1.000	0.264	0.741 (0.681–0.801)
	≥6	1.000	0.316	
	≥7	0.940	0.383	
	≥8	0.860	0.455	
	≥9	0.820	0.535	
	≥10	0.740	0.617	
	≥11	0.580	0.690	
AUDIT-C	≥4	1.000	0.305	0.801 (0.751–0.852)
	≥5	1.000	0.339	
	≥6	0.960	0.420	
	≥7	0.920	0.525	
	≥8	0.780	0.671	
	≥9	0.600	0.792	
AUDIT-3	≥1	0.980	0.336	0.752 (0.696–0.808)
	≥2	0.780	0.610	
AUDIT-CR	≥5	1.000	0.527	0.888 (0.856–0.920)
	≥6	0.960	0.655	
	≥7	0.920	0.741	
	≥8	0.700	0.853	
A2R+A3R	≥4	1.000	0.697	0.898 (0.871–0.925)
	≥5	0.940	0.746	
	≥6	0.700	0.872	
	≥7	0.140	0.989	
AUDIT-3R	≥1	0.980	0.688	0.883 (0.854–0.913)
	≥2	0.700	0.850	

ROC, receiver operating characteristic.

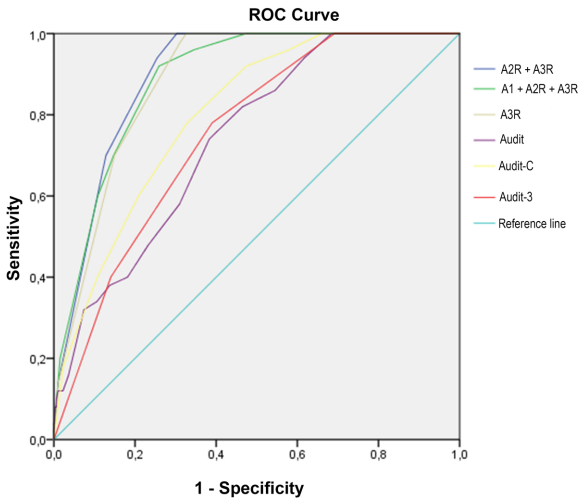

FIGURE 1 | Receiver operating characteristic (ROC) curves for all AUDIT versions to detect BD.

age of 18, eventually engaging in BD (Observatorio Español sobre Drogas [OED], 2016). This same percentage has been observed in the population of youth evaluated in this study.

Furthermore, the presence of females of this age is also evident, confirming the trend that has been warned of in prior national epidemiological surveys (Observatorio Español sobre Drogas [OED], 2016) that found a similar number of males and females engaging in intense alcohol consumption.

Our findings provide further insight into the understanding of the existence of different subgroups within the BD collective, both males and females, based on the seriousness of their behavior −a greater quantity of alcohol consumed, for more hours and at a greater frequency−. In addition, it should not be forgotten that among the BD groups that consume the most, both males and females drink similar amounts of alcohol and they do so in the same number of hours. This leads to a clearly greater risk for females, given that they are more vulnerable to the consequences of alcohol consumption. Furthermore, this result quantifies results of previous research (Valencia-Martín et al., 2007; Pilatti et al., 2013) claiming that there is a higher level of consumption by BD males, limiting it only to the subgroups that consume less.

The healthcare and social implications that are generated in the BD minors would be reduced if it were possible to detect and intervene in this behavior as early as possible. This suggests the need for sufficiently powerful screening measures to identify this consumption pattern with the least possible error. This would offer improvements not only in the clinical and prevention areas but also in the area of research (Foxcroft et al., 2015; Walton et al., 2015; Arnaud et al., 2016) given that a more adjusted classification of the subjects would permit greater precision in the obtained results.

As found in the literature that was consulted (DeMartini and Carey, 2012; Barry et al., 2015; Cortés et al., 2016; García et al., 2016), of all of the AUDIT versions used, the AUDIT-C is the version that classifies adolescents by improving the correct identification of the non-BD, compared to the AUDIT. However, upon transforming the items, adjusting them through both wording and in response scale to the most widely accepted BD definition, the adjustment of identification of this consumption pattern is increased.

Upon comparing the three versions of the revised AUDIT -AUDITCR/A3r/A2r+A3r- the last combination stands out (A2r+A3r) given that it identifies the greatest number of BDs and reduces the number of false positives. It may be stated that the recommendations of Blank et al. (2015) to focus on items 2 and 3, as well as those of Gmel et al. (2001) and McCambridge and Thomas (2009) to ignore item 1, contribute to an improved classification of BD. In addition to this, if we add improvement in the wording of the items and their response scales, adjusting them to the operational definition of BD, a greater area is obtained under the ROC curve. This suggests that this is a test with the greatest discriminatory capacity of all evaluated in this study. Having an instrument with an area under the ROC curve of 0.898 means that there is an 89.8% probability that, when considering two randomly selected minors, one BD and the other non-BD, the test will correctly classify them.

The reliability obtained through this new combination of items is very similar to that of the complete original scale -0.74, qualified as an acceptable reliability coefficient-. This result is not surprising, given that the items have been reformulated in order to note different aspects of BD. Item 2 reveals a more than intense consumption, as it is conducted over one entire day, whereas item 3 notes the frequency with which BD is engaged in. The combination of both not only informs of having reached a limit in BD in the form of overconsumption, but also if the youth drinks in a manner that extends over a longer period of time.

CONCLUSION

Despite the fact that the AUDIT and its abbreviated versions appear to be appropriate tools to screen adolescents who are engaging in this behavior, the identification of heavy drinkers is improved by using a more parsimonious combination of two items. Even in those cases in which researchers recur to item 3 in order to classify BD/non-BD (Bowring et al., 2013; Mota et al., 2013; López-Caneda et al., 2014b; Blank et al., 2015) it would be more appropriate, given the notable improvement in discrimination of this test, to recur to the revised item 3.

In fact, it is recommended that researchers and clinics use the combination of the two items (A2r+A3r) proposed in this work for a more precise identification of BD minors. Specifically, starting from a cut-off point of 5, it may be possible to identify 94% of the underage BD. The sensitivity and specificity values attained are three points higher than those achieved using the three-item combination proposed by McCambridge and Thomas (2009), but using one less item, facilitating its applicability.

Our study may be limited in that it relies on self-reporting. This method of data collection has been questioned in adult samples, given that it may present an underestimation of consumption (Smith et al., 1990). However, in adolescent populations, self-reports have been found to be reliable and valid when conducted in a confidential manner, compared with other survey protocols (e.g., household survey) (Winters et al., 1990; Knight et al., 2003) in which youth perceived they were at great risk of being identified (Fowler and Stingfellow, 2001; Degenhardt et al., 2013).

According to the recommendations made by Santis et al. (2009), additional research is necessary in order to generalize these results to other geographic areas.

ETHICS STATEMENT

It was not necessary for the study because there was no ethics relevant problems. People just filled out questionnaires/tests, afterward they got feedback on their scores. No manipulation or violation was done. The study was undertaken in compliance with Spanish legislation (approved by the Department of Education) and the code of ethics for research involving human subjects outlined by the University of Valencia Human Research Ethics Committee. The adolescents and their legal representatives signed an informed consent form.

AUTHOR CONTRIBUTIONS

M-TC-T and J-AG-C conceived of the study and collected the data. M-TC-T and M-DS-B analyzed the data. M-TC-T, PM-S, and J-AG-C wrote the paper. M-TC-T, J-AG-C, PM-S, and M-DS-B approved the final version to be published.

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Patterns of Alcohol Consumption in Spanish University Alumni: Nine Years of Follow-Up

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The aim of this study was to empirically identify different profiles of Spanish university alumni, based on their alcohol use over 9 years, and to further characterize them. A cohort study was carried out between 2005 and 2015 among university students (Compostela Cohort-Spain; $n_{2015} = 415$). Alcohol consumption was measured using the Alcohol Use Disorder Identification Test (AUDIT). A two-stage cluster analysis, based on their AUDIT total scores was carried out separately for males and females. The further characterization of every profile was based on demographic data, age at onset of alcohol use, positive alcohol-related expectancies, tobacco and cannabis use, as well as their answers to some European Addiction Severity Index items. Five different clusters were identified: *Low users* (29.2%), *Moderated users* (37.2%), *At-risk users* (14.2%), *Decreasing users* (13.2%) and *Large users* (6.2%) for females, and *Low users* (34.4%), *At-risk users* (25.6%), *High-risk users* (15.6%), *Decreasing users* (14.4%) and *Large users* (10.0%) for males. Being a cannabis user or a smoker was positively associated to those more hazardous clusters in both genders. Regarding females, significant differences in the age of onset and high positive expectancies were found. However, there were few significant differences among the groups in relation to their employment status and social relations. The results reveal the existence of different typologies of alcohol users among university alumni, with differences among males and females. Modifying positive expectancies, limiting access to alcohol at a young age, and reducing uses of other substances uses are key to promote healthier alcohol use profiles and to prevent hazardous uses.

Keywords: alcohol drinking in college, university students, alcohol, cluster analysis, cohort study

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INTRODUCTION

Alcohol use among university students has been a subject of vast research (Mota et al., 2010; Johnston et al., 2011; White and Hingson, 2013). National and international surveys of college students usually reveal high rates of alcohol use among this age demographic (European Monitoring Center for Drugs and Drug Addiction, 2011; Substance Abuse and Mental Health Services Administration, 2013), being male students who tend to drink comparatively more than

females (Courtney and Polich, 2009; Wicki et al., 2010). For instance, O'Malley and Johnston (2002) found rates around 70% of alcohol use in the last 30 days prevalence among American college students, and Moure-Rodríguez et al. (2014) found 7.8% of abstainers among college male students at 20 years old and 11.8% of abstainers among the female ones. However, most reported prevalence and consumption indicators might not be directly comparable among studies since culture-related variations and methodological differences are confounded (Wicki et al., 2010).

In addition to this, certain risk patterns of alcohol consumption, such as binge drinking are increasing among young people around the world (Jernigan, 2001). This pattern of alcohol consumption is characterized by the intake of large amounts of alcohol in a short period of time, reaching blood alcohol concentrations of 0.8 g/l or greater (National Institute on Alcohol Abuse and Alcoholism, 2016). In Spain the proportion of young people who reported having been drunk in the last 30 days increased from 25% in 2006 to 32% in 2013 (Plan Nacional Sobre Drogas, 2015). It is also worth mentioning that the literature suggests that there are aspects of the college environment that specifically tend to support alcohol drinking (O'Malley and Johnston, 2002), and that high-frequency drinking patterns that develop during university appear to persist several years post-graduation (Arria et al., 2016).

Moreover, several short-term consequences associated with an excessive alcohol consumption have been identified, such as unintentional injuries (Miller et al., 2007), having unprotected sex with casual partners (Kiene et al., 2009), drink-driving (Hingson et al., 2009), aggressions (Svensson and Landberg, 2013), or memory blackouts (Mundt et al., 2012). Likewise a growing literature have shown that some patterns of alcohol use—such as heavy or binge alcohol drinking—may lead to structural and functional anomalies in the brain as well as to deficits in several cognitive processes (Hermens et al., 2013; Jacobus and Tapert, 2013; López-Caneda et al., 2014a). Similarly, the few longitudinal studies in university students conducted to date addressing the effects of alcohol misuse in the middle/long-term report that some abnormalities in the brain function may persist or emerge if alcohol consumption is maintained (López-Caneda et al., 2012; Correas et al., 2016) whereas others may recover or brake their evolution if the binge alcohol use is ceased (Winward et al., 2014; López-Caneda et al., 2014b).

On the other hand, long-term consequences in employment status, family and social relationships during the early adulthood of university alumni have hardly been studied, mainly because of limited available longitudinal data and because much of the alcohol literature developed suggested that generally both men and women classified as problem drinkers in college tend to mature out of such behavior after college and become non-problem drinkers as adults (Perkins, 2002; Jackson and Sartor, 2016; Moure-Rodríguez et al., 2016b). Nevertheless, some authors, such as Jennison (2004) found that those with risky binge drinking style in college were either less likely to continue their education or were more likely to find work in less prestigious occupations. Likewise, several studies assessing the employment outcomes have identified long-term effects of heavy/binge drinking on employment status, showing that these risky alcohol consumption patterns were more prevalent among the unemployed (Henkel, 2011), especially in females (Berg et al., 2013).

Furthermore, many studies have observed differential effects of gender pointing to a greater vulnerability to the harmful cognitive effects of alcohol in adolescent and young females as compared to age-matched males (Caldwell et al., 2005; Nederkoorn et al., 2009; Squeglia et al., 2011). But these are not the only studies showing that the gender variable should not be only considered as a confounding factor. Multiple studies have shown important differences between females and males in prevalence of heavy episodic drinking and alcohol risky consumption, and in explicative factors of both patterns of consumption (Moure-Rodríguez et al., 2016b). Moreover, the consequences of different pattern of alcohol consumption over unsafe sex (Moure-Rodríguez et al., 2016a), car accidents (Caamaño-Isorna et al., 2017a), and alcohol related injuries (Caamaño-Isorna et al., 2017b) also have shown differences between females and males.

While heterogeneity among alcohol users has been widely recognized (Mossa et al., 2007; Leggio et al., 2009; Cortés et al., 2010), efforts to identify homogenous subpopulations of alcohol users have been focused primarily on crosssectional data (Basu et al., 2004), resulting in varied typologies with limited ability to account for high variability among alcohol users. Nevertheless, relatively little is known about longitudinal patterns of drinking behavior. In this regard, Harrington et al. (2014) identified eight distinct profiles of problematic alcohol users in an adult population, based on their daily and weekly patterns of alcohol use as well as longitudinal trajectories of drinking, while (Sunderland et al., 2014) found seven distinct profiles of Saturday night drinking behavior among young adults.

For its part, even less research has been conducted from a longitudinal point of view involving alcohol drinking trajectories in university alumni, which entail a limited understanding about how their later life could be influenced by their longitudinal pattern of drinking behavior. Johnsson et al. (2008) studied college students' drinking patterns during the first 4 years at university based on their AUDIT scores, and found four different groups: one with stable risky consumption, other one with decreasing consumption, a third group with increasing consumption, and a fourth one with stable non-risky consumption. They stated that gender influenced the trajectories, but no separate classifications were explored.

Altogether, these findings strengthen the importance to study alcohol consumption evolution at the long-term from adolescence to early-adulthood, a critical developmental transition from the cognitive point of view and the social perspective, and highlight the significance of taking into account the gender-specific patterns of alcohol drinking in order to delimit their potentially different trajectories and deleterious effects more precisely. However, longitudinal studies trying to identify different subpopulations of alcohol users in university alumni are scarce, and beyond that, to the best of our knowledge, none have been conducted separately for males and females in the Spanish context.

The aim of the present study was to empirically identify the different profiles of female and male Spanish university alumni based on their use of alcohol over 9 years, based on a cluster analysis. In addition, the clusters found were characterized in terms of antecedent variables (demographic data, age of onset of alcohol use, positive alcohol-related expectancies, and cannabis and tobacco use) and consequences, such as employment status, family and social relationships at a 9-year follow-up. Based on previous studies, we hypothesized that the effects of alcohol consumption from adolescence (aged 18–19 years) to young adulthood (from 27 to 28 years old) on the socio-economic outcomes will be stronger with persistent and increasing high alcohol consumption patterns and that these effects will be greater in women in comparison with age-matched men.

MATERIALS AND METHODS

Design, Population, and Sample

A cohort study was carried out to evaluate the neuropsychological and psychophysiological consequences of alcohol use among university students (Compostela Cohort-Spain). The study was carried out between November 2005 and February 2015 among students at the University of Santiago de Compostela (Spain). A cluster sampling was performed, randomly selecting at least one of the freshman year classes from the 33 university schools (a total of 53 classes). All students present in the class on the day of the survey were invited to participate in the study ($n = 1{,}382$). This study was approved by the Bioethics Committee of the Universidade de Santiago de Compostela. Subjects were informed both verbally and in written format, as part of the questionnaire, that participation was voluntary, anonymous, and the possibility to opt-out was available at any time. Subjects were informed that they were free to fill or refuse to fill the questionnaire. The sample used in this paper is part of this wider research project, and it is part of that used in other non-duplicate paper arising from the same longitudinal study (Moure-Rodríguez et al., 2016b).

Data Collection Procedures

Participants were evaluated via a self-administered questionnaire in the classroom in November 2005 and again in November 2007. Students that provided their phone numbers were further evaluated by phone at a 4.5- and a 9.25-year follow-up. On all four occasions, alcohol consumption was measured using the Galician validated version of the Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993; Varela et al., 2005). The AUDIT is a brief written screening method developed by the World Health Organization (WHO) to identify current harmful and hazardous drinking that has demonstrated reasonable psychometric properties in university students (Kokotailo et al., 2004). We decided to use the AUDIT because it is widely considered one of the best screening tests for alcohol abuse; it is transnational and it has often been used with university populations. At baseline, participants responded to additional questions about socio-demographic variables, cannabis and tobacco consumption, and positive alcohol-related expectancies. They also answered to European Addiction Severity Index (EuropASI) items about their degree, employment, family and social relationships at a 9-year follow-up.

Definition of Variables

Cannabis and tobacco consumption at 18 years old were measured with the questions "Do you consume cannabis/tobacco when you go out? Never/Sometimes/Most of the Time/Always." The categories were recategorized to No (Never) or Yes (Sometimes, Most of the Time, Always).

Taking the number of positive and negative alcohol-related expectancies into account, a score ranging from 0 to 14 was generated (0 being the maximum of negative expectancies and 14 the maximum of positive expectancies). The scores were divided up into tertiles.

Four categories were defined for age of onset of alcohol use (After 16 years old/At 16/At 15/Before the age of 15). Alcohol use was measured through the AUDIT score at 18, 20, 22, and 27 years old—a continuous variable with values ranging from 0 to 40. The Galician validated version of the (AUDIT) (Varela et al., 2005) set the cut-off value at 5 for risky drinking, and 16 for alcohol dependence.

The EuropASI items asked about their highest degree obtained (High school-vocational training/Bachelor/Master-PhD), their longest period of employment and unemployment (Number of months), their employment pattern in the last 3 years (Employed/Student/Unemployed), their sources of financial support (Own sources-employment or unemployment subsidy-/other people's sources-family or friends-), and if their job is in line with their education (Yes/No). Likewise, they answered EuropASI questions about their current coexistence (Independent/With parents), alcohol-related problems in the home environment (Yes/No), number of close friends, and problems with parents, siblings, partner, and friends (Yes/No).

Finally, several socio-demographic variables were considered, such as place of residence (At the parents' home/Outside of the parents' home), and maternal educational level (Primary school/High school/University).

Statistical Analysis

A two-stage cluster analysis, based on their AUDIT total scores (2005, 2007, 2010 and 2015), was carried out separately for males and females. All subjects with the four aforementioned measures were included in the analysis.

Firstly, a hierarchical cluster analysis was conducted, using squared Euclidean distance as the distance measure across respondents and Ward's method for combining clusters (Ward, 1963). This method was chosen to preliminarily identify the number of clusters, since it is more powerful than other agglomerative clustering techniques that use *F*-values to maximize differences among clusters (Mojena, 1977; Hair and Black, 2002). Based on the resulting dendrograms (Milligan and Hirtle, 2003) and the change in the derived coefficients (within-cluster sum of squares) at each combination step (Burns and Burns, 2009), the five-cluster option was determined to be the optimal solution for both genders. The reliability of this solution was confirmed by entering the means of the five-cluster solution as the starting points (seeds) for an iterative k-means cluster analysis. We found 93.3% agreement in assignment of male

participants to specific clusters between both methods, and 85.8% agreement in females.

To demonstrate external validity of the five types of alcohol users, a set of variables, not included in the cluster analysis but theoretically relevant to clustering variables, were used. This further characterization of every profile was based on socio-demographic variables, age at onset of alcohol use, tobacco use, cannabis use, and positive alcohol-related expectancies at the beginning of the study, as well as their answers to EuropASI items about employment, family and social relationships at the 9-year follow-up. Categorical variables were analyzed using χ^2 analyses to determine global significance and adjusted residuals eadj (Haberman, 1973) to estimate the significance in each cell. These adjusted residuals eadj are almost independent and distributed as standard normal, so values >1.96 or < -1.96 represent a significant deviation compared to the expected value at a 95% confidence level. These residuals are useful in visualizing contingency table data, making it instantly understandable which cells are out of line with expectations, in which direction, and by how much. Continuous variables were analyzed using analysis of variance (ANOVA), and the Scheffé *post-hoc* test. Likewise effect size statistics were examined (Eta-squared and Cramer's V). All statistical analyses were conducted using the IBM SPSS Statistics v. 20.

RESULTS

The response rate at the 9-year follow up was 30.3% ($n = 415$; females $= 325$; males $= 90$). The characteristics of the initial sample and the follow-up samples in both genders were analyzed in relation to maternal educational level, residence, age of onset of use of alcohol, positive expectations about alcohol, AUDIT total score, cannabis consumption and tobacco consumption. There were no significant differences in relation to any of these variables, neither among females nor males, as summarized in **Tables 1, 2**, respectively.

Cluster Solution

Table 3 shows that the clustering solution provided statistically significant differences among the five clusters on every clustering variable. In the case of females (**Figure 1**), the group 1, labeled as Low alcohol users, had the lowest mean scores over time (never above 1.58. At the other extreme, the Large users (group 5) had the highest scores during this 9-year follow up. Between these two clusters, three other groups emerged with different patterns of use. The group 2, the Moderated users, had low scores over time (from 5.13 to 2.42); the At-risk users (group 3) got mean scores in the range from 4.22 to 9.39; and the group 4, labeled as Decreasing users, progressively reduced their scores over time (from 11.00 to 4.16). For every cluster, the last score (AUDIT 4-2015) was the lowest one.

In the case of males (**Figure 2**), the Low users group (cluster 1) got the lowest scores over time (never above 3.10). At the other end, the group 5, labeled as Large users, got the highest mean scores over time. Moreover, there were three more different clusters: the At-risk users (group 2), with mean scores in the range from 5.35 to 8.30; the High-risk users (group 3), with scores never below 6; and the Decreasing users (group 4), whose mean scores decreased from 11.92 to 4.62. Among males, the last score was also the lowest one.

TABLE 1 | Characteristics of female initial sample and follow-up samples.

	Percentage or mean (95%CI)				*p*-value
	Initial (2005) (18-19 years old) *n* = 992	2-year follow-up (2007) (20–21 years old) *n* = 669	4-year follow-up (2010) (22–23 years old) *n* = 461	9-year follow-up (2015) (27–28 years old) *n* = 325	
MATERNAL EDUCATIONAL LEVEL					
Primary school	41.8 (38.4–45.3)	44.2 (40.1–48.4)	43.1 (38.3–48.3)	45.7 (40.1–51.8)	
High school	33.6 (30.2–37.1)	30.5 (26.4–34.7)	30.6 (25.8–35.8)	28.1 (22.5–34.2)	
University	24.6 (21.2–28.1)	25.3 (21.3–29.6)	26.3 (21.4–31.4)	26.2 (20.7–32.4)	0.642
RESIDENCE					
In parental home	24.7 (22.1–27.5)	22.9 (19.7–26.1)	22.2 (18.5–26.0)	20.9 (16.5–25.1)	
Away from the parental home	75.3 (72.6–78.0)	77.1 (74.0–80.3)	77.8 (74.1–81.6)	79.1 (74.9–83.5)	0.720
POSITIVE EXPECTATIONS ABOUT ALCOHOL					
Low	37.1 (33.4–40.9)	37.5 (33.2–42.1)	36.5 (31.4–42.0)	37.9 (31.7–44.3)	
Medium	34.0 (30.3–37.8)	32.6 (28.3–37.3)	34.6 (29.4–40.1)	34.8 (28.6–41.2)	
High	28.9 (25.2–32.7)	29.9 (25.5–34.5)	28.9(23.7–34.4)	27.2 (21.0–33.6)	0.999
AGE OF ONSET OF USE OF ALCOHOL					
After 16 years old	19.0 (16.5–21.8)	17.9 (14.9–21.3)	16.5 (13.0–20.5)	14.5 (10.5 – 19.2)	
At 16 years old	38.9 (35.6–42.2)	38.1 (34.1–42.2)	36.8 (32.0 – 41.7)	36.6 (30.9 – 42.6)	
At 15 years old	25.6 (22.7–28.7)	25.9 (22.3–29.6)	26.5 (22.2–31.1)	28.3 (23.0 – 34.0)	
Before age of 15 years	16.5 (14.0–19.7)	18.1 (15.0–21.5)	20.3 (16.4–24.5)	20.7 (16.0–25.9)	0.438
AUDIT: Total (mean)	5.4 (5.2–5.7)	5.6 (5.1–5.8)	5.6 (5.2–6.0)	5.3 (4.9–5.8)	0.884
Cannabis consumption	18.6 (16.2–21.1)	19.0 (15.9–22.0)	20.6 (16.8–24.4)	18.8 (14.4–23.2)	0.942
Tobacco consumption	31.0 (28.1–34.0)	31.5 (27.9–35.1)	34.3 (29.8–38.7)	32.9 (27.7–38.2)	0.786

TABLE 2 | Characteristics of male initial sample and follow-up samples.

	Percentage or mean (95%CI)				*p*-value
	Initial (2005) (18–19 years old) *n* = 371	2-year follow-up (2007) (20–21 years old) *n* = 206	4-year follow-up (2010) (22–23 years old) *n* = 139	9-year follow-up (2015) (27–28 years old) *n* = 90	
MATERNAL EDUCATIONAL LEVEL					
Primary school	32.0 (26.5–37.8)	35.8 (28.4–43.3)	41.6 (32.8–50.8)	41.6 (31.5–53.5)	
High school	27.6 (22.1–33.3)	27.4 (19.9–34.9)	25.5 (16.8–34.7)	27.0 (16.8–38.9)	
University	40.3 (34.8–46.0)	36.8 (29.3–44.3)	32.8 (24.1–42.0)	31.5 (21.3–43.4)	0.449
RESIDENCE					
In the parental home	29.7(25.1–34.5)	27.8 (21.9–34.1)	28.8 (21.6–36.4)	28.9 (20.0–38.3)	
Away from the parental home	70.3 (65.7–75.1)	72.2 (66.3–78.5)	71.2 (64.0–78.9)	71.7 (62.2–80.5)	0.949
POSITIVE EXPECTATIONS ABOUT ALCOHOL					
Low	29.7 (23.7–36.0)	33.0 (25.1–41.0)	34.2 (25.0–44.3)	31.6 (20.3–43.7)	
Medium	38.0 (32.0–44.4)	30.7 (22.9–38.8)	31.7 (22.5–41.8)	30.4 (19.0–42.5)	
High	32.3 (26.3–38.7)	36.3 (28.5–44.4)	34.2 (25.0–44.3)	38.0 (26.6–50.0)	0.705
AGE OF ONSET OF ALCOHOL USE					
After 16 years old	18.1 (12.5–24.1)	16.8 (9.2–24.7)	15.5 (6.9–25.5)	18.2 (7.8–30.3)	
At 16 years old	36.9 (31.2–42.8)	41.0 (33.5–49.0)	44.0 (35.3–54.0)	48.1 (37.7–60.1)	
At 15 years old	21.6 (15.9–27.5)	20.2 (12.7–28.2)	21.6 (12.9–1.6)	20.8 (10.4–32.8)	
Before age of 15 years	23.4 (17.8–29.4)	22.0 (14.4–30.0)	19.0 (10.3–9.0)	13.0 (2.6–25.1)	0.381
AUDIT: Total (mean)	7.8 (7.2–8.4)	7.4 (6.6–8.2)	7.3 (6.4–8.2)	7.1 (6.0–8.2)	0.784
Cannabis consumption	27.0 (22.3–31.6)	27.7 (21.3–34.0)	25.9 (18.3–33.5)	24.4 (15.0–33.9)	0.885
Tobacco consumption	27.5 (22.8–32.2)	21.8 (16.0–27.7)	23.0 (15.7–30.4)	24.4 (15.0–33.9)	0.636

TABLE 3 | Descriptive statistics of clustering variables by group.

Gender	Cluster	Label	n (%)	Clustering variables			
				AUDIT 1 (2005)	AUDIT 2 (2007)	AUDIT 3 (2010)	AUDIT 4 (2015)
Female	1	Low users	95 (29.2)	$1.33^{2,3,4,5}$	$1.58^{2,3,4,5}$	$1.27^{2,3,4,5}$	$1.13^{2,3,4,5}$
	2	Moderated users	121 (37.2)	$5.13^{1,4,5}$	$4.73^{1,3,4,5}$	$3.93^{1,3,4,5}$	$2.42^{1,3,4,5}$
	3	At-risk users	46 (14.2)	$5.85^{1,4,5}$	$9.39^{1,2,4,5}$	$8.54^{1,2,4,5}$	$4.22^{1,2,5}$
	4	Decreasing users	43 (13.2)	$11.00^{1,2,3}$	$7.60^{1,2,3,5}$	$5.51^{1,2,3,5}$	$4.16^{1,2,5}$
	5	Large users	20 (6.2)	$12.40^{1,2,3}$	$14.00^{1,2,3,4}$	$13.60^{1,2,3,4}$	$7.80^{1,2,3,4}$
TOTAL			325	5.34	5.42	4.61	2.86
Male	1	Low users	31 (34.4)	$2.32^{2,3,4,5}$	$3.10^{2,3,4,5}$	$2.94^{2,3,4,5}$	$1.97^{2,3,4,5}$
	2	At-risk users	23 (25.6)	$5.35^{1,3,4,5}$	$7.70^{1,3,5}$	8.30^{1}	5.87^{1}
	3	High-risk users	14 (15.6)	$9.64^{1,2,5}$	$11.57^{1,2,4,5}$	$10.07^{1,4}$	6.00^{1}
	4	Decreasing users	13 (14.4)	$11.92^{1,2,5}$	$7.85^{1,3,5}$	$6.38^{1,3,5}$	4.62^{1}
	5	Large users	9 (10.0)	$16.44^{1,2,3,4}$	$16.22^{1,2,3,4}$	$11.44^{1,4}$	6.33^{1}
TOTAL			90	7.03	7.59	6.77	4.41

^{1,2,3,4,5}*Significantly different clusters (Scheffé test; $\alpha = 0.05$).*

Antecedent Variables

Table 4 shows the differences found in the antecedent variables among the five female-clusters. With regard to the age of onset of use, statistically significant differences were found. The *Low users* had a significantly lower percentage of females who start drinking before or at 15 (17.4%), and a significantly higher percentage who start after 16 (55.1%). In the case of *Large users*, a significantly higher percentage of them started drinking before 15 (45.0%). The positive alcohol-related expectancies also exhibited significant differences between groups. As such, while the *Low users* had a significantly higher percentage of women with low positive expectancies, the *At-risk*, *Decreasing* and *Large users* displayed a significantly higher percentage of women with high positive expectancies. Furthermore, the *Low users* has a significantly lower percentage of females who are cannabis users (1.1%) or smokers

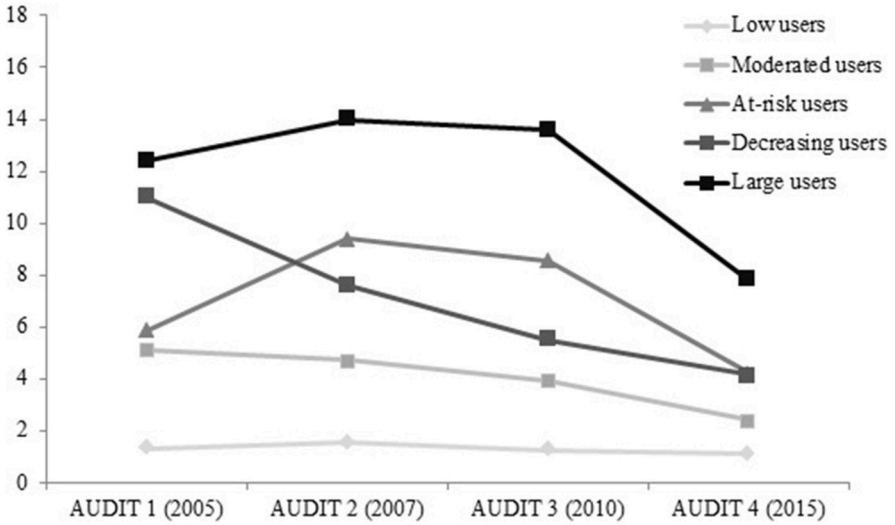

FIGURE 1 | Pattern of alcohol consumption by cluster (Females) based on the AUDIT total score (mean).

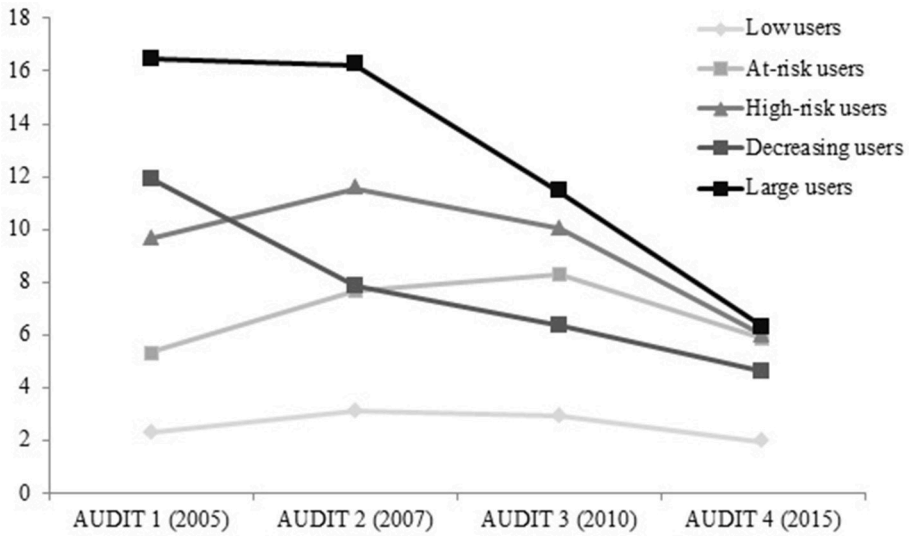

FIGURE 2 | Pattern of alcohol consumption by cluster (Males) based on the AUDIT total score (mean).

(2.1%), while the *Large users* group includes comparatively more cannabis users (70.0%) and smokers (70.0%) than expected.

Table 5 shows the differences found in the antecedent variables among the five male-clusters. In this case, statistically significant differences were found in terms of being a cannabis user or a smoker. This is similar to what has been noted earlier in relation to females, the *Low users* had a significantly lower percentage of members who were cannabis users (3.2%) or smokers (6.5%), while the *Large users* group included comparatively more cannabis users (66.7%) and smokers (55.6%) than expected.

Employment Status, Family, and Social Relationships

Table 6 shows the differences between the female-clusters and their employment status, and family and social relationships. In relation to their education, there was a significantly higher percentage of females who reached a Master's degree or a PhD level among the Large users. Moreover, the number of close friends was found to be significantly different between Low users (4.24) and Large users (6.25). On the other hand, the At-risk users group had a significantly higher percentage of members who have problems in their home environment. In relation to having serious problems with their partner, Low users were negatively

TABLE 4 | Descriptive statistics of antecedent variables by cluster (Females).

	Test statistic	Low users (%)	Moderated users (%)	At-risk users (%)	Decreasing users (%)	Large users (%)	TOTAL (%)
MATERNAL EDUCATIONAL LEVEL							
Primary school	$\chi^2 = 7.640$	49.5	50.0	43.5	34.9	30.0	45.7
High school	$p = 0.469$;	28.4	26.7	30.4	27.9	30.0	28.1
University	$V = 0.109$	22.1	23.3	26.1	37.2	40.0	26.2
RESIDENCE							
At the parents' home	$\chi^2 = 6.064$; $p = 0.194$; $V = 0.137$	26.3	23.1	17.4	11.6	10.0	20.9
Outside the parents' home		73.7	76.9	82.6	88.4	90.0	79.1
AGE OF ONSET OF ALCOHOL USE							
Before 15	$\chi^2 = 88.199$	8.7^-	20.8	18.2	21.4	45.0^+	19.3
At 15	$p < 0.001$	8.7^-	26.7	34.1	47.6^+	25.0	26.4
At16	$V = 0.316$	27.5	41.7^+	38.6	23.8	25.0	34.2
After 16 years old		55.1^+	10.8^-	9.1^-	7.1^-	5.0	20.0
POSITIVE EXPECTANCIES							
Low	$\chi^2 = 60.025$	66.3^+	5.3	27.5	5.6^-	6.7^-	37.9
Medium	$p < 0.001$	19.3^-	41.4	32.5	52.8^+	33.3	34.8
High	$V = 0.322$	14.5^-	23.3	40.0^+	41.7^+	60.0^+	27.2
Cannabis users	$\chi^2 = 59.467$; $p < 0.001$; $V = 0.428$	1.1^-	17.4	26.1	30.2^+	70.0^+	18.8
Smokers	$\chi^2 = 63.814$; $p < 0.001$; $V = 0.443$	2.1^-	42.1^+	45.7^+	44.2	70.0^+	32.9

$^{+,-}$*Significant (positive or negative) associations between the cluster and the category of variable (standardized residuals; $\alpha = 0.05$).*

TABLE 5 | Descriptive statistics of antecedent variables by cluster (Males).

	Test statistic	Low users (%)	At-risk users (%)	High-risk users (%)	Decreasing users (%)	Large users (%)	TOTAL (%)
MATERNAL EDUCATIONAL LEVEL							
Primary school	$\chi^2 = 6.837$	46.7	52.2	28.6	30.8	33.3	41.6
High school	$p = 0.554$	33.3	21.7	21.4	23.1	33.3	27.0
University	$V = 0.196$	20.0	26.1	50.0	46.2	33.3	31.5
RESIDENCE							
At the parents' home	$\chi^2 = 5.353$; $p = 0.253$; $V = 0.244$	38.7	30.4	28.6	23.1	0.0^-	28.9
Outside the parents' home		61.3	69.6	71.4	76.9	100.0^+	71.1
AGE OF ONSET OF ALCOHOL USE							
Before 15	$\chi^2 = 14.942$	8.0	4.5	7.7	23.1	33.3^+	12.2
At 15	$p = 0.245$	16.0	27.3	15.4	23.1	11.1	19.5
At16	$V = 0.246$	36.0	45.5	53.8	46.2	55.6	45.1
After 16 years old		40.0^+	22.7	23.1	7.7	0.0	23.2
POSITIVE EXPECTANCIES							
Low	$\chi^2 = 11.220$	48.1^+	33.3	21.4	18.2	0.0	31.6
Medium	$p = 0.190$	25.9^-	23.8	50.0	27.3	33.3	30.4
High	$V = 0.266$	25.9	42.9	28.6	54.5	66.7	38.0
Cannabis users	$\chi^2 = 23.145$; $p < 0.001$; $V = 0.507$	3.2^-	26.1	14.3	53.8^+	66.7^+	24.4
Smokers	$\chi^2 = 11.008$; $p < 0.05$; $V = 0.350$	6.5^-	30.4	28.6	30.8	55.6^+	24.4

$^{+,-}$*Significant (positive or negative) associations between the cluster and the category of variable (standardized residuals; $\alpha = 0.05$).*

significant associated (1.1%), while At-risk (10.9%) and Large users (15.0%) were positively significant associated.

In the case of males (**Table 7**), no difference in their employment status, and family and social relationships were found to be significant.

DISCUSSION

The major finding of this study was the characterization of five different clusters of university alumni based on their pattern of alcohol use at a 9-year follow-up, separately for females (Low users, Moderated users, At-risk users, Decreasing users and Large users) and males (Low users, At-risk users, High-risk users, Decreasing users and Large users). These groups are similar to those found by Johnsson et al. (2008) based on college students' drinking patterns during the first 4 years at university: one group with stable non-risky consumption (similar to our Low and Moderate users group), another with increasing consumption (similar to our At-Risk and High-risk users), a third one with decreasing consumption (our Decreasing users) and a last one with stable risky consumption (our Large users). The main

TABLE 6 | Descriptive statistics of employment status, family and social relationships at the 9-year follow-up by cluster (Females).

	Test statistic	Low users	Moderated users	At-risk users	Decreasing users	Large users	TOTAL
HIGHEST DEGREE OBTAINED							
High school/ Vocational training	$\chi^2 = 12.237$; $p = 0.141$	5.3%	2.5%	2.2%	0.0%	0.0%	2.8%
Bachelor	$V = 0.137$	84.2%	82.6%	87.0%	83.7%	65.0%$^-$	82.8%
Master/PhD		10.5%	14.9%	10.9%	16.3%	35.0%$^+$	14.5%
Longest period of employment (months)	$F = 0.364$; $p = 0.834$; $\eta^2 = 0.005$	25.53	24.36	25.22	24.84	19.65	24.60
Longest period of unemployment (months)	$F = 1.217$; $p = 0.304$; $\eta^2 = 0.015$	8.32	9.07	6.52	5.40	7.25	7.90
PATTERN OF EMPLOYMENT IN THE LAST 3 YEARS							
Employed	$\chi^2 = 2.302$	70.5%	70.2%	80.4%	86.0%$^+$	65.0%	73.5%
Student	$p = 0.138$	22.1%	14.9%	15.2%	9.3%	25.0%	16.9%
Unemployed	$V = 0.138$	7.4%	14.9%$^+$	4.3%	4.7%	10.0%	9.5%
SOURCE OF FINANCIAL SUPPORT							
Own sources (employment or unemployment subsidy)	$\chi^2 = 4.892$; $p = 0.299$; $V = 0.123$	68.4%	75.2%	80.4%	83.7%	70.0%	74.8%
Other people's sources (family or friends)		31.6%	24.8%	19.6%	16.3%	30.0%	25.2%
Job in line with their education	$\chi^2 = 6.499$; $p = 0.165$; $V = 0.150$	68.4%	73.1%	52.4%$^-$	65.9%	58.8%	66.9%
No. of close friends	F = 4.227; $p < 0.05$; $\eta^2 = 0.050$	4.24[5]	4.61	5.33	4.95	6.25[1]	4.75
CURRENT COEXISTENCE	$\chi^2 = 0.225$						
Independent	$p = 0.994$	65.3%	67.8%	65.2%	65.1%	65.0%	66.2%
With parents	$V = 0.026$	34.7%	32.2%	34.8%	34.9%	35.0%	33.8%
Alcohol-related problems in the home environment	$\chi^2 = 20.287$; $p < .001$; $V = 0.269$	1.3%	0.0%	10.8%$^+$	0.0%	0.0%	1.8%
SERIOUS PROBLEMS							
With their parents	$\chi^2 = 2.110$; $p = 0.716$; $V = 0.081$	5.3%	4.1%	8.7%	7.0%	10.0%	5.8%
With their siblings	$\chi^2 = 2.150$; $p = 0.708$; $V = 0.081$	2.1%	3.3%	2.2%	0.0%	0.0%	2.2%
With their partner	$\chi^2 = 12.302$; $p < 0.05$; $V = 0.195$	1.1%$^-$	4.1%	10.9%$^+$	2.3%	15.0%$^+$	4.6%
With their friends	$\chi^2 = 3.823$; $p = 0.430$; $V = 0.108$	3.2%	5.0%	10.9%	4.7%	5.0%	5.2%

$^{+,-}$*Significant (positive or negative) associations between the cluster and the category of variable (standardized residuals; $\alpha = 0.05$).*
^{1,2,3,4,5}*Significantly different clusters (Scheffé test; $\alpha = 0.05$).*

differences between these two classifications could come from the gender division of our sample and the longer period of our follow-up, that allow us to refine—in terms of gender and alcohol consumption typology—and divide more precisely their group with stable non-risky consumption into Low users and Moderate users in the case of females, as well as their group with increasing consumption into At-risk users and High-risk users in the case of males.

Our results show that the clusters are different for females and males. This fact highlights the relevance of analyzing the data separately, and it is related to a repeated finding in the literature on gender difference in alcohol use: women drink less alcohol than men, something that also occurs among college students (Ham and Hope, 2003).

Regarding the evolution of alcohol consumption over the years, although the five clusters for each gender are very different among them, there is a generalized reduction of the AUDIT scores at the 9-year assessment for every profile, which suggests a common "mature out" of such behavior in the late 20s (Moure-Rodríguez et al., 2016b). This commonality in developmental trajectories has been found previously not only about alcohol use and heavy drinking, but also about smoking, and marijuana use (Chen and Jacobson, 2012).

Moreover, the differences among these five groups in terms of antecedents were examined. In the case of females, significant differences in relation to the age of onset of use were revealed. Our findings are in line with those that point out that the earlier age of onset, the heavier use over the years (Pitkänen et al., 2005; Mota et al., 2010). Likewise, the high positive alcohol-expectancies are found to be related to those more hazardous profiles (At-risk, Decreasing, and Large users), while low positive alcohol-expectancies are associated to the Low users. This is a consistent finding with previous researches (Griffin et al., 2000; Young et al., 2006; Caamaño-Isorna et al., 2008), and highlights the relevance of the positive early expectancies about alcohol use in present and future uses.

Being a cannabis user or a smoker is positively associated to those more hazardous clusters and negatively associated to the Low users, for both females and males. This is a finding in agreement with previous researches (American Academy of Pediatrics. Committee on Substance Abuse, 2001; Hingson et al., 2004), which highlights the harmful role of the polysubstance use.

At this point, it is of utmost importance to note that the main prevention efforts should be set in the adolescence period, because the codes of behavior acquired at that time tend to be maintained in adulthood (Grant et al., 2005). Our findings suggest that the prevention strategies should take into account that modifying positive expectancies, and reducing other substances uses are key to promote healthier alcohol use profiles and to prevent hazardous uses. For instance, the value-based education and life skill training approach has already shown its effectiveness in preventing risky behaviors, such as alcohol or

TABLE 7 | Descriptive statistics of employment status, family and social relationships at the 9-year follow-up by Cluster (Males).

	Test statistic	Low users	At-risk users	High-risk users	Decreasing users	Large users	TOTAL
HIGHEST DEGREE OBTAINED							
High school/ Vocational training	$\chi^2 = 7.987$	3.2%	0.0%	14.3%	15.4%	11.1%	6.7%
Bachelor	$p = 0.435$	77.4%	73.9%	71.4%	76.9%	55.6%	73.3%
Master/PhD	$V = 0.211$	19.4%	26.1%	14.3%	7.7%	33.3%	20.0%
Longest period of unemployment (months)	$F = 0.876$; $p = 0.482$; $\eta^2 = 0.040$	8.61	5.26	9.14	12.23	6.33	8.13
PATTERN OF EMPLOYMENT IN THE LAST 3 YEARS							
Employed	$\chi^2 = 8.929$	67.7%	87.0%	78.6%	76.9%	66.7%	75.6%
Student	$p = 0.348$	25.8%	8.7%	7.1%	7.7%	33.3%	16.7%
Unemployed	$V = 0.223$	6.5%	4.3%	14.3%	15.4%	0.0%	7.8%
SOURCE OF FINANCIAL SUPPORT							
Own sources (employment or unemployment subsidy)	$\chi^2 = 2.866$; $p = 0.580$; $V = 0.178$	77.4%	87.0%	85.7%	69.2%	66.7%	78.9%
Other people's sources (family or friends)		22.6%	13.0%	14.3%	30.8%	33.3%	21.1%
Job in line with their education	$\chi^2 = 2.041$; $p = 0.728$; $V = 0.155$	61.3%	77.3%	71.4%	58.3%	66.7%	67.1%
No. of close friends	$F = 1.497$; $p = 0.210$; $\eta^2 = 0.066$	5.13	4.61	6.43	5.54	5.11	5.26
CURRENT COEXISTENCE	$\chi^2 = 1.854$						
Independent	$p = 0.763$	61.3%	52.2%	57.1%	61.5%	77.8%	60.0%
With parents	$V = 0.144$	38.7%	47.8%	42.9%	38.5%	22.2%	40.0%
Alcohol-related problems in the home environment		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
SERIOUS PROBLEMS							
With their parents	$\chi^2 = 5.808$; $p = 0.214$; $V = 0.254$	16.1%$^+$	4.3%	0.0%	0.0%	11.1%	7.8%
With their siblings	$\chi^2 = 5.907$; $p = 0.206$; $V = 0.256$	9.7%$^+$	0.0%	0.0%	0.0%	0.0%	3.3%
With their partner	$\chi^2 = 2.726$; $p = 0.605$; $V = 0.174$	3.2%	0.0%	7.1%	0.0%	0.0%	2.2%
With their friends	$\chi^2 = 1.374$; $p = 0.849$; $V = 0.124$	6.5%	8.7%	7.1%	0.0%	11.1%	6.7%

$^{+,-}$*Significant (positive or negative) associations between the cluster and the category of variable (standardized residuals; $\alpha = 0.05$).*

substance abuse in adolescents (European Monitoring Centre for Drugs and Drug Addiction, 2008). In addition, regulatory development and legal control are necessary to limit access to alcohol at young ages.

In relation to their social relationships at the 9-year follow-up, the number of close friends was significantly higher among female Large users than female Low users. This could be related to the fact that a high percentage of Large users have reached a Master or PhD, in the sense that college attendance provides an environmental context affording greater opportunities for drinking (Carter et al., 2010) and keeping in touch with friends, and may prolong the sense of being in-between childhood and the responsibilities of adulthood (Merrill and Carey, 2016), compared to those who have already joined the labor market.

On the other hand, the females from the At-risk and Large users groups are positively associated to serious problems with their partner. This finding is in line with previous studies reporting that a persistent drinking trajectory is associated with being separated, divorced or never married (Schulenberg et al., 1996; Hicks et al., 2010). However, in the case of males, there is no difference among clusters in having serious problems with their partner, a gender difference in line with some previous researches (Cranford et al., 2011, 2015) that could be explained by the fact that alcohol consumption is part of the male gender role (Iwamoto and Smiler, 2013).

Finally, there were no significant differences among clusters in most of the analyzed consequences, in the case of either females or males. However, it might be thought that differences in employment and social situations will become greater and significant later on their lives. The continuation of this research project will allow us to confirm or refute this hypothesis in the future.

There are three possible limitations in our study. (1) Selection bias and non-representativeness, because of the loss of subjects in the follow-up, especially in the case of the small sample of males. However, the statistical analysis found no significant differences between the initial and follow-up samples in relevant variables neither in males nor in females. Nevertheless, future studies might confirm the subgroups found among males with a larger sample. (2) Since the question about expectancies is not specifically validated, expectancies may have not been correctly measured. (3) This study relied on self-report measures, so it is impossible to know if participants have underreported or over-reported their uses, if their responses were biased by gender stereotypes activation, or even by inconsistent personal feelings or memories related to their age. Nonetheless, the AUDIT questionnaire has been internationally validated in adolescents and young adults, and self-report of alcohol and other drug use has been demonstrated to be usually reliable or even better than other approaches to detect substance use (Babor et al., 1989; Winters et al., 1990).

The major strength of the study is the 9-year follow-up of Spanish university alumni with longitudinal measures of drinking, as well as the use of a cluster analysis technique to

females and males separately. Our results reveal the existence of dissimilar typologies of alcohol users in Spanish university alumni, which were in turn different for males and females. There were few significant differences among the groups in relation to their employment status and social relations at the 9-year follow up. For its part, the differences among the groups found in terms of antecedents suggest that the prevention strategies should take into account that modifying positive expectancies, limiting access to alcohol at young ages, and reducing other substances uses are key to promote healthier alcohol use profiles and to prevent harmful uses.

AUTHOR CONTRIBUTIONS

FC-I, FC designed the study. LM, EL collected the data. PG, FC-I, AR, LM analyzed and interpreted data. PG wrote the first version of the manuscript. All authors collaborated on writing the final article, have approved the final version for publication and guarantee the accuracy or integrity of this work in all its aspects.

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ELSA 2016 Cohort: Alcohol, Tobacco, and Marijuana Use and Their Association with Age of Drug Use Onset, Risk Perception, and Social Norms in Argentinean College Freshmen

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The transition from high school to college is a high-risk stage for the initiation and escalation of substance use. Substance use and its associated risk factors have been thoroughly described in developed countries, such as the United States, but largely neglected in Argentina, a South American country with patterns of a collectivist culture. The present cross-sectional study describes the occurrence of alcohol, tobacco, and marijuana use and the association between these behaviors and the age of onset of substance use and cognitive (i.e., risk perception) and social (i.e., prescriptive) variables in a large sample of Argentinean college freshmen (n = 4083, 40.1% men; mean age = 19.39 ± 2.18 years). The response rate across courses was ≥90% and was similarly distributed across sex. Participants completed a survey that measured substance use (alcohol [with a focus on heavy drinking and binge drinking behaviors], tobacco, and marijuana), age of onset of the use of each substance, perceived risk associated with various substance use behaviors, prescriptive norms associated with substance use, and descriptive norms for alcohol use (AU). The results indicated that AU is nearly normative (90.4 and 80.3% with last year and last month use, respectively) in this population, and heavy drinking is highly prevalent (68.6 and 54.9% with heavy episodic and binge drinking, respectively), especially among those with an early drinking onset (97.8 and 93.6% with last year and last month use and 87.8 and 76.3% with heavy episodic and binge drinking, respectively). The last-year occurrence of tobacco and marijuana use was 36 and 28%, respectively. Early substance use was associated with the greater use of that specific substance. The students overestimated their same-sex friend's AU, and women overestimated the level of AU of their best male friend. At the multivariate level, all of the predictors, with the exception of the parents' prescriptive norms, significantly explained the frequency of marijuana and tobacco use and frequency of hazardous drinking. Overall, despite important cultural and contextual differences between Argentina and the United States, our findings suggest that certain vulnerability factors have a similar influence across these cultural contexts.

Keywords: college, substance use, perceived risk, prescriptive norms, age of substance use onset

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INTRODUCTION

Several studies indicate a progressive, age-related increase in the consumption of psychoactive substances among Argentinian youth. A nation-wide survey (SEDRONAR, 2014) revealed lifetime alcohol, tobacco, and marijuana use in 51, 5.8, and 21.4% of ≤14 year old Argentinean adolescents, respectively, but these percentages rose to 89, 52.1, and 28.3% among 17–18 year old adolescents. Other Argentinian studies indicated that one-third of college students reported lifetime marijuana use (Pilatti et al., 2014), whereas the last-year occurrence of marijuana use varied between 18% in freshmen (Vera et al., 2015) and 30% in all 5-year college students (Pilatti et al., 2014). Although last-year marijuana use rose to 59% among young adults (Pilatti et al., 2015), the last-month occurrence of tobacco use was fairly similar in college students (33%; Pilatti et al., 2014) and older youth (39.5%; Pilatti et al., 2015). Nearly half of female and male college students reported consuming > 56 and 70 g of pure alcohol, respectively, every time they drank (Pilatti et al., 2014). Between 60% and 71% of college students (Vera et al., 2015; Pilatti et al., 2016a,b) engaged in binge drinking episodes (i.e., the consumption of ≥56 and 70 g of pure alcohol in ≤2 h for women and men, respectively; NIAAA, 2004). Substance use at these ages can interfere with normal brain development (Squeglia et al., 2009; Goriounova and Mansvelder, 2012) and hinder the acquisition of social and educational skills that are needed to achieve independence in adulthood (Masten et al., 2009).

The transition from high school to college is a high-risk stage for the initiation and escalation of substance use (Cho et al., 2015; Derefinko et al., 2016; Skidmore et al., 2016). As explained by different theoretical models, notably the developmental perspective on college AU (Schulenberg and Maggs, 2002), individuals confront new schedules, tasks, and educational and economical responsibilities during this transition and most likely will see their social network profoundly reorganized (Arnett, 2000).

Substance use during this transition has been mostly studied in United States college samples (Ham and Hope, 2003; Grossbard et al., 2010; Quinn and Fromme, 2011; Small et al., 2011; Cho et al., 2015; Derefinko et al., 2016) and not as intensely in other countries, including Argentina. Unknown is whether the risk factors that have been identified in the United States population apply to patterns of substance use in college students who have different cultural backgrounds. The importance of advancing the study of psychological variables in more diverse geographical and cultural groups (Henrich et al., 2010) should not be underestimated. In Argentina, alcohol drinking is a normal part of daily life, and thus this culture can be classified as "wet" (Bloomfield et al., 2003). Argentina also features a recent history of political and economic instability, which has affected alcohol drinking patterns (Munne, 2005). Several cultural differences also exist between the United States and Argentina, and some involve idiosyncratic components of college life. In the United States, the minimum legal age to buy alcohol is 21, whereas the minimum legal age is 18 in Argentina. Thus, unlike their United States counterparts, Argentinian college students spend most of their college years having legal access to alcohol. Also important is that most college students in Argentina attend universities that are close to home, and they live exclusively off-campus. Moreover, United States and Argentinian college students exhibit patterns of individualistic *vs*. collectivist cultures, respectively (Chiou, 2001).

Unknown are the factors that differentiate college students who will engage in regular drug use from those who will not. The perceived risk that is associated with the use of psychoactive substances is one such factor (Johnston et al., 2015). Drugs that are perceived as more dangerous, such as heroin, are less commonly used than those that are perceived as less dangerous, such as marijuana (Maričič, 2013; SEDRONAR, 2014). The perceived risk that is associated with marijuana use distinguished between college students who used marijuana from those who did not (Kilmer et al., 2007; Lopez-Quintero et al., 2011). This evidence, however, is inconclusive. A study of Spanish adolescents found no significant relationship between risk perception and the consumption of various psychoactive substances (Trujillo et al., 2007). Intervening factors may explain these seemingly contradictory patterns. Risk perception is modulated by sex (Petronella-Croisant et al., 2013) and the frequency of drug use (Thornton et al., 2013). Women perceived the use of alcohol, tobacco, and marijuana use as riskier compared with men (Maričič, 2013; Petronella-Croisant et al., 2013), although both sexes had a similar level of risk perception for cocaine and heroin use (Petronella-Croisant et al., 2013). Occasional consumption is perceived as less risky than regular consumption, which in turn is rated as less risky than daily use (Thornton et al., 2013).

The early onset of substance use is another factor that is associated with a heightened risk of developing drug-related problems. Earlier alcohol (Hingson et al., 2006; Dawson et al., 2008), tobacco (Baumeister and Tossmann, 2005; Kendler et al., 2013), and marijuana (Hall and Degenhardt, 2009) consumption is associated with a greater risk of developing substance use disorders. Some authors have postulated that the risk that is associated with substance use onset is substance-specific (i.e., early AU leads to alcohol- but not marijuana-related problems; Ohannessian et al., 2015). Other authors have suggested a broader effect, in which the initiation of use of any substance (e.g., alcohol or tobacco) heightens the risk of using these and other psychoactive substances (Wagner et al., 2005; Hingson et al., 2008; Pilatti et al., 2014).

Social norms (Perkins et al., 1999; Borsari and Carey, 2003) influence drug use directly through the active offering of a substance (Graham et al., 1991; Baer et al., 2001; Wood et al., 2001) and indirectly through descriptive norms (i.e., perceptions about substance use behaviors among relevant social groups) and injunctive norms (i.e., perception of the degree of approval of substance consumption that is held by these social groups; Baer and Carney, 1993; Baer et al., 2001; Neighbors et al., 2011). Young people tend to overestimate the amount and frequency of alcohol consumption of their peers and the perceived approval of binge drinking (Borsari and Carey, 2003).

The association between social norms and substance use has mostly focused on alcohol (Read et al., 2005; LaBrie et al., 2010b; Lewis et al., 2010), although some studies indicated that marijuana (LaBrie et al., 2010a; Buckner, 2013) and tobacco

(Zaleski and Aloise-Young, 2013) use approval is significantly associated with their frequency of use. The closeness between the examinee and the reference group significantly modulated these effects (Borsari and Carey, 2003; Lewis et al., 2010).

Very few studies have described the ways in which these factors affect drug use in Argentinean college students, let alone in large samples with adequate sex representation. Men and women use drugs differently (Becker and Hu, 2008; Lev-Ran et al., 2013; Substance Abuse and Mental Health Services Administration [SAMHSA], 2014). Despite recent attempts to foster the visibility of women in epidemiological and basic research (McCullough et al., 2014), most studies continue to equate the role of different risk factors across these populations. Men perceive less risk associated with substance use compared with women (Alvarado et al., 2013; Maričič, 2013; Petronella-Croisant et al., 2013), which may be one explanation for their greater use of substances (Pilatti et al., 2014). Sex-related differences in AU, however, appear to be shrinking (Balodis et al., 2009; Grucza et al., 2009; Keyes et al., 2011), although they still persist for heavy drinking.

The present study included a very large sample ($n = 4083$) of Argentinean college freshmen and separately examined the occurrence of alcohol, tobacco, and marijuana use in women and men and their associations with contextual (i.e., age of onset), cognitive (i.e., risk perception), and social (i.e., prescriptive norms) variables. We also analyzed the relationship between prescriptive norms and perceived risk associated with the consumption of alcohol, tobacco, and marijuana. As mentioned, there is a notorious lack of previous studies analyzing these variables in our target population (i.e., Argentinian freshman). This made our expected outcomes hard to predict. Yet, based on previous work, mostly conducted with United States samples, we outlined a series of preliminary expectations. We expected a large occurrence (i.e., ≥50%) of binge drinking, a behavior that would be expected to be exacerbated among early drinkers (EDs; Hingson et al., 2009). One hypothesis was that early drinking would also affect tobacco and marijuana use (Hingson et al., 2008; Pilatti et al., 2014). We expected greater marijuana use (Suerken et al., 2014) and binge drinking (Johnston et al., 2015; Pilatti et al., 2016b) in men than in women and a negative association between risk perception and substance use (Johnston et al., 2015). With regard to social norms, we expected to find an overestimation of peers' AU (Borsari and Carey, 2003) and a positive association between perceived approval of substance use and substance involvement (Neighbors et al., 2011).

MATERIALS AND METHODS

Design

This was a cross-sectional study that described the occurrence of substance use in freshman college students and the effect of various risk factors on different indicators of substance use.

Participants

This study was part of a larger project (Estudio Longitudinal Sobre Alcohol [ELSA]) that assesses alcohol and other drug use in college students in Argentina. Data from the first-wave cohort in 2016 were used in this study. We invited 16 departments of the National University of Cordoba (UNC), Argentina, and 11 accepted. We also invited most sections of National Technological University (UTN) in Córdoba, Argentina. The invitation was sent to and accepted by top officials of each university. The invitation described the study and asked for access to their courses and students for the purpose of administering the survey. UNC is the second largest university in the country, and UTN attracts middle-class high-school graduates from central and northwestern Argentina. These individuals belong to families of large- and medium-sized production farmers, professionals, and local merchants. Thus, they represent a socioeconomic microcosm of the larger Argentinian society. A total of 4122 students fully or partially completed the survey. The response rate across courses was ≥90% and was similarly distributed across sex. Of these surveys, eight cases (five men) were judged as invalid based on extreme inconsistency in the responses, 10 cases (seven men) were almost fully incomplete (i.e., only provided some sociodemographic information), 16 cases (five men) were underage (17 years old), and five cases (three men) were already part of the 2014 ELSA cohort. These 39 cases were thus removed from the analysis. The final sample was composed of 4083 freshmen (40.1% [1639] men), 18–30 years old. The vast majority (96.9%) were between 18 and 25 years of age (mean age, 19.55 ± 2.28 years and 19.28 ± 2.11 years for men and women, respectively). For their participation, the students participated in a raffle in which two cash prizes were given (each ∼USD$72). The sample characteristics are presented in **Table 1**.

Procedure

The authors administered the survey (paper and pencil format) in the classrooms with the assistance of trained and advanced psychology students. The researchers explained the aim of the study, emphasizing the confidentiality of the data and the voluntary nature of participation. The participants were

TABLE 1 | Description of socio-demographic variables as a function of sex.

	Men	Women
Age		
Mean Age	19.55 ± 2.28	19.28 ± 2.11
18-25	96.6%	97.1%
26-30	3.4%	2.9%
University		
UNC	60.8%	90%
UTN	39.2%	10%
Employment Status		
Do not work	81.7%	86.8%
Employed	18.3%	13.2%
State of origin		
Cordoba	67%	65.8%
Other	33%	34.2%

UNC, National University of Cordoba; UTN, National Technological University; State of origin, State where the participants spent most of their lifetime (Cordoba is the city, and the State where the study was conducted).

instructed on how to complete the instruments, and the researchers answered questions concerning survey completion. No personally identifiable information was collected. The students, however, were told that the general aim of the study was to obtain longitudinal data on substance use. Therefore, they were invited to provide their e-mail address and phone number to be contacted in the following stages of the longitudinal study. The students provided written consent before completing the survey. The consent form was on the first page, which could be removed and placed in a separate envelope. Survey administration took ∼35 min, and data collection occurred between April and June 2016. Seven trained and advanced psychology students helped with data entry. These students were part of the research team and were previously trained on ethics associated with data management. Different files were generated to separate the contact information from the survey responses. All of the study procedures were approved by the university's internal review board, and the protocol was reviewed by the National Agency for Promotion of Science and Technology (FONCyT).

Measures

Dependent Variables

Alcohol use

Alcohol use was defined as drinking at least one standard drink (i.e., 14 g pure ethanol; NIAAA, 2004) of any alcoholic beverage. An image described the volume (i.e., in milliliters) of different alcoholic beverages that corresponded to one standard drink. Students reported lifetime, last year, last month, and last week AU and age at first AU ("How old were you the first time you consumed one standard drink or more of any alcoholic beverage?"). Based on previous work (Lee et al., 2012), the students were classified as EDs if they reported first AU by the age of 14 or late drinkers (LDs) if they reported first AU at 15 or older. Two questions asked about the number of standard drinks consumed each day (from Monday to Sunday) in a typical week and each day during the week of heaviest alcohol consumption in the past 3 months.

Hazardous alcohol use

We assessed heavy episodic drinking (≥4 and 5 standard drinks in one drinking session for women and men, respectively), binge drinking (≥4 and 5 standard drinks in ≤2 h for women and men, respectively), and drunkenness episodes (Wechsler et al., 2000). The participants indicated the frequency of engaging in heavy episodic and binge drinking episodes within the previous 6 months (from 0 = I do not drink alcohol/I do not drink that amount of alcohol to 8 = four or more times per week). Answers to these two questions were recoded to calculate the number of heavy and binge drinking episodes per month. Three questions asked about the occurrence of drunkenness episodes in their lifetime and in the last 6 months and the number of drunkenness episodes within the previous month.

Marijuana use

Based on previous work (Johnston et al., 2015), we asked about lifetime, last year, last month, and last week marijuana use. The participants indicated the age at first marijuana use ("How old were you the first time you used marijuana?"). Based on previous work (Gruber et al., 2012b; Schuster et al., 2016), participants who indicated first marijuana use by the age of 16 were classified as early marijuana users (EMUs), and those who reported first marijuana use at 17 or older were classified as late marijuana users (LMUs). We asked one question to assess the frequency of marijuana use within the previous 6 months (from 0 = I did not use marijuana to 8 ≥ 4 times per week). These answers were recoded to calculate the number of days of marijuana use per month.

Tobacco use

We used a similar set of questions to measure lifetime, last year, last month, and last week tobacco use. The participants indicated the age at first tobacco use (at least one whole cigarette). Based on previous work (Morrell et al., 2011), participants who reported first tobacco use by the age of 15 were classified as early smokers (ESs), and those who reported first tobacco use at 16 or older were classified as late smokers (LSs). We asked one question to assess the frequency of tobacco use within the previous 6 months (from 0 = I did not use tobacco to 8 ≥ 4 times per week). These answers were recoded to calculate the number of days of tobacco use per month. The participants also indicated the number of cigarettes they usually consumed per smoking day (0 = I did not use tobacco, 1 = 1–4 cigarettes per day, 2 = 5–9 cigarettes per day, 3 = 10 = 14 cigarettes per day, 4 = 15 = 19 cigarettes per day, and 5 ≥ 20 cigarettes per day).

Independent Variables

Perceived risk associated with substance use

To assess the perceived risk of using alcohol, tobacco, and marijuana, we adapted questions from the Monitoring the Future study (Johnston et al., 2005) and another study (Yeomans-Maldonado and Patrick, 2015). Specifically, we asked questions about the perceived risk of moderate daily drinking (1–2 standard drinks), heavy episodic drinking (4–5 standard drinks per drinking occasion), drinking 4–5 standard drinks every weekend, drinking enough alcohol to get drunk, combining alcohol and marijuana, and combining alcohol with energy drinks. Three items asked about the perceived risk of daily smoking, smoking on weekends or sometimes per month, and smoking ≥10 cigarettes within a smoking day (e.g., "How much do you think people risk harming themselves [physically, in their health, or in other ways] if they smoke 10 or more cigarettes in one day?"). Four items assessed the perceived risk of using marijuana only once or twice, occasionally (less than once per month), regularly (1–3 times per month), or frequently (once or more per week). Response options ranged from 1 = no risk to 5 = much risk. Answers were summed for each substance, yielding a variable that represented the perception of risk for alcohol ($\alpha = 0.75$), tobacco ($\alpha = 0.76$), and marijuana ($\alpha = 0.91$) use.

Injunctive norms

Based on previous work on alcohol (Neighbors et al., 2008b), tobacco (Riou Franca et al., 2009), and marijuana (Neighbors et al., 2008a), we developed three questionnaires to measure the perceived injunctive norms for alcohol, tobacco, and marijuana

use (i.e., peer and parental approval/disapproval for the use of each substance).

Perceived injunctive norms for alcohol use

Two sets of five questions each measured perceived peer or parental approval of the participants' AU. The items asked about perceived approval/disapproval of moderate (1–2 standard drinks) and heavy (4-5 standard drinks) daily drinking, drinking 4–5 standard drinks every weekend, drinking enough alcohol to get drunk, and driving a car after drinking alcohol (e.g., "How would your closest friends/parents feel if you drank 4 or 5 standard drinks of alcohol almost daily?"). The response scale ranged from 0 = strong disapproval to 4 = strong approval. The questions concerning parents always had the option to answer "I have no relationship with my parents/I have no parents." The answers (range, 0–4) to each set of questions were summed, thus yielding two variables in which higher scores reflected a higher level of approval of AU by peers ($\alpha = 0.80$) and parents ($\alpha = 0.76$).

Perceived injunctive norms for cigarette smoking

Two sets of three questions assessed perceived peer ($\alpha = 0.84$) and parental ($\alpha = 0.89$) approval of the participants' cigarette smoking. The items asked about perceived approval/disapproval of occasional and daily smoking and smoking $\geq$ 10 cigarettes in a smoking day and used the same response options as those described for AU.

Perceived injunctive norms for marijuana use

Two sets of five questions assessed perceived peer ($\alpha = 0.94$) and parental ($\alpha = 0.92$) approval/disapproval of lifetime, occasional (less than once per month), regular (1–3 times per month), and frequent (once or more per week) use of marijuana. One question asked about the perceived approval/disapproval of driving a car after using marijuana. The response format was the same as described above.

Descriptive norms for alcohol use

Based on the Drinking Norms Rating Form (Baer et al., 1991), we asked participants to estimate the number of standard drinks their closest female friend and closest male friend drank each day in a typical week in the past 3 months. Answers to each of these questions were summed to estimate the perceived weekly drinking by each reference friend. Internal reliabilities were adequate for both best female friend ($\alpha = 0.79$) and best male friend ($\alpha = 0.82$) indicators.

Data Analysis

Descriptive analyses (i.e., frequency, percentage, central tendency, and deviation indices) were conducted for the overall sample and separately for each sex to describe the occurrence of alcohol, tobacco, and marijuana use. Sex differences in tobacco and marijuana use were determined using the χ^2 test or Student's *t*-test for nominal and continuous dependent variables, respectively. We described for the total sample and for each sex the age at which each substance was most likely to be used the first time, the percentage of early and late users, and the percentage of users who began at a specific age ($<$12 to $>$20 years). Differences in the occurrence of substance use as a function of age of onset (early, late) for each substance were analyzed using the χ^2 test or Student's *t*-test.

We described the percentage of students who consumed alcohol on each day of the typical or heaviest week of alcohol consumption. Among those who reported alcohol consumption, we calculated the average number of standard drinks consumed on each of these days. These analyses were conducted for the total sample, for early and LDs, and for men and women. Differences in the average number of standard drinks consumed during the typical week and the heaviest week of alcohol consumption as a function of sex and drinking onset (early, late) were analyzed using Student's *t*-test.

The effect of age of first use on the frequency of use was analyzed separately for each substance using the χ^2 test or Student's *t*-test for nominal and continuous dependent variables, respectively. We also analyzed the effect of age of first use of a given substance (e.g., marijuana) on the occurrence of use of another substance (e.g., tobacco or alcohol). These analyses were conducted in the subsample that had reported lifetime use of that substance (i.e., abstainers or drug-naive participants were excluded from this latter analysis).

A mixed analysis of variance (ANOVA) analyzed own AU, perceived typical same-sex AU, and opposite-sex best friend's AU. These three indicators of AU were considered within-subject repeated measures, with sex as the between-subjects factor. Tukey's *post hoc* comparisons were used to analyze significant interactions in the ANOVA.

For each substance, we also evaluated Pearson product-moment correlations between injunctive norms for parents and peers and risk perception associated with the use of that substance and different indicators of substance use. Specifically, for alcohol, the indicators were frequency of heavy and binge drinking, total amount of alcohol consumed during a typical or heaviest week, and total number of drunkenness episodes. For tobacco, the indicators were frequency of tobacco use and number of cigarettes smoked per smoking day. The frequency of marijuana use was the only indicator for that substance.

Multiple regression analyses were performed to evaluate the relationship between a set of independent variables and (a) the frequency of binge drinking, (b) the frequency of tobacco use, and (c) the frequency of marijuana use. Although different indicators of AU could have been chosen, we focused on binge drinking because of its robust association with alcohol-related problems. Separate regressions were run for each of these dependent variables and for each sex. For each analysis, the predictors were early onset of use of the substance under analysis, perceived peer or parental approval of use of the substance, perceived risk of substance use, and (for alcohol only) perceived alcohol consumption of the best female and male friend. Standard multiple regression analyses were used. This method simultaneously added all of the independent variables in the model and yielded regular multiple correlation coefficients (R^2) and standardized regression coefficients.

Descriptive, correlational, and regression analyses were conducted using SPSS 17.0 software. Statistica 7.0 software was used for the ANOVAs. The overall α value was set at 0.05. When appropriate, Bonferroni correction was used to control

for multiple comparisons. Specifically, the α for correlations between risk factors and the indicators of substance use was set at 0.00078 (i.e., 0.05/64 comparisons; see **Tables 4**, **5**). The α for associations or differences between different indicators of substance use and sex or age of onset was set at 0.003 (i.e., 0.05/19 comparisons; see **Table 2**). It is important to note that the Bonferroni correction is a conservative method to control for type I error (Curtin and Schulz, 1998; Ranstam, 2016), yet can increase type II error. Nonetheless, certain conditions (i.e., large sample size or when the exploration of the data is relatively hypothesis-free) maintain the risk of false negative outcomes (i.e., type II error) at a reasonable level, even after using Bonferroni (Perneger, 1998; Ranstam, 2016). In these analyses in which Bonferroni was applied, effect sizes were estimated to provide further information on the magnitude of the effects found. Effects sized were interpreted as described by Cohen (1988, 1992a,b)

We consider other alternatives to analyze the data without inflating the risk of a type I error. We could, instead of the multiple bivariate associations, have used a principal component analysis. This approach, however, would have seriously diminished obtaining a detailed analysis of these relationships (Curtin and Schulz, 1998).

Descriptive values and statistical notations (i.e., χ^2 values, *F*-values, *p*-values for each analysis, etc.) for most of the inferential analyses are shown in the tables.

RESULTS

Descriptive Results

Alcohol Use

Alcohol was by far the most consumed substance. The vast majority of the participants reported consuming at least one standard unit of alcohol in their lifetime and within the previous year and previous month. Almost 70 and 55% of the sample engaged in at least one episode of heavy episodic drinking and binge drinking, respectively, within the previous 6 months. Despite the elevated occurrence of heavy and binge drinking, less than half of the students reported drunkenness episodes within the same timeframe. These results are presented in **Table 2**. As shown in **Table 3**, ∼33 and 18.3% of the sample engaged in heavy episodic drinking and binge drinking, respectively, at least once per week.

Tobacco Use

Half of the sample indicated lifetime use of tobacco, with approximately one-third of the students reporting smoking cigarettes within the previous year (**Table 2**). Most current tobacco users exhibited daily smoking (**Table 3**).

Marijuana Use

Marijuana use had the lowest prevalence (**Table 2**) compared with alcohol and tobacco. The majority of marijuana users reported low-frequency patterns of consumption (**Table 3**). The percentage of students who reported a high frequency of marijuana use (≥3 times per week; 3.9%) was greater than the percentage of students who exhibited a similar frequency of binge drinking (1.3%).

Alcohol Use during the Typical and Heaviest Weeks of Alcohol Consumption

The mean number of standard drinks of alcohol that were consumed during the typical and heaviest weeks were 7.39 ± 9.12 and 13.75 ± 17.06, respectively. The lowest percentages of students reported drinking Sunday to Wednesday (range, 2.3–9.6%), whereas the highest percentages of students reported drinking on Friday and Saturday (50.8 and 77.1%, respectively). A similar pattern was found during the heaviest week of consumption, although the percentages were more spread out across days, with an increasing number of students who reported drinking on weekdays (e.g., drinking on Wednesday and Thursday increased from 5.9 and 12.8% to 15.7 and 28.4% in the typical and heaviest weeks, respectively). The number of standard drinks consumed each day of the typical and heaviest weeks also changed during the week. Specifically, in a typical week, the participants reported drinking an average of around two standard drinks each day from Sunday to Wednesday, three drinks on Thursday, and around five drinks on Friday and Saturday. In the heaviest week of alcohol consumption, they reported drinking an average of about four standard drinks each day from Sunday to Wednesday, five drinks on Thursday, and between 6.55 and 7.55 drinks on Friday and Saturday, respectively.

Onset of Substance Use

Age of Onset of Alcohol Drinking

Among lifetime drinkers, the majority (70.1%) reported the first consumption of at least one standard drink between 14 and 16 years of age, with nearly 60% of all drinkers doing so by the age of 15. Only 2% of the drinkers reported first AU at 18 or older. Nearly 30% of the drinkers (29.9%) were classified as EDs, and the rest were classified as LDs. Among lifetime drinkers, the mean age of onset of AU was 15.21 ± 1.58 years. As expected, EDs reported a significantly lower age of drinking onset (mean = 13.44 ± 0.98 years) than LDs (15.97 ± 1.11 years; $t = 66.57$, $p \leq 0.001$).

Age of Onset of Tobacco Use

Among lifetime smokers, the age at first tobacco use was concentrated within the age range of 15–17 years (60.2%). Forty percent of the smokers reported first tobacco use by the age of 15, and 16.3% of them began at 18 or older. Among lifetime smokers, the mean age of first tobacco use was 15.83 ± 1.95 years, and ESs (13.96 ± 1.26 years) reporting first tobacco use at a significantly younger age than LSs (17.08 ± 1.18 years; $t = 57.60$, $p \leq 0.001$).

Age of Onset of Marijuana Use

Among lifetime users of marijuana, the majority reported first marijuana use within the age range of 16–18 years (65.9%). Nearly 19% reported first use by the age of 15, and 34.1% of them began at 18 or older. Among lifetime marijuana users, the mean age of first marijuana use was 17.03 ± 2.02 years. As expected, EMUs reported a significantly younger age of first marijuana use

TABLE 2 | Occurrence of alcohol, tobacco and marijuana use: for the total sample and as a function of sex and age at each substance onset.

	Total sample					Ever alcohol users				Ever tobacco users				Ever marijuana users			
	Total	Men	Women	χ^2/t	EfS	LD	ED	χ^2/t	EfS	LS	ES	χ^2/t	EfS	LUM	EUM	χ^2/t	EfS
Alcohol																	
Lifetime	94.6	96.2	93.6	13.50*	0.06	100	100	–	–	99.5	99.3	0.49	0.01	99.6	99.5	0.18	0.01
12M	90.4	92.4	89	13.41*	0.06	94.5	97.8	19.32*	0.07	96.5	96.3	0.10	0.01	96.9	97	0.01	0.00
30D	80.3	84.9	77.1	37.53*	0.10	81.2	93.6	95.82*	0.15	89.9	91.3	1.36	0.02	91.9	93	0.63	0.01
7D	50.4	59.6	44.2	92.95*	0.15	46.2	70.3	185.68*	0.21	61.5	67.4	7.41	0.04	69	73.4	3.32	0.03
HED	68.6	76	63.7	68.33*	0.13	66.7	87.8	179.41*	0.21	79.8	83.6	4.75	0.03	83.1	87.5	5.23	0.04
Binge	54.9	64.1	48.8	91.68*	0.15	50.8	76.3	211.74*	0.23	65.8	70.6	5.27	0.04	68.6	77	12.28*	0.05
Drunkenness																	
Lifetime	70.1	75.7	66.4	40.57*	0.10	67.9	89.6	198.04*	0.22	83.8	87.7	6.01	0.04	90.2	93.5	4.95	0.03
6M	44.4	51.1	39.9	49.38*	0.11	39.8	64.3	188.99*	0.22	53.3	57.5	3.46	0.03	58.1	68.4	15.43*	0.06
30D	23.9	29.3	20.3	43.57*	0.10	20.1	37.7	130.23*	0.18	29	36.5	12.68*	0.06	32.5	44.8	22.55*	0.07
Q D 30D	0.50 ± 1.32	0.69 ± 1.63	0.38 ± 1.04	7.47*	0.12	0.38 ± 1.08	0.89 ± 1.79	10.79*	0.17	0.57 ± 1.24	0.90 ± 1.86	4.85*	0.08	0.71 ± 1.59	1.08 ± 1.85	3.97*	0.06
Tobacco																	
Lifetime	51.3	52.7	50.4	2.07	0.02	47.5	69.5	154.76*	0.19	100	100	–		80	87	12.13*	0.05
12M	36.3	36	36.5	0.09	0.00	32.1	52.9	146.06*	0.19	70	72.1	1.10	0.02	60.6	67.7	7.75	0.04
30D	27.4	27.4	27.4	0.00	0.00	23.6	41.1	122.75*	0.17	48.3	61.4	34.51*	0.10	48.8	57.3	10.17*	0.05
7D	21.4	21.2	21.6	0.00	0.00	18.4	32.6	92.10*	0.15	34.7	52.5	64.66*	0.13	38.4	48.2	13.87*	0.06
Q C Day	1.75 ± 3.64	1.91 ± 3.98	1.64 ± 3.40	2.24	0.04	1.44 ± 3.28	2.81 ± 4.23	10.47*	0.17	2.68 ± 3.56	4.56 ± 5.38	9.50*	0.15	3.08 ± 4.44	4.14 ± 5.23	4.13*	0.06
Marijuana																	
Lifetime	36	45.1	30	96.42*	0.15	30.6	55.8	213.53*	0.23	49.9	70.5	86.99*	0.15	100	100	–	
12M	27.5	35.5	22.1	88.59*	0.15	22.1	45.4	207.55*	0.23	37.9	55	58.47*	0.12	74.2	79.7	5.89	0.04
30D	17.5	23.4	13.6	64.14*	0.13	13	31.4	176.44*	0.21	22.7	39.9	70.06*	0.13	40.2	61.3	62.49*	0.12
7D	9.8	13.6	7.3	44.28*	0.10	7.1	18	101.27*	0.16	12.1	23.9	49.54*	0.11	18.4	40.7	87.09*	0.15

*LD, late drinkers; ED, early drinkers; LS, late smokers; ES, early smokers; LUM, late users of marijuana; EUM, early users of marijuana; Lifetime, lifetime use; 12M, last year occurrence; 30D, last month occurrence; 7D, last week occurrence; HED, heavy episodic drinking (4/5 standard drinks in one drinking session); Binge, binge drinking (4/5 standard drinks in ≤2 h); Q D 30D, number of drunkenness episodes within the previous month; Q C Day, quantity of cigarettes consumed per smoking day; EfS, effect size. *$p \leq 0.003$.*

TABLE 3 | Frequency of binge and heavy drinking and frequency of tobacco and marihuana use: for the total sample and as a function of sex.

	Alcohol											
	HED			Binge			Tobacco			Marijuana		
	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women
No use	31.5	24.1	36.4	45.1	35.9	51.2	67.8	67.5	68	76.2	69	81.1
≤1 M	10.5	10.7	10.3	13.4	15.8	11.8	5.3	5.2	5.3	7.9	10	6.6
1 M	8.8	8.2	9.2	11.5	11.9	11.3	2.1	2.8	1.7	2.6	3.5	2.1
2 M	9.7	9.8	9.7	7	8	6.3	2.5	2.7	2.4	3	3.4	2.7
3 M	7	6.6	7.3	4.7	4.7	4.7	2.1	1.9	2.3	2.1	2.3	2
1 W	17.2	19.5	15.7	11.3	14.6	9.1	3.4	4.1	2.9	2.2	2.8	1.8
2 W	11.9	15.9	9.2	5.7	7.3	4.7	2.7	2.3	3	1.9	2.8	1.4
3 W	2.6	4.1	1.6	1.1	1.5	0.7	3	3	2.9	1.5	2.3	1
≥4 W	0.7	1	0.5	0.2	0.3	0.2	11.1	10.4	11.5	2.4	3.9	1.4

HED, heavy episodic drinking, defined as the consumption of ≥4/5 standard drinks in one drinking session (women/men); Binge drinking = defined as the consumption of ≥4/5 standard drinks in ≤2 h (women/men).

(15.33 ± 0.91 years) than LMUs (18.23 ± 1.70 years; $t = 38.18$, $p \leq 0.001$).

Group Differences

Sex Differences

Men reported a significantly higher occurrence and average number of general and hazardous (heavy, binge, and drunkenness episodes) AU compared with women. Men had a significantly higher occurrence of marijuana use compared with women. No sex differences were found for tobacco. These results are presented in **Tables 2**, **3**. Men also reported drinking a significantly greater amount of alcohol (standard units) during the typical (10.21 ± 11.21) and heaviest (19.75 ± 21.25) weeks of AU compared with women ($\text{mean}_{\text{typical}} = 5.49 \pm 6.75$; $\text{mean}_{\text{heaviest}} = 9.72 \pm 11.94$).

Men and women had a similar pattern of ages of alcohol, tobacco, and marijuana initiation. Across sex, most of the participants exhibited (a) first AU by the age of 14–16, (b) first tobacco use by the age of 15–17, and (c) first marijuana use by the age of 16–18. Despite this general trend, men reported a slightly but significant lower mean age of alcohol onset ($\text{mean}_{\text{men}} = 14.95 \pm 1.68$ years; $\text{mean}_{\text{women}} = 15.39 \pm 1.47$ years; $t = 8.62$, $p \leq 0.001$), tobacco onset ($\text{mean}_{\text{men}} = 15.65 \pm 2.01$ years; $\text{mean}_{\text{women}} = 15.96 \pm 1.90$ years; $t = 3.46$, $p \leq 0.001$), and marijuana onset ($\text{mean}_{\text{men}} = 16.77 \pm 1.98$ years; $\text{mean}_{\text{women}} = 17.28 \pm 2.03$ years; $t = 4.80$, $p \leq 0.001$) compared with women. The percentages of men who were classified as early users of alcohol (36.5%) and marijuana (46.4%) but not tobacco (42.5%) were significantly higher than the percentages of women (alcohol = 25.3%; tobacco = 38.4%; marijuana = 36.4%; $\chi^2_{\text{alcohol}} = 54.23$, $p \leq 0.001$; $\chi^2_{\text{tobacco}} = 3.50$, $p = 0.061$; $\chi^2_{\text{marijuana}} = 15.08$, $p \leq 0.001$).

Age at Drinking Onset and Use of Alcohol, Tobacco, and Marijuana

Early drinkers reported significantly greater AU for all the drinking indicators than their peers who began drinking alcohol at older ages. All of the tobacco and marijuana use indicators were significantly greater in EDs than in LDs. These results are presented in **Table 2**. EDs also reported drinking a significantly greater amount (standard units) of alcohol during the typical (11.73 ± 11.51) and heaviest (22.69 ± 22.10) weeks of AU compared with LDs ($\text{mean}_{\text{typical}} = 6.16 \pm 7.39$; $\text{mean}_{\text{heaviest}} = 11.12 \pm 13.18$).

Age at Tobacco Onset and Use of Tobacco, Alcohol, and Marijuana

Early smokers reported a significantly higher occurrence of last month and last week but not last year tobacco use compared with LSs. ESs also smoked a greater number of cigarettes per smoking day compared with LSs. ESs reported a significantly higher occurrence of last month drunkenness compared with LSs. ESs reported a significantly greater occurrence of all of the indicators of marijuana use compared with LSs. These results are presented in **Table 2**.

Age at Marijuana Onset and Use of Marijuana, Alcohol, and Tobacco

Early marijuana users reported a significantly higher occurrence of all indicators of marijuana use compared with LMUs. EMUs reported a significantly greater use of tobacco and a greater occurrence of binge drinking and drunkenness episodes compared with LMUs. These results are presented in **Table 2**.

Effects sizes (**Table 2**) for the associations between substance use and sex were low for marihuana and alcohol (i.e., between 0.10 and 0.15 and between 0.06 and 0.15, respectively), whereas those for tobacco ranged between 0.0 and 0.04. The effect size of early drinking onset on subsequent alcohol (0.07–0.23), tobacco (0.15–0.19) or marihuana (0.16–0.23) use was larger than the effect of early tobacco or early marihuana use on subsequent use of each of these substances. The effect of early tobacco onset was larger for subsequent marihuana use (0.11–0.15) than for subsequent use of tobacco (0.02–0.15) or for AU (0.01–0.08). The effect of early use of marihuana was larger for the subsequent use

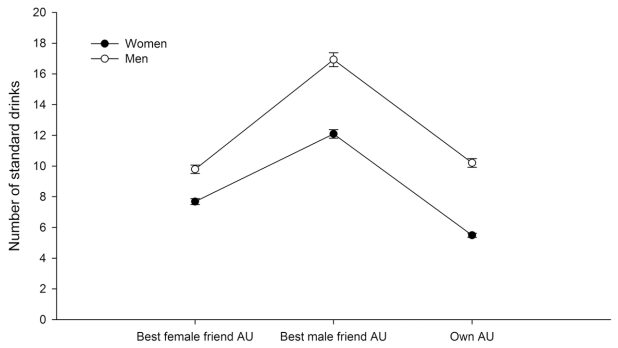

FIGURE 1 | Alcohol use (AU), expressed as the mean number of standards drinks consumed in a typical week, by each participant (own AU) and perceived number of standards drinks consumed in a typical week by the best female friend and best male friend. The vertical lines indicate the standard error of the mean. Refer to the text for significant differences that were found in the statistical analysis.

of marihuana (0.04–0.15) than for the subsequent use of tobacco (0.04–0.06) or use of alcohol (0.0–0.07).

Own vs. Perceived Amount of Alcohol Use as a Function of Sex

The mixed ANOVA revealed a significant Sex × Indicator of Alcohol Use interaction ($F_{2,7342} = 39.40$, $p \leq 0.001$; **Figure 1**). The *post hoc* analyses indicated significant sex differences in the total amount of own AU, in which men drank more alcohol than women within a typical week of alcohol consumption. Moreover, women perceived that either their best female friend or best male friend drank significantly more heavily than they did. Men perceived that they drank a significantly lower amount of alcohol than their best male friend but as much as their best female friend.

Correlations

Perceived Risk Associated with Substance Use

Alcohol use

The perceived risk of AU was significantly and negatively correlated with all indicators of AU. Women (Pearson $r_s = -0.19$ to -0.32) and men (Pearson $r_s = -0.23$ to -0.34) presented a similar pattern of correlations (**Table 4**).

Tobacco use

The perceived risk of tobacco use was significantly and negatively correlated with the frequency and amount of tobacco use, a pattern that was fairly similar across men ($r_s = -0.19$ to -0.16) and women (Pearson $r_s = -0.22$ to -0.19; **Table 5**).

Marijuana use

The perceived risk of marijuana use was negatively and significantly correlated with the frequency of marijuana use. The size of this correlation was the highest among the three substances and greater among men (Pearson $r = -0.42$) than among women (Pearson $r = -0.35$; **Table 5**).

Injunctive Norms

Alcohol use

The perceived levels of both peer and parental approval of AU were positively and significantly correlated with hazardous alcohol drinking (heavy and binge drinking and number of drunkenness episodes) and the quantity of alcohol consumed during the typical and heaviest weeks of alcohol intake. The effect size was stronger for perceived peer approval (Pearson $r_s = 0.21$ to 0.35) than for perceived parental approval (Pearson $r_s = 0.09$ to 0.21). Although men and women presented very similar patterns of correlations, the association between drunkenness episodes and perceived parental approval was quite low among women (Pearson $r = 0.09$; **Table 4**).

Tobacco use

Students who perceived greater peer and parental approval of tobacco use reported a significantly higher frequency and amount of tobacco use, although the effect was greater for perceived peer approval. In contrast to alcohol, the association between parents' norms and tobacco use were stronger for women (Pearson $r_s = 0.30$ and 0.29 for frequency and amount, respectively) than for men (Pearson $r_s = 0.25$ and 0.21 for frequency and amount, respectively; **Table 5**).

Marijuana use

The perceived levels of peer and parental approval of marijuana use were positively and significantly correlated with the frequency of marijuana use. The effect size for peers (Pearson $r = 0.49$ and 0.43 for men and women, respectively) was stronger than for parents (Pearson $r = 0.35$ and 0.25 for men and women, respectively; **Table 5**).

Descriptive Norms for Alcohol Use

All indicators of own AU were positively and significantly correlated with descriptive norms (**Table 4**). Among women, the size of the associations was similar, regardless of the sex of the best friend. Among men, the associations that involved a male friend were stronger than those that involved a female friend.

Injunctive Norms and Perceived Risk Associated with Substance Use

The level of approval of alcohol (**Table 4**), tobacco (**Table 5**), and marijuana (**Table 5**) use was negatively and significantly associated with the perceived risk of using each of these substances. Across sex, the size of the correlations was stronger for peers than for parents as the reference group.

The effect sizes between the independent variables and AU were larger for those variables that involved the peers. More in detail, many of the effect sizes of the correlations between descriptive norms and AU were large (i.e., between 0.20 and 0.72). The effect sizes of the correlations between injunctive norms and AU were larger when the reference group was the peers (i.e., between 0.21 and 0.35) than when the reference group was the parents (i.e., between 0.09 and 0.21). The effect sizes of the correlations between peers' injunctive norms and tobacco or marihuana use were medium and close to large, respectively; whereas those involving the parents were medium for both substances. The effect size of the correlation between perceived

TABLE 4 | Correlations between perceived risk, social and injunctive norms (parents and friends) with alcohol use.

	TW FF	TW MF	FD	MD	IN F	IN P	PRA	F HED	F B	TW	IW	Q D E
TW FF		0.77*†	0.33*‡	0.24*⁞	0.23*⁞	0.12*⁞	−0.19*⁞	0.48*‡	0.44*‡	0.59*†	0.63*†	0.20*⁞
TW MF	0.78*†		0.25*⁞	0.28*⁞	0.31*‡	0.17*⁞	−0.23*⁞	0.56*†	0.49*‡	0.71*†	0.72*†	0.26*⁞
FD	0.30*‡	0.27*⁞		0.56*†	0.30*‡	0.14*⁞	−0.24*⁞	0.26*⁞	0.24*⁞	0.23*⁞	0.24*⁞	0.15*⁞
MD	0.22*⁞	0.28*⁞	0.69*†		0.31*‡	0.11*⁞	−0.23*⁞	0.26*⁞	0.22*⁞	0.25*⁞	0.27*⁞	0.14*⁞
IN F	0.32*‡	0.30*‡	0.37*	0.31*‡		0.37*‡	−0.40*‡	0.35*‡	0.34*‡	0.30*‡	0.30*‡	0.23*⁞
IN P	0.10*⁞	0.10*⁞	0.09*⁞	0.02	0.28*⁞		−0.33*‡	0.18*⁞	0.21*⁞	0.18*⁞	0.17*⁞	0.14*⁞
PRA	−0.21*⁞	−0.19*⁞	−0.22*⁞	−0.17*⁞	−0.38*‡	−0.27*‡		−0.34*‡	−0.31*	−0.30*‡	−0.30*‡	−0.23*⁞
F HED	0.51*†	0.49*‡	0.32*‡	0.24*⁞	0.35*‡	0.17*⁞	−0.32*‡		0.77*†	0.77*†	0.70*†	0.38*‡
F B	0.43*‡	0.41*‡	0.27*⁞	0.18*⁞	0.31*‡	0.15*⁞	−0.28*⁞	0.78*†		0.65*	0.62*†	0.37*‡
TW	0.64*†	0.62*†	0.29*⁞	0.22*⁞	0.33*‡	0.16*⁞	−0.28*⁞	0.75*†	0.63*†		0.84*†	0.33*‡
IW	0.67*†	0.66*†	0.29*⁞	0.22*⁞	0.33*‡	0.16*⁞	−0.30*‡	0.72*†	0.62*†	0.85*†		0.31*‡
Q D E	0.27*⁞	0.25*⁞	0.16*⁞	0.11*⁞	0.21*⁞	0.09*⁞	−0.19*⁞	0.40*‡	0.37*‡	0.36*‡	0.36*‡	

*The upper triangle presents results among men. The lower triangle presents results among women; TW FF, Perceived weekly drinking for the closest female friend; TW MF, Perceived weekly drinking for the closest male friend; FD, perceived quantity of female drinkers; MD, perceived quantity of male drinkers; IN F = perceived peers' norms for alcohol use; perceived risk for alcohol use; IN P, perceived parents' norms for alcohol use; PRA, perceived risk for alcohol use; F HED, frequency of heavy drinking; F B, frequency of binge drinking; TW, total alcohol consumption during a typical week; IW, total alcohol consumption during the heaviest week of alcohol consumption; QED, total number of drunkenness episodes. *$p \leq 0.001$; The ⁞,‡, † signs indicate low, medium and large effect sizes.*

TABLE 5 | Correlations between perceived risk and injunctive norms (parents and friends) with tobacco and marijuana use.

	Tobacco					Marijuana				
	PRT	IN P	IN F	FT	QC		PRM	IN P	IN F	FM
PRT		−0.13*⁞	−0.22*⁞	−0.19*⁞	−0.16*⁞	PRM		−0.27*⁞	−0.51*†	−0.42*‡
IN P	−0.17*⁞		0.38*‡	0.25*⁞	0.21*⁞	IN P	−0.25*⁞		0.36*‡	0.35*‡
IN F	−0.25*⁞	0.33*‡		0.29*⁞	0.29*⁞	IN F	−0.55*†	0.29*⁞		0.49*‡
FT	−0.22*⁞	0.30*‡	0.37*‡		0.75*†	FM	−0.35*‡	0.25*⁞	0.43*‡	
QC	−0.19*⁞	0.29*⁞	0.32*‡	0.74*†						

*PRT, perceived risk for tobacco use; IN P, perceived parents' norms for tobacco use; IN F, perceived peers' norms for tobacco use; FT, frequency of tobacco use; QC, quantity of cigarettes consumed per smoking day; PRM, perceived risk for marijuana use; IN P, perceived parents' norms for marijuana use; IN F, perceived peers' norms for marijuana use; FM, frequency of marijuana use. The upper triangle presents results among men. The lower triangle presents results among women. *$p \leq 0.001$; The ⁞,‡,† signs indicate low, medium and large effect sizes.*

risk and substance use was close to large for marihuana, medium for alcohol (i.e., most around 0.30) and low for tobacco (see **Tables 4**, **5**).

Regression Analyses

Frequency of Binge Drinking

Among women, the independent variables accounted for 27% of the variance of binge drinking ($F_{\text{change}6,1954} = 120.44, p \leq 0.001$). All of the predictors, with the exception of the perceived parental approval of AU, significantly explained the frequency of binge drinking. Early drinking onset ($\beta = -0.14$, $t = -7.07$, $p \leq 0.001$), perceived peer approval of AU ($\beta = 0.11$, $t = 4.93$, $p \leq 0.001$), perceived amount of alcohol consumption of the best female friend ($\beta = 0.20$, $t = 6.53$, $p \leq 0.001$) or male friend ($\beta = 0.17$, $t = 5.61$, $p \leq 0.001$), and perceived risk ($\beta = -0.13$, $t = -6.26$, $p \leq 0.001$) were significantly associated with a higher frequency of binge drinking. Similar results were found among the subsample of men. Five of the six predictors significantly explained 33% of the variance ($F_{\text{change}6,1310} = 109.81, p \leq 0.001$). Early drinking onset ($\beta = -0.11$, $t = -4.57$, $p \leq 0.001$), perceived peer approval of AU ($\beta = 0.13$, $t = 4.84$, $p \leq 0.001$), perceived amount of alcohol consumed by the best female friend ($\beta = 0.17$, $t = 4.55$, $p \leq 0.001$) or male friend ($\beta = 0.26$, $t = 6.95$, $p \leq 0.001$), and perceived risk ($\beta = -0.14$, $t = -5.40$, $p \leq 0.001$) but not perceived parental approval of AU were significantly associated with a higher frequency of binge drinking.

Frequency of Tobacco Use

Among women, a significant model emerged for the four independent variables, with an R^2 that accounted for 21% of the variance in the self-reported frequency of tobacco use ($F_{\text{change}4,1165} = 74.35, p \leq 0.001$). Early tobacco use ($\beta = -0.18$, $t = -6.86$, $p \leq 0.001$), perceived peer approval of tobacco use ($\beta = 0.27$, $t = 9.78$, $p \leq 0.001$), perceived parental approval of tobacco use ($\beta = 0.15$, $t = 5.44$, $p \leq 0.001$), and perceived risk ($\beta = -0.12$, $t = -4.34$, $p \leq 0.001$) were significantly associated with more frequent tobacco use. Among men, the total explained variance ($R^2 = 0.14$) was somewhat lower compared with women ($F_{\text{change}4,781} = 31.82, p \leq 0.001$). Early tobacco onset ($\beta = -0.11$, $t = -3.20$, $p \leq 0.05$), perceived peer approval of tobacco use ($\beta = 0.18$, $t = 4.85$, $p \leq 0.001$), and perceived parental approval of tobacco use ($\beta = 0.16$, $t = 4.29$, $p \leq 0.001$) were significantly and positively associated with a higher frequency of smoking

cigarettes. Perceived risk was negatively associated with tobacco use ($\beta = -0.13$, $t = -3.74$, $p \leq 0.001$).

Frequency of Marijuana Use

Among women, the independent variables explained 25% of the total variance of the frequency of marijuana use ($F_{\text{change}4,687} = 58.06$, $p \leq 0.001$). Early marijuana onset ($\beta = -0.11$, $t = -3.18$, $p \leq 0.01$), perceived peer approval of marijuana use ($\beta = 0.31$, $t = 8.04$, $p \leq 0.001$), perceived parental approval of marijuana use ($\beta = 0.10$, $t = 2.77$, $p \leq 0.01$), and perceived risk ($\beta = -0.19$, $t = -4.95$, $p \leq 0.001$) were significantly associated with the frequency of marijuana use. Among men, the variables explained 36% of the total variance ($F_{\text{change}4,659} = 92.60$, $p \leq 0.001$). Early marijuana use ($\beta = -0.18$, $t = -5.51$, $p \leq 0.001$), perceived peer approval of marijuana use ($\beta = 0.32$, $t = 8.45$, $p \leq 0.001$), perceived parental approval of marijuana use ($\beta = 0.15$, $t = 4.50$, $p \leq 0.001$), and perceived risk associated with marijuana use ($\beta = -0.22$, $t = -6.14$, $p \leq 0.001$) were significantly associated with more frequent marijuana use.

DISCUSSION

The present study described alcohol (with a focus on binge and heavy episodic drinking), marijuana, and tobacco use in a large sample ($n = 4083$) of Argentinean college freshmen. We also assessed (a) the modulation of these patterns by personal beliefs about the risk of use of these substances (in varying degrees of intensity), (b) the modulation of these patterns by the perception of their use and approval by peers and parents, and (c) whether the onset of use of a given substance influences the use of that substance or the other substances. Recent studies (Keyes et al., 2011; Slade et al., 2016) suggest that the gap in drug use between men and women is shrinking. An important aim of the present study was to analyze sex differences in these effects. Previous studies by our group included smaller, albeit substantially similar, samples and found that the age of onset of AU was an important facilitator of hazardous drinking behaviors. Therefore, we assessed the generality of this effect of age of onset for other substances.

As expected, lifetime and last year use of alcohol was normative (i.e., 94.6 and 90.4%, respectively), and only 2% of ever-drinkers drank a full drink at or after the legal age (i.e., ≥18 years, in Argentina). These percentages are greater than those that were reported for United States college students in the Monitoring the Future study (Johnston et al., 2015). One caveat of this comparison is that the Monitoring the Future study defined college students as respondents who were 1–4 years beyond high school, whereas all of the respondents in the present study were college freshmen.

An important finding was the higher occurrence of hazardous AU. Nearly 70 and 55% of the students reported heavy episodic or binge drinking in the last 6 months. Moreover, approximately 33 and 20% of the sample engaged in heavy episodic drinking and binge drinking, respectively, on a weekly basis. These figures are somewhat similar to those reported by the Monitoring the Future study, although they asked about heavy drinking within the previous 2 weeks. Tobacco use (51.3 and 36.3% lifetime and last year use, respectively) and marijuana use (36.0 and 27.5% lifetime and last year use, respectively) was lower than AU. The figures for marijuana use were markedly lower than those reported by the Monitoring the Future study in the United States (50.4 and 38.0% lifetime and last year use, respectively), although this comparison should be framed within the context of the aforementioned difference in the years of college enrollment. Unlike alcohol and marijuana users, most of the tobacco users in the present study reported almost daily tobacco consumption. This underscores the addictive liability of nicotine. A previous study found that 21% of those who had ever tried nicotine became dependent on the substance compared with 11 and 4% of those who had ever used alcohol or marijuana, respectively (Schramm-Sapyta et al., 2009).

Last year tobacco use was similar to recent studies that were conducted with college freshmen in Argentina (Vera et al., 2015) and the United States (Suerken et al., 2014). An interesting comparison can be made concerning another nationwide Argentinean study (SEDRONAR, 2010). Last year tobacco use in the present study was similar to (although somewhat lower than [5.5%]) SEDRONAR, but last year marijuana use in our sample (35.5 and 22.1% for men and women, respectively) almost doubled compared with reports by SEDRONAR 6 years ago. A recent study of United States college students (Suerken et al., 2014) reported a 29.8% prevalence of marijuana use in the last 6 months. The Monitoring the Future study of senior high-school students in the United States reported a gradual increase in the last-year use of marijuana from 2006 to 2011, but this increase leveled off afterward (Johnston et al., 2015). Altogether, these results suggest a steady increase in recent (i.e., last year and last 6 months) use of marijuana among late adolescents, although regional differences are likely to occur, particularly when focusing on specific patterns of marijuana use. The prevalence of intensive marijuana use (i.e., in the last 7 days) in the present study was 13.6 and 7.3% for men and women, respectively, which is ostensibly lower compared with college students in Spain (22.2 and 20.0%, respectively; Moure-Rodríguez et al., 2016). The apparent increase in marijuana use among Argentinean adolescents is concerning. Marijuana use has been associated with lower academic performance, a higher risk of dropping out of college (Suerken et al., 2014), and the use of other illegal drugs (Babor et al., 2010).

The analysis of sex differences in the frequency of binge and heavy drinking and frequency of tobacco and marijuana use revealed an interesting pattern. Men and women exhibited a fairly similar prevalence of these behaviors when focusing on less-than-weekly use (i.e., once, twice, or three times per month). After this threshold of use, the frequency of alcohol and marijuana but not tobacco use was an average of two-times higher in men than in women (e.g., the biweekly use of marijuana was 1.4 and 2.8% for men and women, respectively). This reflects the closing gap between sexes in drug use (Wallace et al., 2003; Keyes et al., 2011; Slade et al., 2016), which may be more conspicuous among those who do not present patterns of heavy drug use (Corbin et al., 2008). A previous study (Johnston et al., 2006) found that the narrowing gap between sexes in AU was not the same for all ethnic groups. Latino youths exhibited the largest

sex gap in the 30-day prevalence of AU (11%) compared with American Caucasians, Asian Americans, and American Indians. Sex differences within Latino samples were also notable, with a peak of 14% among those of Mexican ancestry, followed by 10% among Puerto Rican Americans. Individuals from other Latin American countries presented a 9% sex gap (Johnston et al., 2006), which is similar to the 7.8% sex gap that was found in our sample of Argentinian college students.

An interesting comparison of alcohol consumption patterns can be made between a typical drinking week and an intense drinking week. In a typical drinking week, similar to the findings of recent studies (Foster et al., 2015; Howard et al., 2015; Lau-Barraco et al., 2016), drinking was concentrated on Friday and Saturday. On each of those days, the participants ingested an average of five standard drinks. During an intense drinking week, drinking was spread out over weekdays and the weekend. A descriptive, yet striking, result was that the participants reported drinking an average of 7.55 standard drinks (106 g pure alcohol) on the heaviest Saturday outing, which increased to an average of 10 standard drinks (140 g pure alcohol) in men. Peaks of alcohol consumption during specific time-windows are associated with a higher likelihood of alcohol-related accidents (Foster et al., 2015), underscoring the need to center prevention efforts on reducing AU during these time-windows.

Our findings and other recent studies (Barry et al., 2016) suggested that alcohol was the entry-point substance for the majority of the participants. The onset of AU preceded the use of tobacco, which, in turn, preceded the use of marijuana (Gruber et al., 2012a). We identified substance-specific associations (Ohannessian et al., 2015). The early use of alcohol, tobacco, and marijuana was associated with a higher likelihood of consuming each of these substances. Despite this, an early drinking onset was significantly associated with a greater occurrence of all indicators of tobacco and marijuana use. Moreover, the effect sizes of the associations between early drinking onset and subsequent use of all three substances were larger than the effect of early tobacco or marihuana use on subsequent use of these substances. Altogether, these findings suggest a broader effect of alcohol initiation that heightens the risk of consuming alcohol and using other substances (Wagner et al., 2005; Hingson et al., 2008).

Compared with representative data from a national survey (SEDRONAR, 2010), we observed a decrease in the mean age of onset of the use of alcohol (∼15 vs. ∼17), tobacco (∼16 vs. ∼17), and marijuana (∼17 vs. ∼19). The findings from SEDRONAR were derived from a sample of 12–65 year old individuals, which may result in telescoping bias. Nonetheless, this notable decrease in the age of first use raises concerns about the significant effect of early substance use on future risk behaviors (Barry et al., 2016).

Similar to previous work that was mostly conducted in the United States (LaBrie et al., 2010a; Neighbors et al., 2011), we found a significant and positive association between the level of perceived approval and the use of alcohol, tobacco, and marijuana. Unsurprisingly, peer-related variables exerted a stronger effect than parent-related variables (Parsai et al., 2009). Interestingly, the role of parental norms was both substance- and sex-specific. Parents seemingly had a stronger impact on AU (only at the bivariate level) and marijuana use among men, whereas parents had a stronger impact on tobacco use among women. These findings suggest promising avenues for intervention and highlight the need to implement sex- and substance-specific programs. Injunctive norms, at least those for peer approval, can be altered by information-based manipulation (Prince and Carey, 2010; Ridout and Campbell, 2014). The findings also suggest that at least some risk factors for substance use may be universal. College life, social organization, and other important contextual factors (e.g., legal age to buy alcohol) are notably different between the United States and Argentina. Despite these differences, however, the present study indicated that certain vulnerability factors exert similar effects across these cultural contexts.

Students perceived their own drinking behaviors as lower than those of same-sex students. Women also perceived that opposite-sex students drank larger amounts of alcohol than they did. The latter more likely reflects sex differences in drinking behaviors, in which men reported greater AU than women. These findings support previous studies that suggested that students overestimated the drinking of their peers (Neighbors et al., 2008b).

Similar to previous work (Johnston et al., 2015), perceived risk was negatively associated with substance use, in which students who perceived alcohol, tobacco, and marijuana use as less risky reported greater use of each substance compared with students who perceived use as more risky. At the multivariate level, this cognitive variable significantly explained a greater frequency of binge drinking and tobacco and marijuana use. Notably, the effect size of perceived risk was greater for marijuana use at the bivariate and multivariate levels compared with alcohol and tobacco use. We also found a positive and significant association between perceived risk and injunctive norms. The students who perceived greater approval also perceived a lower risk associated with the use of that substance.

The present study has limitations. The cross-sectional design does not allow the determination of causal relationships between variables. A bidirectional rather than unilateral effect might underlie addictive behaviors, in which some conditions be a consequence rather than cause of drug exposure. This reciprocal association might be seen as an ongoing feedback cycle, in which lower risk perception promotes substance use, which, in turn, decreases the perceived risk of using that substance. Similar reciprocal relationships have been reported for impulsivity and drug use (Malmberg et al., 2013). Longitudinal studies that begin before direct contact with a substance are needed to further elucidate the role of risk and protective factors in the emergence of addictive behaviors. Another limitation of the present study was the assessment of descriptive norms only for alcohol and not for tobacco or marijuana.

Despite these limitations, a main contribution of this study was the description of substance use behaviors in a large sample of Argentinean college freshman (from many and different careers) and the relationship between these behaviors and the onset of substance use, descriptive and injunctive social norms, and perceived risk of using those substances. The findings suggest avenues of intervention in this target group. Programs that are directed toward delaying the onset of AU, which was shown to

be a "gateway" drug with broader effects on the use of other substances, or modulating the perception of peers' drug use and approval may be particularly useful among these individuals. Interventions that target the influence of perception of drug use may also be beneficial, particularly if the aim is to reduce marijuana use.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the National University of Cordoba's internal review board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the National Agency for Promotion of Science and Technology (FONCyT).

AUTHOR CONTRIBUTIONS

AP and RP designed the study, collected the data, and analyzed the data. JR helped designed the study and provided input in the data analysis. RP and AP wrote the initial version of the manuscript. All authors corrected and approved the final version of the MS.

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MINI REVIEW
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Personality Traits Related to Binge Drinking: A Systematic Review

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The pattern of alcohol consumption in the form of binge drinking (BD) or heavy episodic drinking has increased notably worldwide in recent years, especially among adolescent and young people, being currently recognized as a global health problem. Although only a minority of binge drinkers will develop a substance use disorder, BD may have negative personal and social consequences in the short and medium term. The objective of this article is to review the findings on personality traits related to binge drinkers and to emphasize the aspects that should be examined in order to make progress in this area. The main characteristics of personality related to the practice of BD, regardless of the theoretical model used, are high Impulsivity and high Sensation seeking, as well as Anxiety sensitivity, Neuroticism (Hopelessness), Extraversion and low Conscientiousness. The data obtained may have theoretical implications to elucidate the endophenotype of BD, but they are especially useful for their preventive applications. Integration into prevention programs of emotional self-control skills, decision-making, social skills, and strategies to manage negative emotions will minimize the risk factors or consequences of BD associated with personality and will improve their effectiveness. In the future, it is necessary to harmonize a common measurement instrument for the assessment of personality, develop longitudinal studies with large samples that also integrate biological and neurocognitive measurements, and determine the reciprocal relationship between personality and BD together with its modulating variables, as well as the possible cultural differences.

Keywords: binge drinking, heavy episodic drinking, personality traits, impulsivity, sensation seeking, neuroticism, anxiety, prevention

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INTRODUCTION

The pattern of binge drinking (BD) or heavy episodic drinking is increasing and expanding worldwide (1). Although it is recommended to define the BD as the consumption of high quantities of alcohol (≥4/5 drinks for women/men) within a time period of 2 h (2), there is no consensus and it is frequent to consider the consumption in one occasion/sitting. BD supposes an important public health problem of which it is still necessary to know better the vulnerability factors responsible for its initiation, maintenance, or increase in frequency and intensity.

Individuals who practice BD are exposed to numerous adverse psychological and health-related outcomes (3). Acute alcohol intoxication includes accidents caused by driving while intoxicated, unwanted sexual behavior, and fights or other disruptive behaviors with possible legal implications. The repeated pattern of alcohol intoxication is related to cognitive impairments (4, 5), worse

health-related quality of life (6), and an increased risk of suffering psychiatric symptomatology/disorders (7, 8).

The study of the characteristics or personality traits associated with the engagement of BD patterns, such as possible factors of risk or vulnerability, as well as the influence that consumption has on them, is of great theoretical and applied relevance. In this sense, it is now being suggested that personality is an endophenotype that is sensitive for identifying different subtypes of alcohol use disorders (9), also considering that the modification of behaviors linked to extreme personality traits may be beneficial for prevention and treatment of BD. Focusing on studies in adolescents and young people is not only motivated by the time of appearance and boom of the practice of BD but also because in this period of development and maturation of the organism the biological and behavioral impact of alcohol intoxications is more serious (4, 5).

This article reviews existing data on personality characteristics associated with the practice of BD (considering the several definitions) and its evolution, as well as the possible relationships with other variables that increase the risk or are protective for the maintenance and problematic evolution of the consumption. We also mention limitations and future directions that may allow for progress in this area of research.

METHOD

The search, selection, and critical assessment of relevant studies were performed according to the PRISMA guidelines (10). The data search was conducted through the computerized databases PubMed and Scopus with "Binge drinking" (or "Heavy drinking" or "Heavy episodic drinking") and "Personality" as keywords, from January 2006 to February 2017 (**Figure 1**). The search and selection were performed independently and blindly by two authors, and discrepancies resolved by consensus.

RESULTS

Table 1 presents the studies included in the present review, considering the sample characteristics, BD criteria, assessment of personality, and main results.

Impulsivity and Sensation Seeking

The two most studied personality traits for BD are Impulsivity and Sensation seeking. Impulsivity is a multidimensional construct associated with poor planning skills, difficulty maintaining attention, and risk-taking behavior. Sensation seeking is defined as the general need for adventure and excitement, the preference for unforeseeable situations and friends, and the willingness to take risks simply for the experience of living them. Many studies have observed higher scores in binge drinkers in both Impulsivity (11, 12, 26, 27, 29) and Sensation seeking (12, 16, 22, 25, 26, 30, 31, 34), when compared with non-binge drinkers. Both traits are considered risk factors for lifetime, whose joint presence has been labeled as "disinhibited personality" (18), although they are especially present in adolescence, characterized by increased impulsive decision making and behavior (40). Similarly, the scores of Impulsivity and Sensation seeking are related to the number of drinks consumed per episode (14, 20, 23) and the frequency of BD (17, 18, 23).

The existing data have been obtained independently of the personality model or the measurement instrument used, either by conceptualizing Impulsivity and Sensation seeking as independent but related features or considering Sensation seeking as a facet of impulsivity. In this second case, the meta-analysis of Stautz and Cooper (40) about the Impulsivity facets as risk factors for problematic alcohol use in adolescence, including BD, were in this order: Sensation seeking, Lack of premeditation, Negative urgency, and Lack of perseverance. These are the dimensions evaluated by the UPPS Impulsive Behavior Scale, frequently used in this field of study. The Negative urgency or tendency to act rashly when experiencing negative emotions is related to BD (34, 35) and is also the only facet related to its severity (16) and to alcohol use disorders as well (34). According to this, BD has been conceptualized as a maladaptive short-term coping strategy devoted to relieving negative affective states (16), which is congruent with the expectations of tension reduction with alcohol that present the binge drinkers, especially in men (14). In the same way, the consideration of facets from Sensation seeking (Thrill and adventure, Experience seeking, Disinhibition, and Boredom susceptibility) indicates that Thrill and adventure and Boredom susceptibility are associated with BD (3). Both facets are externalizing and have psychopathological connections, according to the model of Krueger et al. (41).

A very relevant aspect is that the relationship between BD and Impulsivity and/or Sensation seeking can be modulated by several factors. It should be noted that personality profile of BD could be modulated by sex since the highest levels of Impulsivity and/or Sensation-Seeking come from the men's scores (11, 12, 29). Moreover, Sensation seeking is the strongest predictor of personality for discriminating binge drinkers from non-drinkers and moderate drinkers in men (22). The expectancies of consumption are mediating in the relationships between the personality traits and BD. Thus, binge drinkers with high Impulsivity show positive expectancies (17), whereas in subjects with high Sensation seeking the greater frequency of episodes of BD is modulated by the positive consequences from drinking (23). Recent work by Lannoy et al. (24) points to the existence of three types of binge drinkers according to their facets of Impulsivity and drinking motives: Emotional (higher Sensation seeking and Urgency), Recreational (higher Lack of Premeditation and Perseverance), and Hazardous (moderate to high drinking motives). This proposal represents an advance with possible practical implications in the future.

The Big Five Personality Model

This personality model considers five dimensions: Extraversion, Neuroticism/Emotional stability, Conscientiousness, Openness (to new experiences)/Intellect, and Agreeableness. Personality data using the Big Five model are inconclusive in cross-sectional studies of BD. High Extraversion is the feature most consistently associated with BD (22, 29, 31), also being related to a higher frequency of BD and more negative consequences (37). In relation to Conscientiousness, which negatively correlated with impulsivity (42), although binge drinkers exhibit usually low scores (5, 19, 32, 37), high values (especially in men) have been

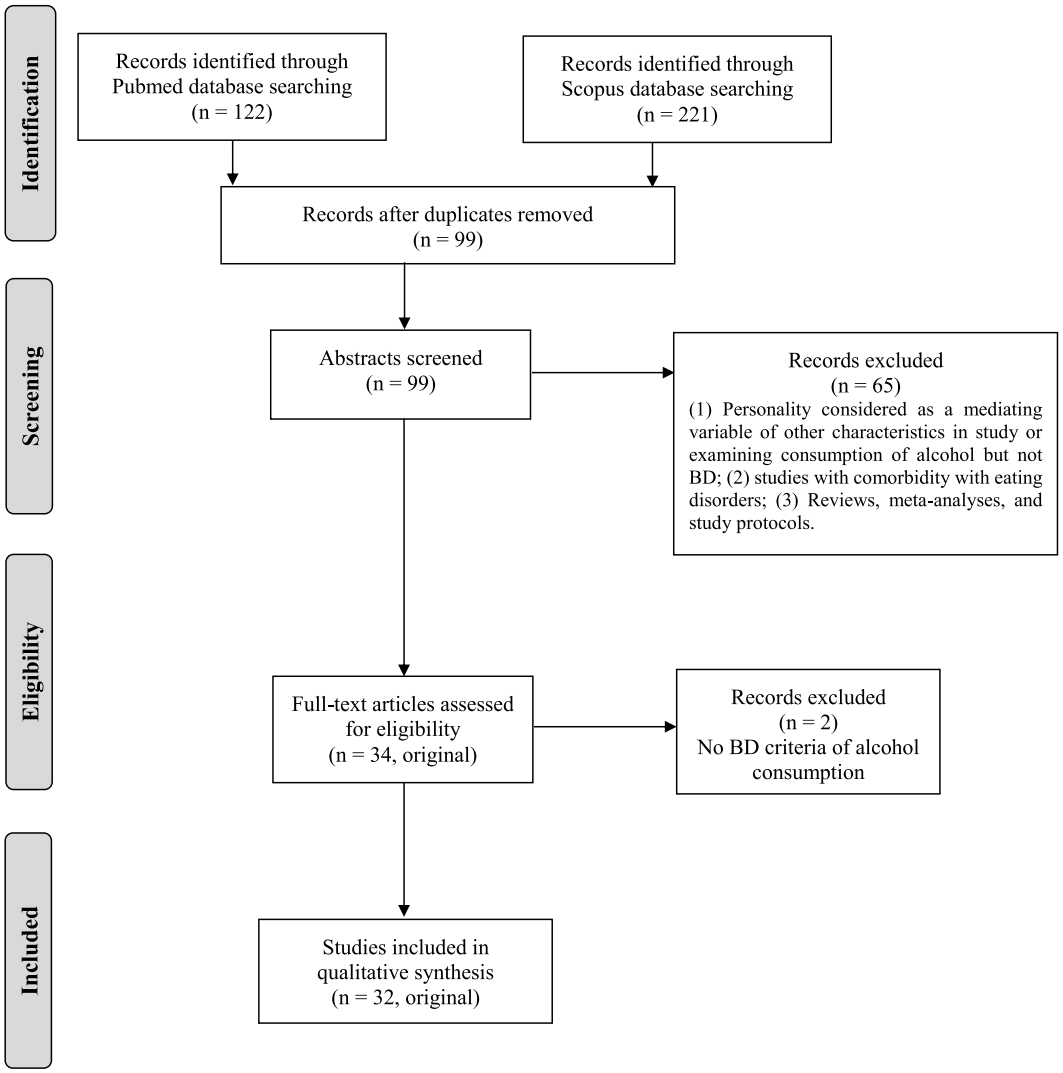

FIGURE 1 | Flowchart for the selection of articles, bibliographic search from January 2006 to February 2017.

also described (29). In this sense, a lower level of self-oriented Perfectionism, which could be considered as a form of hyper Conscientiousness, has also been observed in BD (21). Low Conscientiousness is considered as associated with less prosocial and more health-promoting behaviors (dietary and lifestyles) in general (43). Finally, high Openness has been related to BD in women (28). Some studies have not found relationships between these personality characteristics and BD (32, 33), although they are characterized for including small samples of BD, basically of social drinkers.

The Neuroticism/Emotional stability is the strongest predictor of personality trait that discriminates between binge drinkers and non-drinkers and moderate drinkers in women (22), with low scores in binge drinkers. This could suggest that a higher emotional instability avoids heavy alcohol intake. However, with the Zuckerman personality model (ZKPQ), a higher Neuroticism-anxiety has been observed in binge drinkers, although this is a consequence of the results from women (12). High levels of Neuroticism also explain the negative consequences of alcohol consumption in both sexes (29). The review by De Wever and Quaglino (44) suggests the need to study further the involvement of affective factors (anxiety and depression), which may be premorbid and appear or are aggravated by the consumption. Neuroticism is precisely the most important personality dimension related to many forms of psychopathology, including anxiety, depression, and substance use disorders (12).

Other traits of interest studied are the type-D personality and the Boredom proneness. The first is characterized by a high tendency toward experiencing negative emotions and inhibiting the expression of emotions and behaviors in social situations. Boredom proneness is associated with undesirable emotional states such as depression, hopelessness, loneliness, amotivational orientation and is negatively related to life satisfaction and autonomy orientation. Both are considered risk variables for

TABLE 1 | Results of the empirical studies published on binge drinking (BD) and personality traits (from 2006 to February 2017), according to the characteristics of the sample, BD criteria, and the assessment instruments used.

Reference	Sample characteristics	BD criteria	Personality instruments	Main results
Adan (11)	160 university students, 80 binge/80 non-binge drinkers (40 women in each group) 21.38 years	≥4/5 drinks for women/men within 2 h at least once in the previous 30 days	Functional Impulsivity and Dysfunctional Impulsivity (FIDI)	The scores in Dysfunctional Impulsivity were higher in the BD group compared to the non-binge group, while no differences were found in Functional Impulsivity. Men showed a higher degree of Functional and Dysfunctional Impulsivity, although in Dysfunctional Impulsivity significant differences were observed only in the BD group. Circadian typology controlled (all intermediate type).
Adan et al. (12)	140 university students, 70 binge/70 non-binge drinkers (40 women in each group) 21.33 years	≥4/5 drinks for women/men within 2 h at least once in the previous 30 days	Zuckerman and Kuhlman personality questionnaire (ZKPQ)	Binge drinkers presented higher scores in the Neuroticism-Anxiety and Impulsivity-Sensation seeking dimensions than non-binge drinkers. The Neuroticism-Anxiety results are mainly due to the women's scores, while the higher scores in Impulsivity-Sensation seeking are due mainly to the men's scores. Circadian typology controlled (all intermediate type).
Ashenhurst et al. (13)	2,245 students (1,345 women) 18.4 years at inclusion	≥4/5 drinks for women/men at a sitting	Zuckerman and Kuhlman personality questionnaire (ZKPQ): only Impulsive and Sensation seeking scale	**Longitudinal study:** 6 years follow-up, from end of high school to 2 years after college. Impulsivity and Sensation seeking at inclusion were higher in frequent and increasing trajectories compared to moderate, occasional, rare, or decreasing trajectories. Only increasing trajectory enhanced the Impulsivity scores, while the frequent trajectory showed the highest decrease in Impulsivity. Sensation seeking decreased in all groups, but in the increasing trajectory scores were still the highest.
Balodis et al. (14)	428 university students (152 women) 20.00 years.	≥4/5 drinks for women/men on drinking occasions	Barrat Impulsiveness Scale (BIS); Comprehensive Effects of Alcohol Questionnaire (CEOA)	Binge drinkers did not exhibit higher Impulsivity levels than non-binge drinkers. BIS scores correlated with the number of drinks consumed and the length of the BD episode (risk for impaired control). Women reported higher sociability and sexuality expectations, whereas men reported greater tension reduction expectations with alcohol.
Bhochhibhoya et al. (8)	334 university students (166 women) 20.68 years.	≥4/5 drinks for women/men on one occasion the past 30 days	Denollett's type-D personality scale (DS14)	People with higher risk of type-D personality and mental disturbance (Kessler Psychological Distress Scale) showed a higher probability for drinking more alcohol (including a BD pattern).
Biolcati et al. (15)	721 adolescents (61% girls) 15.98 years.	≥4/5 drinks for women/men in one night	Boredom Proneness Scale (BPS)	Boredom proneness predicted drinking social expectancies. Disinhibition and relief from pain played an important mediating role between Boredom and alcohol outcome.
Bo et al. (16)	162 university students (82 women) 18–25 years.	Binge score based on: number of drinks/h, number of times intoxicated, and percentage of time drunk when going out drinking	UPPS-P Impulsive Behavior Scale	BD was associated with Sensation seeking, but when controlling for sex, age, and global alcohol consumption, only the impulsivity component of Negative urgency predicted severity of BD.
Carlson and Johnson (17)	302 university students (198 women) 20.74 years.	≥4/5 drinks for women/men within 2 h during the past year	Barrat impulsiveness scale (BIS)	Impulsivity scores were related to BD frequency. Impulsivity was not significantly associated with drinking for participants with low levels of positive expectancies but was increasingly related to alcohol use with higher levels of positive expectancies.

(*Continued*)

TABLE 1 | Continued

Reference	Sample characteristics	BD criteria	Personality instruments	Main results
Carlson et al. (3)	293 university students (199 women) 20.73 years.	≥4/5 drinks for women/men within 2 h during the past year	Barrat Impulsiveness Scale (BIS); Sensation Seeking Scale (SSS-V); Aggression Questionnaire (AQ)	Controlling for demographic variables (sex, age, residing away from parents, residing off campus, and parental socioeconomic level), only Motor impulsiveness, Thrill and adventure seeking, and Boredom susceptibility were associated with BD frequency. With the exception of verbal aggression, aggressive personality traits were no related to BD.
Castellanos-Ryan et al. (18)	76 adolescents (55 girls) 14.00 years at inclusion.	≥4/5 drinks for women/men on 1 or more occasions in the past 6 months	Substance Use Risk Profile Scale (SURP); Impulsivity and Sensation seeking dimensions	**Longitudinal study:** 2-year follow-up (14–16 years) Sensation seeking was associated with the unique variance in BD frequency and part of this overlap was mediated by reward-related disinhibition (go/no-go task). Impulsivity was associated with a 2-year average of conduct disorders symptoms, and deficits in response inhibition (visual tracking Stop task) partially mediated on it.
Clark et al. (19)	142 binge-drinking university students (98 women) 21.2 years.	≥4/5 drinks for women/men consumed in a row	Neuroticism-Extraversion-Openness (NEO) Five Factor Inventory; Positive Alcohol Metacognitions Scale; Negative Alcohol Metacognitions Scale	Conscientiousness and positive alcohol metacognitions about cognitive self-regulation were the only two predictors of weekly levels of alcohol use when controlling for sex. In males, low Conscientiousness and positive alcohol metacognitions were risk factors for increased levels of alcohol use in BD.
Doumas et al. (20)	346 high school students (177 women) 17.2 years.	≥3/5 drinks for women/men in a row in a 2-h period during the last 2 weeks	Zuckerman and Kuhlman personality questionnaire (ZKPQ): Only Impulsive Sensation seeking scale	Higher levels of Impulsive Sensation seeking were associated with higher levels of BD. Protective behaviors in manner of drinking modulated the results, whereas use of more drinking strategies in participants with high Impulsive Sensations seeking diminished the frequency of BD.
Flett et al. (21)	207 university students (131 women); 70 binge drinkers (37 women) 18.89 years.	≥5 drinks in a single occasion in the past 2 weeks	Multidimensional Perfectionism Scale; Frost Multidimensional Perfectionism Scale	Binge drinkers, with two or more binge episodes in the past 2 weeks, had lower levels of self-oriented Perfectionism and higher levels of parental criticism.
Lac and Donaldson (22)	506 university students (351 women) 19.34 years.	≥4/5 drinks for women/men at least once in the past 30 days	Sensation seeking 8-items version; Big Five Personality taxonomy	Binge drinkers presented higher scores in Sensation seeking and Extraversion, and lower in Neuroticism, than non-drinkers and moderate drinkers. Sensation seeking was the strongest personality trait for men and Neuroticism for women, which discriminated the drinking type (non-drinkers, moderate drinkers, and binge drinkers).
Lang et al. (23)	206 university students (110 women) 19.5 years.	≥4/5 drinks for women/men on one occasion in the past month	Brief Sensation Seeking Scale-4 (BSSS-4)	Students with high Sensation seeking reported drinking more and had a higher frequency of BD than students with low levels. They also experienced more positive consequences as a result of their drinking. Positive consequences mediated the relation between Sensation seeking and both drinking and BD frequency.

(*Continued*)

TABLE 1 | Continued

Reference	Sample characteristics	BD criteria	Personality instruments	Main results
Lannoy et al. (24)	867 binge drinkers (374 women) and 924 non-binge drinkers (388 women) university students 21.44 years.	>5 drinks for women/men per occasion (alcohol unit 10 g) having between 0.5 and 4 occasion per week	UPPS-P Impulsive Behavior Scale; Drinking Motives Questionnaire-Revised (DMQ-R)	Binge drinkers had lower scores of Negative urgency and Sensation seeking and higher scores on Lack of premeditation than non-binge drinkers. Binge drinkers were not a unitary group. Drinking profiles: (1) Emotional: higher values for Negative urgency and Sensation seeking; (2) recreational: higher Lack of premeditation and Lack of perseverance; and (3) Hazardous: moderate to high values of drinking motives (enhancement, social order, coping, conformity).
Leeman et al. (25)	312 university students (184 women) ≥18 years.	≥4/5 drinks for women/men at a single sitting	Sensation Seeking Scale (SSS, form V), only Disinhibition subscale	BD predictors were sex (male), intensity of best friend's drinking, and Sensation seeking (disinhibition).
Leeman et al. (26)	3,106 high school students (1,696 girls) 15.86 years.	≥4/5 drinks for women/men in a row the past 30 days	Zuckerman and Kuhlman Personality Questionnaire (ZKPQ), only Impulsive Sensation seeking scale	Impulsivity, Sensation seeking, having a paid part-time job and non-participation in extracurricular activities, were positively associated with BD and more alcohol consumption overall. Only Impulsivity had significant associations with related problems (drug and gambling).
Mackie et al. (27)	393 adolescents (265 girls) 13.00 years at inclusion	≥4/5 drinks for women/men on one occasion in the past 6 months	Substance Use Risk Profile Scale (SURP); Brief Symptom Inventory (BSI) for depression and anxiety	**Longitudinal study:** 18-month follow-up (14–16 years) Individuals that scored higher in Hopelessness and Impulsivity were more likely to report engaging in BD. Elevated levels of Depression symptoms predicted faster rates of increase in alcohol use. High Anxiety sensitivity and Anxiety symptoms showed a faster rate of increase in alcohol use compared with only high Anxiety sensitivity without Anxiety symptoms. Adolescents with elevated levels of Impulsivity and heavier drinking were less likely to a normative decline in Depression symptoms.
Martin et al. (28)	153 women university students 19.72 years.	≥4 drinks in a time during the past two weeks	Ten-Items Personality Inventory for assessed Big Five traits	Openness was the only personality trait related to BD. Women with higher levels of Openness who engaged in extreme exercise, fasting, or purging were more at risk for heavy and problematic alcohol use.
Motos et al. (29)	213 university students binge drinkers (121 women) 18.20 years.	≥40/60 g alcohol for women/men in 2/3 h the past 6 months	Reduced Neuroticism-Extraversion-Openness (NEO) Five Factor Inventory; Behavioral Inhibition System (BISys)	The influence of personality was quite limited. Binge drinkers presented especially high levels of Neuroticism and Extraversion. Impulsivity and Conscientiousness, along with age, explained most of the weekly consumption behavior among men. Only Impulsivity and Neuroticism contributed to explain the consequences of consumption.
Mushquash et al. (30)	317 school students (168 girls), Canadian aboriginal 16.00 years.	≥4/5 drinks for women/men on one occasion	Substance Use Risk Profile Scale (SURP)	Sensation seeking and Hopelessness predicted BD. All personality traits predicted alcohol-related problems.
Pilatti et al. (31)	298 women university students 18.27 years.	≥4 drinks on one occasion last three months	BigFive Questionnaire for Children (BFQ-C); Sensation Seeking Scale (SSS, form V)	Regular drinkers with BD and moderate drinkers had higher scores in Extroversion and alcohol expectancies for social facilitation than abstainers. Regular drinkers with BD exhibited, compared to moderated drinkers, higher scores in Extroversion, Experience seeking, Disinhibition, and alcohol expectancies for social facilitation.

(*Continued*)

TABLE 1 | Continued

Reference	Sample characteristics	BD criteria	Personality instruments	Main results
Rush et al. (32)	208 university students (118 women) 56 binge drinkers 18.54 years.	≥4/5 drinks for women/men in a row across at least one sitting in the past month	Neuroticism-Extraversion-Openness (NEO) Five Factor Inventory	Binge drinkers did not differ from non-bingers in the NEO five dimensions when compared with college norms. The comorbidity between binge eating and drinking was related to higher levels of Neuroticism and a tendency to lower Conscientiousness (uncontrolled style of impulse control).
Scaife and Duka (33)	60 young (30 women) moderate and heavy social drinkers 20.6 years.	Score calculate by average drinks per hour, number of time being drunk in the previous 6 months and percentage of time getting drunk when drinking	Revised Neuroticism-Extraversion-Openness (NEO) Five Factor Inventory; Spielberger State-Trait Anxiety Inventory (STAI)	Binge drinkers rated lower in Openness than non-binge drinkers (only approached significance). Anxiety ratings did not show any differences with regard to BD.
Shin et al. (34)	190 young (115 women) from community sample 18–25 years.	≥4/5 drinks for women/men in a row at least 2–3 days per month in the past year	UPPS Impulsive Behavior Scale	Negative urgency and Sensation seeking were positively associated with BD and alcohol use disorders during emerging adulthood.
Shin et al. (35)	268 young (139 women) from community sample 21.9 years.	≥4/5 drinks for women/men in a row at least 2–3 days per month in the past year	UPPS Impulsive Behavior Scale	Negative urgency played a significant role in BD, as well as peer use and parental alcoholism.
Whelan et al. (5)	692 adolescents (312 girls) 14.56 years. at the inclusion	A minimum of three life time episodes leading to drunkenness	Novelty-seeking scale of Temperament and Character Inventory-Revised (TCI-R); Neuroticism-Extraversion-Openness (NEO) Five Factor Inventory; Substance Use Risk Profile Scale (SURP)	**Longitudinal study:** 2-year follow-up (14–16 years). Higher Novelty-seeking (Disorderliness and Extravagance) and lower Conscientiousness characterized both current and future binge drinkers. Agreeableness and Impulsivity classified current but not future binge drinkers. Anxiety sensitivity (SURP) predicted only future BD.
Winograd et al. (36)	988 university students drinkers (494 women) 18.2 years.	≥4/5 drinks for women/men in within a 2 h period	Goldberg's International Personality Item Pool (IPIP), sober and drunk assessed	Perceived drunken personality associated with less Conscientiousness, Openness, Agreeableness and Neuroticism, and more Extraversion. Women reported larger decreases in Conscientiousness, Openness, and Neuroticism than men. Men reported larger decreases in Agreeableness (more aggressive when drunk). Binge drinkers reported increases in Extraversion (in contrast to decreases in non-binge drinkers), and greater decreases in Neuroticism (more anxiolytic effects) and Agreeableness.
Winograd et al. (37)	374 university students (187 drinking buddies; 202 women) 18.4 years.	≥5 drinks at a single sitting 1 or more times per month	Goldberg's International Personality Item Pool (IPIP), sober and drunk assessed	Extraversion was positively associated with more frequency of BD and more negative consequences, whereas Conscientiousness was associated with less BD and fewer consequences (sober and drunk). Under intoxication, drinkers reported lower levels of Agreeableness (impaired control of aggressiveness and low empathy), Conscientiousness (lower self-control) and Openness/Intellect, and higher Extraversion (more sociability) and Emotional Stability (more stress-dampening and anxiolytic effects).

(*Continued*)

TABLE 1 | Continued

Reference	Sample characteristics	BD criteria	Personality instruments	Main results
Winograd et al. (38)	374 university students (187 drinking buddies; 202 women) 18.4 years.	≥5 drinks at a single sitting in the past 30 days	Goldberg's International Personality Item Pool (IPIP), sober and drunk assessed	Personality drunk types: (1) Intoxication-related decreases in Conscientiousness and Openness below average. (2) High in Agreeableness when sober and decreasing less than average in Conscientiousness and Openness, and increasing more than average in Extraversion when drunk. (3) Intoxication related to larger decreases in Conscientiousness and Openness and smaller increases in Extraversion. (4) Low in Extraversion when sober and increasing more than average in Extraversion and decreasing more than average in Conscientiousness when drunk.
Zhang et al. (39)	3,110 young adults (1,648 women) at the final recording 30.9 years.	≥5 drinks in a row during the past 12 months	Mini International Personality Item Pool (Mini-IPIP) of the Big Five Personality factors	**Longitudinal study:** 15-year follow-up, participants in grades 9–12 (USA) at inclusion. Risk profiles of personality for frequent BD: (1) Reserved (high Conscientiousness and low Extraversion, Openness and Agreeableness). Those with higher rates of frequent BD may be at risk for type I alcoholism. (2) Resilient (high Extroversion, Openness and especially Agreeableness). Those with a greater tendency toward social contacts may be more vulnerable to social drinking circumstances.

UPPS Impulsivity: Urgency, Lack of premeditation, Lack of perseverance, and Sensation seeking. UPPS-P considers two facets of Urgency: Positive and Negative.

mental health, since type-D personality predicts the amount of alcohol consumed (8) and Boredom proneness influences the social expectancies (15) of BD.

Substance Use Risk Profile Scale (SURP)

In the area of risk for substance consumption, including alcohol, the SURP scale has been developed, which evaluates four dimensions: Anxiety sensitivity, Sensation seeking, Impulsivity, and Hopelessness (a lower order factor of Neuroticism). To a lesser or greater extent, all of these dimensions appear to be implicated as risk factors in BD. In several studies using the SURP, binge drinkers scored higher in Sensation seeking, Impulsivity and Hopelessness than non-bingers (5, 27, 30), and all the personality traits were related to alcohol problems (30). This scale, with very adequate psychometric properties, is the one selected to assess personality in the "Preventure" prevention program, which will be discussed later.

Changes and Evolution of the Personality Traits Related to BD

In longitudinal studies, Impulsivity and Sensation seeking are prognostic factors for the maintenance and intensification of the BD pattern (5, 13) and alcohol/drug-related problems and other disorders (18, 27). This is observed independently of the personality instrument of measurement. Ashenhurst et al. (13) proposed a deviant pattern of personality maturation without a reduction in both Impulsivity and Sensation seeking as age increases in young adults who developed an increasing trajectory of BD. Anxiety sensitivity also predicts future BD (5). Faster rates of increase in alcohol use have been related to high Anxiety sensitivity and coexisting anxiety symptoms (27).

Zhang et al. (39) have proposed several alcohol consumption trajectories, based on a cohort followed for 15 years, which can give meaning to the heterogeneity of existing results with the Big Five model. These authors suggest two risk profiles, the "Resilient" one, more vulnerable to social pressure for drinking, and the "Reserved" one, with higher risk for alcoholism. The first is characterized by high Agreeableness, Extroversion, and Openness, whereas the second is defined by high Conscientiousness and low Extraversion, Openness, and Agreeableness. High Extraversion also appeared related to BD in other longitudinal study (5).

In connection with the consumption expectations, it is interesting to examine the effects on the perceived personality related to intoxication as compared with the sober state. Using the Big Five personality model, it has been observed that binge drinkers report increases in Extraversion, and greater decreases in Neuroticism (anxiolytic effects) and Agreeableness (more aggressive) than non-binge drinkers, a pattern modulated by sex (36, 37). Four different drunk types have been noted (38), whose consideration in the future may complement the explanatory model of BD (**Table 1**).

Interventions Considering Personality Traits

There is no doubt that investing time and resources in promoting health at an early age, prior to the onset of consumption, has positive repercussions, including minimizing the pattern of BD. The alcohol selective prevention program "Preventure," a brief

personality-targeted intervention for youth, is an outstanding example of this strategy (45). This program covers three main components: psychoeducational, motivational interviewing, and cognitive behavioral. The intervention has been particularly effective in preventing the growth of BD in early adolescents of both sexes with high Sensation Seeking and Impulsivity and in girls with higher Anxiety sensitivity. This has been evidenced over 36-month follow-up in Australia (46), at a 24-month postintervention in England (47), and at a 12-month follow-up in the Netherlands (45) to mention only studies with longer follow-up periods.

Although our review is focused on personality, an overall explanatory model of BD must also incorporate attitudes, motives, expectancies, or metacognitions referring to consumption, since these are mediating variables in the relationships between personality and BD (17, 44), in addition to participating in the prediction of alcohol-related problems (23, 30). Binge drinkers, regardless of their personality characteristics, exhibit higher alcohol expectancies for social facilitation (31) and positive metacognitions (19) than regular moderate drinkers and abstainers. This is especially important in selective prevention, in which the restructuring of dysfunctional metacognitions (e.g., drinking alcohol to avoid negative judgments from others) may help in the control of drinking, while the establishment of adaptive emotional regulation strategies (16, 24) may increase the success of the interventions. As a harm reduction strategy, moreover, educating in protective patterns of drinking is effective in reducing the BD frequency in individuals with high Impulsivity and Sensation seeking (20).

Prevention should be initiated at an early school age and not limited to specific actions, since the general objective should be to promote the empowerment and integral health of young people. The inclusion of multiple elements to promote protective factors seems to be the best strategy to revert to healthier habits and a better quality of life in the short and long term. From this perspective, and for a greater success of these approaches, it is necessary to consider the personality characteristics that represent a vulnerability factor for the initiation and maintenance of BD.

LIMITATIONS AND FUTURE DIRECTIONS

There is great heterogeneity in the scales used for personality assessment, based on various theoretical models, which makes it difficult to compare the results of different studies. An effort is required to agree on a measurement instrument that integrates those dimensions or facets that represent the main risk factors in BD. We consider that the use of the SURP is very appropriate. Moreover, when it is complemented with the Big Five dimensions of Conscientiousness (for its relevance in health habits) and Extraversion, it could improve the information collected on personality. Furthermore, only a minority of articles has compared the scores obtained with normative data from their corresponding countries, or in the cases where these do not exist, making some sort of conversion to normative scores (z, T,…). That is, finding higher or lower scores of a certain dimension in BD with respect to another group does not always imply that these are values outside the normal population range.

The epidemiological characteristics of the samples, especially sex, age, and race, are rarely analyzed as factors of interaction with the personality traits associated with BD. Most studies collect this information merely as descriptive of the sample, analyze it independently, or only consider it as a control. It is essential to develop future works that explore the modulating effect of epidemiological variables on representative samples, since the studies that have done so have pointed out that the data are not generalizable to the entire population.

It is also required to consider and control for other variables that are known to influence the appearance and maintenance of BD when they are not the objective of the study, highlighting the presence of psychiatric symptomatology or mental disorders, stressful life events, and circadian rhythmicity. In relation to the latter, an adequate sleep (48) and a morning typology (49) are protective factors for heavy drinking and for extreme personality traits.

The development of longitudinal studies, a minority to date, is the only way to elucidate the specific weight of the personality traits in the initiation and maintenance of BD and/or relate problems, as well as the impact of BD practice in personality. At the same time, this would allow us to define the age with the greatest vulnerability and the best time for the implementation of prevention programs.

For an integral and explanatory perspective of BD, studies should integrate also biological and neurocognitive evaluations. BD is not a unitary phenomenon but consists of a combination of history, personality, and brain domains (5), and this is how it should be examined. Only this approach will help to delineate subgroups of risk for BD and to interpret different trajectories and consequences of its practice in the short, medium, and long term.

Finally, multicenter and multicountry studies will allow us to explore whether there are sociocultural differences in BD, and whether these require specific adaptations in both preventive and treatment approaches. The "Preventure" program, for example, has only been carried out in Anglo-Saxon countries and its development in a Mediterranean or Latin American country may lead to different effectiveness and may require some methodological adjustment.

AUTHOR CONTRIBUTIONS

AA and JFN collected the materials and resources needed for this review and wrote this article. DAF provided suggestions and revised each draft of the manuscript.

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Gender Differences in Risk Factors for Adolescent Binge Drinking and Implications for Intervention and Prevention

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Alcohol use, particularly binge drinking (BD), is a major public health concern among adolescents. Recent national data show that the gender gap in alcohol use is lessening, and BD among girls is rising. Considering the increase in BD among adolescent girls, as well as females' increased risk of experiencing more severe biopsychosocial negative effects and consequences from BD, the current review sought to examine gender differences in risk factors for BD. The review highlights gender differences in (1) developmental-related neurobiological vulnerability to BD, (2) psychiatric comorbidity and risk phenotypes for BD, and (3) social-related risk factors for BD among adolescents, as well as considerations for BD prevention and intervention. Most of the information gleaned thus far has come from preclinical research. However, it is expected that, with recent advances in clinical imaging technology, neurobiological effects observed in lower mammals will be confirmed in humans and *vice versa*. A synthesis of the literature highlights that males and females experience unique neurobiological paths of development, and although there is debate regarding the specific nature of these differences, literature suggests that these differences in turn influence gender differences in psychiatric comorbidity and risk for BD. For one, girls are more susceptible to stress, depression, and other internalizing behaviors and, in turn, these symptoms contribute to their risk for BD. On the other hand, males, given gender differences across the lifespan as well as gender differences in development, are driven by an externalizing phenotype for risk of BD, in part, due to unique paths of neurobiological development that occur across adolescence. With respect to social domains, although social and peer influences are important for both adolescent males and females, there are gender differences. For example, girls may be more sensitive to pressure from peers to fit in and impress others, while male gender role stereotypes regarding BD may be more of a risk factor for boys. Given these unique differences in male and female risk for BD, further research exploring risk factors, as well as tailoring intervention and prevention, is necessary. Although recent research has tailored substance use intervention to target males and females, more literature on gender considerations in treatment for prevention and intervention of BD in particular is warranted.

Keywords: adolescence, binge drinking, gender, intervention, comorbidity, prevention

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INTRODUCTION

Binge drinking (BD) is a major public health concern, and adolescents are particularly vulnerable to the biological and social consequences of BD compared to adults (1). Internationally, BD is more prevalent among adolescents aged 15–19 compared to all other adults aged 25 and older (2–6). For example, recent United States national data estimates that 17.7% of high school students (7) and 39% of college students (8) reported BD in the past month, with college students often consuming at least two to three times the definition of BD (9). Rates of BD in Europe and Australia are typically higher than in the U.S. For example, one study of 36 European countries found that 39% of 15- and 16-year-olds reported BD in the past month (10). More importantly, it is well established that an early onset of alcohol use is a strong predictor of future alcohol dependence (11, 12). Significantly, about half of individuals meeting life-time diagnostic criteria for an alcohol use disorder (AUD) do so by the age of 21, with two-thirds meeting criteria by the age of 25 (13–21).

While estimates have traditionally shown higher rates of BD in males, recent national data show that the gender gap in BD is lessening, with a concomitant increase in rates of alcohol use and BD among girls and women (17). In fact, some studies have found that girls are drinking as much, if not more, than their male peers, and girls are also initiating alcohol use earlier and engaging in more binge-like alcohol drinking, while these changes have not been seen among boys in recent decades (7, 17, 22–24). Due to these increasing rates of alcohol initiation and problems among girls, some efforts have been made to create gender-informed interventions and preventions in order to better target adolescent girls (24, 25).

It is also well known that girls are more vulnerable to the negative consequences from alcohol use and BD compared to boys. Across the lifespan, females are more likely to experience alcohol-related health problems at lower drinking rates compared to males, and are also more likely to experience more severe negative alcohol-related health and psychosocial consequences compared to males (26–29). In addition to vulnerability in adolescence, there are also important gender differences in the impact of adolescent BD on later functioning in adulthood. Notably, females are more likely to experience a more rapid and severe progression from BD to addiction, a phenomenon known as "telescoping" (26). Moreover, while boys who stop abusing alcohol after adolescence are similar to men without any history of alcohol abuse (30), girls who stop abusing alcohol after adolescence continue to differ from women without a history of alcohol abuse in areas of illegal drug use, antisocial behavior, and mental health problems (31). Although prevalence rates of AUD are lower in women compared to men, women with AUD are more likely to experience more negative alcohol-related consequences (31).

In the present review, we will first review some of the literature on gender differences in neurobiological risk factors that predispose an adolescent or emerging adult to engage in BD, given developmental differences between males and females (32, 33). We will also review gender differences in alcohol sensitivity as well as differences in reward neurocircuitry and neurobiological processes in learning and memory that explain differences in risk for BD and response to BD. We will then review some of the literature on gender differences in psychiatric comorbidity among adolescents and emerging adults and the association between this comorbidity and BD. This is especially relevant since 60% of substance-using adolescents have a comorbid psychiatric diagnosis (34). Next, we will review the role of gender in social/peer influences during adolescence and emerging adulthood and how this may influence binge-drinking behavior. Lastly, we summarize findings from existing prevention and intervention research on adolescent and emerging adult BD and important gender considerations in prevention and intervention.

METHOD

An extensive literature search was conducted using MEDLINE/PubMed and Academic Search Premier to identify peer-reviewed publications on adolescent and emerging adult BD published since 2000. There are various definitions for BD across the literature (1, 2, 35) and, thus, we included the literature that defined BD broadly as consuming a large alcohol quantity per drinking occasion (as defined by the WHO, NIAAA, and SAMHSA; 1). For instance, the NIAAA defines BD as consuming at least 4 or 5 (women or men, respectively) drinks in approximately 2 h and achieving a blood alcohol concentration (BAC) of at least 80 mg% (4). In general, all of these definitions include intoxication as a hallmark sign. Thus, we considered literature that defined BD by any of these definitions. We first conducted a broad search using terms for (1) BD, (2) adolescence or emerging adult, and (3) gender/sex to identify all articles that highlighted gender differences in BD. Articles that (1) did not focus on adolescents or emerging adults (age range 13–24); (2) did not consider gender/sex; and (3) did not pertain to BD as defined by either the NIAAA, WHO, or SAMHSA (as described earlier) were excluded. Furthermore, only articles that pertained to risk factors for BD, and not effects or consequences of BD, were selected. We reviewed only articles that reported on gender differences and pertained to (1) social influences, (2) neurobiological and biological aspects of BD risk, (3) psychiatric or mental health symptoms and BD risk, and (4) intervention and prevention for BD (see **Figure 1**). Annotated bibliographic searches of relevant review articles and/or books were also conducted.

RESULTS

Figure 1 presents results from the literature search. The initial search yielded a number of studies that focused on gender differences in adolescent BD regarding differential effects and consequences of BD across males and females [see Ref. (36–39) for reviews]. Furthermore, a number of studies reported on BD prevention and intervention, but few focused on gender differences in BD treatment. Therefore, in the sections that follow, we report on identified literature but also incorporate findings from other studies related to problem alcohol use in order to inform potential gender differences in these areas.

Neurobiological Processes and Risk for BD

Adolescence is a crucial stage of development during which addiction becomes a prominent public health concern (40–46).

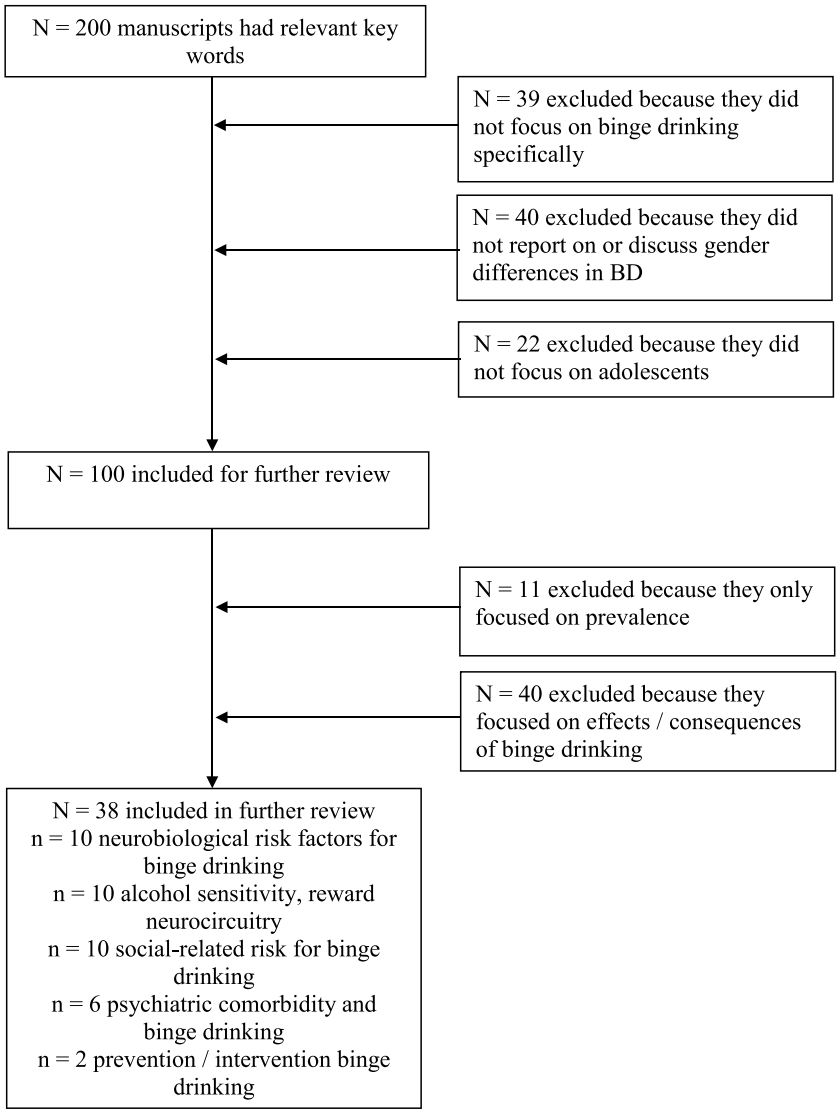

FIGURE 1 | Literature search results. Studies included in this count were specific to all criteria. Given limited studies, discussion also includes relevant studies that pertain to alcohol use and substance use more generally.

In the following section, we review literature on adolescents' unique vulnerability to BD. We first summarize evidence for the role of alcohol sensitivity and reward neurocircuitry in BD during adolescence and highlight gender differences in these processes. We then review the role of adolescent neurobehavioral development in BD as well as important gender differences in development that differentially influence males' and females' risk for BD (see **Table 1** for overview of studies and findings).

Sensitivity to Alcohol during Adolescence

Basic Research

The fact that binge ethanol drinking occurs mostly in adolescents and emerging adults is due, at least in part, to the fact that individuals are affected bi-phasically by ethanol in an age-dependent manner (66–69). More specifically, adolescents, compared to adults, show greater sensitivity to lower doses of alcohol, which are perceived as positive and rewarding (e.g., behavioral and autonomic activation), and lower sensitivity to higher doses of alcohol, which are perceived as aversive (e.g., motor ataxia) (44, 45, 70–74). It is believed that this bi-phasic sensitivity in turn not only increases adolescents' risk for BD but also puts adolescent binge drinkers at increased risk for developing alcohol dependence later in adulthood.

One system largely involved in alcohol sensitivity is the mesocorticolimbic system, which is also the reward neurocircuity system (see **Figure 2** for explanation of mesocorticolimbic system). Importantly, binge-like alcohol use leads to increases in mesolimbic dopamine and glutamate, which are associated with the development of alcohol dependence (75, 76). For example, animal studies have shown that adolescent binge-like alcohol

TABLE 1 | Overview of studies on gender differences in alcohol sensitivity, neurobiological development, and risk for internalizing and externalizing disorders.

Study	Sample	Binge drinking (BD) measure	Findings
Marco et al. (47)	28 M, 28 F Wistar adolescent rats (PND 0–46)	–	M: increased expression of endocannabinoid-associated genes in frontal cortex following early life stress F: decreased expression of endocannabinoid-associated genes in frontal cortex following early life stress
Koss et al. (48)	5 M, 8 F adolescent rats (PND 20, 35, 90)	–	Both M and F showed decrease in dentritic spines in mfPFC over 90 days postnatal (adulthood); F only showed decrease in basilar dentrites between puberty (P35) and adulthood (P90)
Raznahan et al. (49)	306 F, 312 M (aged 5–25)	–	Sexual dimorphic subcortical maturation F: reach earlier peak volume in striatum (age 12.1 vs. 14.7), thalamus (age 13.8 vs. 17.4) cortex (8 vs. 9.1) M: reach earlier peak volume in pallidum (age 7.7 vs. 9.5)
Blanton et al. (50)	40 F, 32 M community sample (aged 8–18)	–	F: smaller left amygdala (AMY) volume associated with better emotional control M: larger left AMY volume associated with better emotional control
Burghy et al. (51)	28 F, 29 M (age M = 18.44, SD = 0.19)	–	F only: early life stress (retrospective report) predicted increased cortisol levels and decreased AMY-vmPFC connectivity 14 years later F only: AMY-vmPFC connectivity associated with depressive symptoms
Shih et al. (52)	414 M, 402 F community sample (M = 15.2, SD = 0.29)	–	F: higher levels of total and interpersonal stress F: more likely to become depressed in response to stress
Shulman et al. (53)	4,052 F, 4,218 M (aged 10–25)	–	M: higher sensation seeking and lower impulse control vs. F
Adan et al. (54)	60 M, 80 F college students (aged 18–25, M = 21.33)	BD group: at least one past month BDE (30 M, 40 F)	M: binge drinkers characterized by higher sensation seeking F: binge drinkers characterized by higher neuroticism-anxiety
Barnes et al. (55)	9,168 F, 9,542 M 7th–12th graders (aged 12–18, M = 15.1)	Past-year frequency BDE	M stronger relationship between BD and delinquency vs. F
Kuntsche and Müller (56)	1,015 M, 639 F fifth to seventh grade students (aged 11–14, M = 12.5)	–	M: more likely to endorse alcohol enhancement motives F: more likely to endorse coping motives for drinking
Hussong et al. (57)	206 F, 233 M (232 children of alcoholics; T1 aged 10–16, M = 12.7)	Past-year frequency BDE	M only: externalizing symptoms related to increase BDE over 3 years
Chassin et al. (13)	236 M, 210 F (238 children of alcoholics, 208 controls; T1 aged 10–16, M = 13.22)	Past-year frequency BDE (BD groups based on onset and frequency: early-heavy *n* = 93, late-moderate *n* = 134, infrequent *n* = 43, non-BD *n* = 176)	M only: externalizing disorders and low depression related to early-heavy BD F only: depression related to infrequent BD (vs. non-BD)
McGue et al. (58)	Sample 1: 625 F, 607 M children of alcoholics Sample 2: 323 F twin pairs (201 MZ) 318 M twin pair (215 MZ)	–	Sample 1: Lifetime externalizing disorders higher in M vs. F children of alcoholics Sample 2: M only: Genetic factors underlying disinhibitory psychopathology related to increased risk of early alcohol use
Danielsson et al. (59)	578 M, 644 F seventh grade students (T1 age 13)	Past-year frequency BDE	M = F: seventh grade BD and smoking predicted ninth grade BD F only: heavy drinking linked to bullying and peer stress
Edwards et al. (60)	7,268 M, 6,709 F community cohort (age T1 M = 12.8, T2 M = 18.66)	AUDIT	F only: longitudinal increase in depressive symptoms between age 12–17 linked to increases in problem alcohol use at age 18
Needham (61)	5,738 F, 5,089 M (T1 age M = 15.3, SD = 1.6)	Past-year frequency BDE	M = F: longitudinal bidirectional relationship between depression and BD
Walsh et al. (62)	1,808 F NSA-R sample (aged 12–17, M = 14.5)	Past-year frequency BDE	In F sexual violence incidents linked to acute increase in BD around the time of the incident
Stevens et al. (63)	274 M, 104 F enrolled in SU treatment (age M = 15.75, SD = 1.03)	GAIN substance use assessment and diagnostic tool	F only: higher levels traumatic stress associated with more severe substance use problems

(*Continued*)

TABLE 1 | Continued

Study	Sample	Binge drinking (BD) measure	Findings
Foster et al. (31)	636 F community sample (aged 17–29)	DSM-III-R AUD, adolescent onset (AO) desisting *n* = 33, AO persisting *n* = 14, young adult (YA) onset *n* = 43, YA persisting *n* = 27	F: with adolescent-onset AUD greater psychopathology and psychosocial impairment F: with past adolescent AUD still showed impairment in adulthood despite "recovery"
Rohsenow et al. (64)	202 F, 200 M college students (aged 21–24, M = 21.4)	TLFB mean weekly drink quantity	M: lower sensitivity to alcohol effects vs. F based on scores on Self-Rating Effects of Alcohol form
Heath et al. (65)	2,818 F (190 genetic AUD risk), 1,766 M (182 genetic AUD risk), community sample	Maximum alcohol consumption/occasion	M: with genetic AUD risk lower alcohol sensitivity vs. M without AUD risk F: with genetic AUD risk reported more frequent BD vs. F without genetic AUD risk
Bell et al. (66)	12 F (7 peri-adolescent), 12 M (7 peri-adolescent) alcohol-preferring (P) rats (PND 30)	Ethanol intake	F: adolescents more ethanol intake vs. M adolescents M: adults more ethanol intake vs. F adults
Dhaher et al. (67)	Ethanol naïve high alcohol drinking (HAD-1 and HAD-2) rats (PND 21–24)	Ethanol intake, BD = ethanol licking binges	M > F: ethanol consumption and BD (ethanol licking binges) M HAD-2: consistent ethanol intake over 30 days vs. F HAD-2 increasing ethanol intake over 30 days
Schramm-Sapyta et al. (68)	144 M and F peri-adolescent CD Sprague-Dawley rats (PND 21)	Ethanol intake	M = F: no differences in ethanol-conditioned taste aversion

Only studies highlighting gender differences are presented. PND = postnatal days. BDE = binge drinking episodes, defined as 4/5 or more drinks for females/males per occasion.

exposure results in increased ethanol intake and preference later in adulthood as well as a prolonged ethanol-induced increase in mesocorticolimbic dopamine and tolerance to ethanol-induced increases in mesocorticolimbic glutamate during adulthood (77). This finding of altered dopaminergic activity in the adult mesocorticolimbic reward neurocircuit following adolescent binge-like ethanol exposure has been replicated many times (78–80). Furthermore, adolescents also show less sensitivity to withdrawal symptoms following BD, which through negative reinforcement may exacerbate binge-like behavior (81, 82). For example, there is evidence that adolescent binge ethanol exposure followed by protracted withdrawal resulted in a lower ethanol-withdrawal-associated decrease in mesocorticolimbic dopamine than that observed in similarly treated adult rats (83).

With respect to gender differences, there is evidence for differences in mesocorticolimbic activity, which may lead to differences in binge-like alcohol use. For example, stimulant-induced increases in nucleus accumbens dopamine are lower in female rodents compared with their male counterparts (91–93). Clinically, men show a greater mesolimbic dopamine response than women (27, 94), which in part demonstrates males' greater sensitivity to the rewarding effects of alcohol. The caudate nucleus, also called the dorsal striatum (caudate–putamen or CPU in rodents, **Figure 2**), mediates habit learning and perseverative behavior, both of which characterize loss-of-control drinking. Estradiol in the dorsal lateral striatum (lateral portions of the caudate nucleus) mediates, in part, stimulant-induced behavioral responses as well as escalation and reinstatement of drug taking behavior (27). These estradiol effects on stimulant-induced and -taking behavior were seen in ovariectomized female rats, but not male rats (91, 95). Importantly, progesterone treatment can reduce these estrogenic effects in female rats as well as reducing stimulant intake in women, but not men (96–98).

In addition to sensitivity and reward, the mesocorticolimbic system is also involved in learning and memory, which are dynamic processes that influence BD. Animal studies have shown unique sex differences in the neurobiological processes of learning and memory. In a study examining the acquisition of an operant response for sucrose, it was found that both adult and adolescent female rats acquired the response quicker than their male counterparts (99). Moreover, these authors reported that after 1 week of training, adolescent female rats responded more than adolescent male rats, whereas adult female and male rats did not differ in their number of responses or reinforcers. Exercise has been shown to decrease ethanol intake during adolescence and appears to have a greater beneficial effect in adult women vs. men (100, 101). In addition, exercise has been shown to facilitate adult neurogenesis in the parahippocampal region of the brain, which has also been implicated in enhanced learning and is disrupted by drugs of abuse including alcohol (102, 103). Thus, it is interesting to note that voluntary exercise during adolescence reduces ethanol intake and preference to a greater extent in female vs. male high ethanol-consuming C57BL/6J mice (104). This is particularly relevant since the hippocampus (HIPP) is vulnerable to ethanol-associated damage, with evidence that adolescents may be more sensitive to this effect than adults.

As noted above, estradiol activity in the lateral caudate nucleus mediates stimulant-induced and -taking behavior, which can be disrupted by progesterone treatment (27, 91). This is important since the caudate nucleus mediates habit formation and is implicated in later stages of the addiction/dependence cycle. Within the multiple memory systems and mesocorticolimbic reward

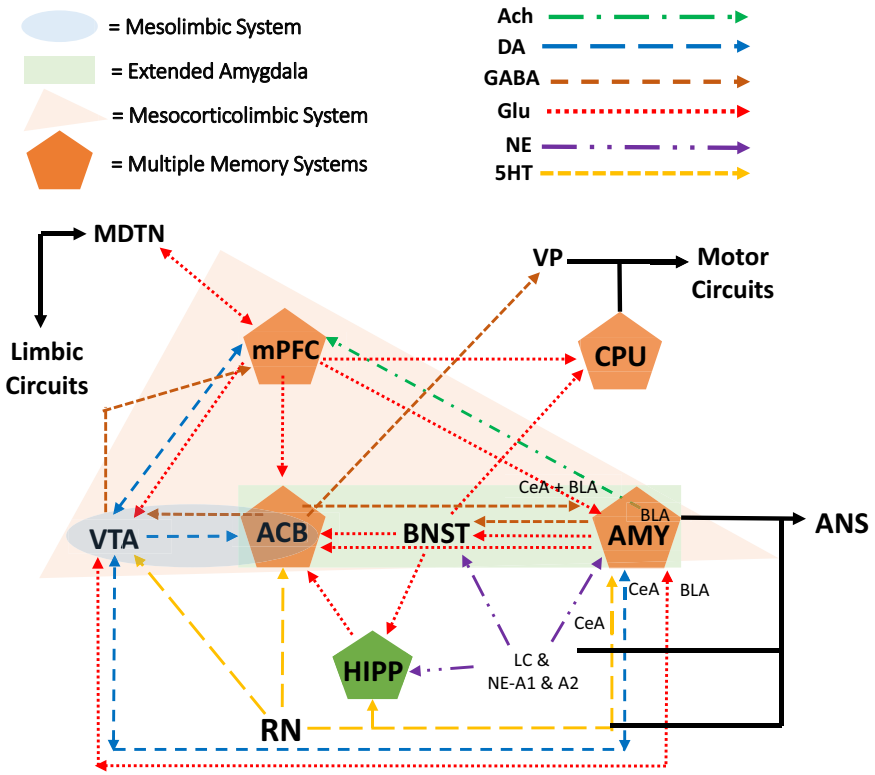

FIGURE 2 | The mesocorticolimbic dopamine reward neurocircuitry mediates orientation toward and acquisition of rewards (e.g., alcohol). At the core of the system are dopamine projections from the ventral tegmental area (VTA), of the midbrain/mesencephalon, to the nucleus accumbens (ACB; i.e., ventral striatum of the limbic circuit). As part of the reward neurocircuit, the nucleus ACB receives dopaminergic projections from the VTA and mediates the intoxicating and euphoric effects of ethanol as well as conditioning of these rewarding effects (i.e., learning and memory). The extended amygdala (AMY) includes nuclei of the AMY, the bed nucleus of the stria terminalis (BNST), and the nucleus ACB shell. The prefrontal cortex (PFC) has reciprocal projections with all of these brain regions while integrating this information with that of other brain regions as well (84, 85). Within the PFC, the medial portions are considered part of the limbic circuit (mPFC). This limbic circuit is associated with the Papez circuit that has been modified to include other brain regions as well (86). Essentially, (a) nuclei of the AMY receive sensory input from the periphery while sending input to the peripheral autonomic nervous system (ANS), (b) the AMY sends and receives information, in part through the stria terminalis, from the septum and hypothalamus, (c) the septum sends and receives information, in part through the fornix, from the hippocampus (HIPP), (d) the HIPP, in turn, sends projections to the hypothalamic mammillary bodies *via* the fornix, (e) the mammillary bodies, in turn, project to the anterior thalamus and mediodorsal thalamic nucleus, which (f) project to the cingulate gyrus and medial PFC (mPFC), and which (g) project back to the entorhinal cortex and HIPP [for recent discussions on the relationship with addiction see Ref. (70, 87–90); Pariyadath et al. (89); Renteria et al. (90)].

neurocircuitry, endocannabinoid activity modulates emotion and anxiety as well as learning and memory [see Ref. (105) for their roles in addiction]. Given a role for early life stress in vulnerability for addiction and associated behaviors (discussed later), it is noteworthy that the maternal deprivation model of this disorder leads to increased expression of several endocannabinoid-associated genes in the frontal cortex, but not the HIPP, of male rats; whereas the opposite is seen in female rats (47). Early life stress also affects neuroimmune activity, with this effect implicated in adolescent addiction vulnerability (106, 107). Thus, it is noteworthy that during adolescence female rats display greater microglial activation than their male counterparts, suggesting a more adaptive immune system in females during adolescence (107).

Clinical Research

While much of the research on alcohol sensitivity, reward, and learning has utilized animal models, evidence for adolescents' greater sensitivity to alcohol has also been shown in human studies. For example, one study examined college seniors over 4 years and found that hangover insensitivity was significantly correlated with intoxication insensitivity and future alcohol problems, even after controlling for demographic variables (64). With respect to gender differences, experimental studies have shown that that males will drink more alcohol when available and also reach higher BAC's compared to females (108). In humans, adolescent females appear to be more sensitive to the negative effects of alcohol and experience them at lower doses (65), while males may be more sensitive to the rewarding effects. These differences in effects emerge around the time of puberty and, thus, it is hypothesized that hormone-related changes across males and females are in part responsible (108). While this may be a protective factor for adolescent females (109), they are also more likely to progress more rapidly to addiction than males, due to "telescoping" (110). Still, research on gender differences in risk for

BD to dependence trajectories specifically is lacking. As we will discuss next, what may be more important are gender differences in neurobiological-related development that may differentially influence trajectories of risk for BD among males and females.

Gender Differences in Neurobehavioral Development

In addition to differences in alcohol sensitivity, reward circuitry, and neurobiological processes of learning and memory, there are also gender differences in development that may differentially influence males' and females' risk for BD. For example, females undergo many neurobiological changes earlier than males, and this is in part related to the earlier onset of puberty in females (111, 112). According to the dual systems model, although the striatum matures more quickly than the prefrontal cortex (PFC) in females, it is also suggested that females undergo more extensive maturation in the PFC compared to the striatum in both humans (49, 113) and animals (48, 114). This sex-specific trajectory highlights how females develop greater levels of inhibitory control and lower peak levels of sensation seeking compared to males (53).

In addition to gender differences related to inhibitory control and sensation seeking, the triadic model hypothesizes that there are also gender differences in the development of the amygdala (AMY) as well as differences in connectivity between the PFC and AMY, which influence emotional control (115). In particular, the triadic model posits that development in the AMY and connectivity between the AMY and the PFC may have a greater influence on emotional functioning in females compared to males (33, 50, 51). While, to date, few studies have longitudinally examined the effects of these preclinically assessed neurobiological processes on later risk for BD, we do know that emotion regulation, inhibitory control, and sensation seeking have been linked to BD (54). Thus, these unique neurobiological trajectories in development may manifest as different risk paths to BD among males and females. In the next section, we review literature on the link between psychiatric issues and BD, in particular highlighting distinct risk phenotypes across adolescent males and females.

Psychiatric Comorbidity and BD

Adolescence is a vulnerable period for developing psychiatric issues (116), in part due to developmental-related brain changes that occur during adolescence (117, 118). The link between psychiatric disorders and substance use is also well established, and it is estimated that up to 60% of adolescents with substance use disorders also meet criteria for another psychiatric disorder (119). Furthermore, the sex-specific neurobiological changes that occur during adolescent development put males and females at differential risk for internalizing and externalizing disorders. For example, gender differences in the development of the AMY as well as connections between the AMY and PFC may increase females' vulnerability to anxiety and depression (51), while males' higher peak levels of sensation seeking and slower development of impulse control leaves them more vulnerable to externalizing symptoms (53). Furthermore, gender differences in neurobiological development that occur during adolescence also lead to gender differences in vulnerability to stress and differences in how males and females respond to stress (120). In animal models, protracted stress leads to depressive-like behaviors in females but not males (121). In humans, interpersonal stress is more closely linked to cortisol stress response and internalizing symptoms in female compared to male adolescents (52). Taken together, this highlights how these differences in development and in turn risk for psychiatric issues may beget unique BD risk profiles for males and females.

Externalizing Disorders and BD

The link between externalizing symptoms (including behavioral disinhibition, impulsivity, sensation seeking, and defiant behaviors) and substance use has been well documented in the literature (21, 122). As discussed previously, males consistently exhibit higher levels of sensation seeking and behavioral disinhibition throughout development, while females show greater inhibitory control (53). Thus, this externalizing risk phenotype for substance use appears to be more prominent in adolescent boys compared to girls (21). For example, in a recent study of college students, male binge drinkers were characterized by their higher scores on impulsivity and sensation seeking compared to non-BD males, and this pattern was not seen in females (54). Another study also found stronger associations between delinquency and BD in males only (55). Adolescent males are also more likely to report drinking for positive reinforcing effects as well as sensation and risk seeking (26, 56).

There is also evidence that environmental and genetic origins underlying associations between externalizing symptoms and substance use differ by gender. For example, one study found externalizing symptoms mediated the relationship between problematic alcohol use and parental alcoholism in males, but not in females (57). In another study of children of alcoholics, early BD was related to externalizing disorders in boys, but not in girls (13). In another similar study examining children of alcoholics, genetic factors associated with disinhibition and externalizing symptoms were predictive of early drinking for boys only; for girls in the study, environmental risk factors were more closely linked to alcohol initiation (58). Thus, given adolescent males' higher levels of sensation seeking and lower inhibitory control, and evidence for males' unique vulnerability to genetic factors underlying the link between externalizing symptoms and BD, it is not surprising that this externalizing risk phenotype for BD and other problem alcohol use is more prominent in males.

Internalizing Disorders and BD

Internalizing symptoms, including depression and anxiety, have also been linked to BD (54). As explained above, there are important gender differences in risk for developing internalizing disorders that occur with pubertal development, with girls being twice as likely to develop anxiety and depression compared to boys (117). In addition to the higher rates of internalizing disorders in females, females are also more vulnerable to stress compared to boys (120). Even in animal studies, adolescent female rats exhibited depressive-like behavior following stress, while male rats did not experience depressive-like symptoms (52).

As such, in contrast to males, females' substance use risk profile is better characterized by internalizing symptoms, such as anxiety, depression, stress vulnerability, and other negative

mood symptoms. For example, among a study of college students, female binge drinkers were characterized by higher scores on neuroticism-anxiety compared to non-BD females, while male binge drinkers were better categorized by traits related to sensation seeking and impulse control (54). In addition to females' heightened vulnerability to stress, females are even more likely to engage in BD in response to stress (123). For example, one Swedish study found that peer bullying and other risk factors had a greater effect on drinking in females than in males (59). Similarly, adolescent girls who abuse alcohol are more likely to have experienced a high level of stressful life events and exhibit post-traumatic stress symptoms, but this is not seen in boys (26).

Females' higher vulnerability for internalizing disorders also increases their risk for addiction, in part, due to self-medicating tendencies (28). For example, one study found that among females only, greater increases in depression symptoms were also linked to greater increases in problem alcohol use and BD over time (60). Similarly, other studies have shown longitudinal bidirectional relationships between BD and depressive symptoms across adolescence that are particularly strong for females (61). Moreover, among females who began drinking in adolescence, those who continued drinking in adulthood showed high levels of depression during adolescence relative to those who stopped abusing alcohol (31). In addition to females' greater vulnerability to stress and internalizing symptoms, females may also be more prone to BD following trauma.

Trauma and BD

Exposure to potentially traumatic events—such as physical assault or abuse, sexual assault or abuse, and witnessed violence in the home or community—is common in adolescence, with approximately two-thirds of youth reporting exposure to one or more events (124, 125). Trauma exposure has been linked to increased risk of BD and problematic alcohol use, with evidence indicating higher rates of BD among adolescents exposed to childhood maltreatment (126) and greater risk for problematic alcohol use among adolescents exposed to assault and other forms of violence (127). In addition, adolescents exposed to multiple types of victimization are more likely to experience more alcohol abuse (128) than peers who experience fewer victimization types. Hazardous drinking can also increase risk for future trauma and victimization (129, 130). BD also can co-occur with traumatic experiences, in particular, sexual victimization (i.e., drug/alcohol-facilitated and incapacitated sexual assault).

While both male and female adolescents experience sexual victimization, adolescent girls are at heightened vulnerability to sexual assault (131). A recent study of adolescent girls aged 12–17 found that girls who reported drug/alcohol-facilitated and incapacitated sexual assault were more likely to report past-year alcohol abuse than girls with other types of assault or no assault (132). Similarly, sexual victimization predicted acute increases in BD in a national sample of adolescent girls, although victimization did not predict overall escalation of BD over time (62).

Evidence suggests that girls may also be more likely to engage in BD and experience more negative psychological sequelae as a result of trauma experience compared to boys (63). There is evidence that child abuse and neglect predicts later problem drinking for girls, but not boys (133), and that girls (but not boys) who start abusing alcohol during adolescence are more likely to have experienced early traumatic stress (31). Taken together, in addition to females' increased vulnerability to stress and increased likelihood of BD in response to acute stress, females are also more vulnerable to binge drink in response to more prolonged stress as a result of trauma.

Taken together, this recent research suggests that male and female adolescents exhibit unique BD risk phenotypes: while boys exhibit the traditional externalizing risk phenotype, girls' risk phenotype is characterized by "internalizing" symptoms, such as high stress reactivity, and the presence of mood disorders and internalizing symptoms (54). These gender differences are related to gender differences in adolescent neural development and are also consistent with findings that adolescent males drink to enhance positive mood states while females drink to avoid negative mood states (134). These findings also highlight the importance of considering trauma in BD, and furthermore, gender differences in males and females' vulnerability to BD following trauma and stress. Given girls' increased vulnerability to stress and higher stress reactivity, it is not surprising that the link between trauma exposure and BD is particularly salient in girls.

Social Influences on BD in Adolescence and Emerging Adulthood

From a social and environmental perspective, across many cultures, adolescence is considered a period of self-exploration and experimentation when individuals start to gain more independence and autonomy from adult caregivers (**Table 2**). First, this increased autonomy—in combination with developmental-related changes in reward-seeking and decision-making (43–45, 112)—puts adolescents in a vulnerable position of experimentation with less supervision which can result in risky behaviors, such as BD. Second, peer relationships become more important and social influences are prominent during adolescence (135), and are also a key risk factor for alcohol use (136). A number of social-related influences, including social norms, peer pressure, and peer affiliation, have all been shown to influence BD and other alcohol use behaviors (137–139).

With respect to gender differences on the impact of social influence on behavior, there is even a link between sex-specific brain development and social behavior (109). For one, there is some evidence that girls are more sensitive and vulnerable to social influences, such as peer pressure and peer affiliation compared to boys (24). Association with other drinking peers is particularly influential on BD (140), and some studies have found that drinking peers are a greater risk for BD among females compared to males (59, 141). For example, one study of Brazilian high school students found that peer affiliation was more closely related to BD for girls compared to boys; more specifically, girls who reported being closer to school-based friends vs. family or church friends were more likely to binge drink, and this relationship was not seen among males (142). Furthermore, some studies have shown that adolescent girls are more likely to report drinking in order to obtain peer approval compared to boys (24).

Social norms regarding drinking, or rather, individuals' perceptions of peers and others' BD, also influence one's own

TABLE 2 | Overview of studies highlighting gender differences in social influences on binge drinking (BD) among adolescents.

Study	Sample	BD measure	Findings
Jalling et al. (140)	85 F, 77 M high school students (aged 12–18, M = 15.09)	AUDIT; frequency BDE	M = F: perceptions of peer BD influenced BD M: parent-report externalizing behavior predicted BD F: social problems predicted BD
Brooks-Russell et al. (141)	1,212 F, 950 M 10th and 11th grade students	Past month frequency alcohol use	M > F: descriptive drinking norms mediated relationship b/w drinking with peers and alcohol use
Zarzar et al. (142)	437 M, 454 F public and private school students (aged 15–19)	Frequency BDE	F only: BD associated with being "close with" school peers vs. church peers (friendship network)
Franca et al. (143)	570 F, 156 M college students (age M = 21.19)	Frequency BDE	M = F: BD associated with overestimation of peer drinking M > F: BD frequency
Griffin et al. (144)	1060 F, 888 M seventh grade students (*n* = 3 schools)	Alcohol quantity/occasion	M > F: reported friends with pro-drinking attitudes M < F: peer drinking norms (i.e., F reported higher peer drink norms)
Elek et al. (145)	4,030 M and F seventh grade students	Past month quantity and frequency alcohol use	Relationship b/w personal drinking norms and substance use stronger for M vs. F M vs. F: descriptive drinking norms stronger predictor of lifetime alcohol use for F vs. M
Hong et al. (146)	731 M, 875 F ninth grade students	Past 2-week frequency BDE	7th grade descriptive norms greater effect on predicting ninth grade BD in M vs. F
Lewis and Neighbors (147)	115 M, 111 F college students (age M = 19.85, SD = 2.39)	Past 3-month frequency BDE	M = F: overestimate same-sex peers' drinking F > M: same-sex drinking norms stronger relationship with BD in F vs. M
De Visser and McConnell (148)	503 F, 228 M college students (aged 18–25, M = 19.8)	Past month frequency BDE	M > F: intentions of getting drunk F: beliefs in traditional gender roles associated with less BD and drinking intentions M: no relationship between gender role beliefs and alcohol use
Clinkinbeard and Barnum (149)	6,265 F, 4459 M college students (aged 18–25, M = 22.03)	Past 2-week frequency BDE	M > F: BD frequency M only: endorsement of feminine qualities associated with less BD and alcohol-related consequences M = F: endorsement of dominant masculine traits associated with more frequent BD and alcohol-related consequences F only: general masculine traits associated with less alcohol-related consequences
Young et al. (150)	42 F college students (aged 18–22)	Past 2-week frequency BDE	All F reported pressure to BD in order to "impress" male peers
Vetter-O'Hagen, et al. (151)	32 M and F Sprague-Dawley rats (PND 26)	Ethanol intake	M > F: M consumed more ethanol relative to body weight M < F: M less sensitive to aversive alcohol effects when in presence of peer (i.e., social context)

Only studies highlighting gender differences are presented. BDE = binge drinking episodes, defined as 4/5 or more drinks for females/males per occasion.

drinking behavior. Descriptive norms refer to beliefs about the prevalence of BD among peers while injunctive norms pertain to the perceived social pressure to conform and engage in BD with other peers (137). Social drinking norms are largely dependent on cultural context, and although the majority of studies have examined social drinking norms using US college samples (137), there are some studies that have examined this phenomenon in other areas across Europe (18, 143, 152, 153). There is a pattern across findings that boys are more likely to endorse more permissive or pro-drinking norms (injunctive norms) and perceive higher prevalence rates of BD (descriptive norms) compared to girls (137, 144). However, findings are mixed as to the influence of social norms on actual BD, with some evidence that girls are more influenced by social norms compared to boys (145), and other evidence that social norms are more influential on boys' BD (146). Thus, further research regarding differential influences of peer norms on BD is warranted.

Along the same lines as drinking norms, gender norms and gender stereotypes are also important to consider in BD (147, 154, 155). Across cultures, there is a double standard for drinking, such that among males, BD is considered more socially acceptable and masculine, while females are often more likely to be judged negatively for BD, as it is seen as less feminine (148, 156). Thus in this way, gender stereotypes may reinforce and perpetuate BD for males (148, 156), while for females, the negative outlook of BD may be a protective factor against BD (149, 156). Still, another study of college females found that females who engaged in more frequent BD did so as a means to feel more equal to their male peers and as a way to impress their male peers (150). Thus, this largely depends on one's identification with gender roles as well as their motives for BD.

Animal literature has also shown sex differences in adolescent social drinking behavior. Among a study of adolescent Sprague-Dawley rats, adolescent males consumed more ethanol

than females when they were in the presence of other peers, and furthermore, males were less sensitive to ethanol's aversive properties when in the presence of a peer (151). Similarly, in another study of adolescent rats, males consumed more ethanol when in social situations compared to when alone, while females consumed more ethanol when alone; however, there were differential effects across females based on social anxiety-like behavior (157). Female rats with high levels of social anxiety-like behavior had higher ethanol intake in social vs. isolated situations. These findings from animal models (44, 70, 78, 158) suggest that social situations and influences may be more influential on males' BD behavior. Taken together, these differences in social influences are likely to influence drinking behavior and, therefore, should be addressed in prevention and intervention, and in fact recent research has focused on gender-specific interventions for girls that are based on social learning theory, which is discussed below (see section below; see also sections for sex differences in neurobiological processes of learning and memory).

Gender Considerations in BD Prevention and Intervention

While there is extensive literature on treating problem alcohol use and AUDs in adults and adolescents, less research has focused on the importance of treating BD in adolescents. One issue is that due to a lack of discrepancy in the literature over BD vs. other alcohol-related problems, treatment literature often does not differentiate target populations, which is important since binge drinkers are a unique typology (1). Psychosocial interventions are recommended as the first-line treatment for alcohol and substance use disorders more generally (34), and cognitive-behavioral skills training and motivational enhancement therapy are the recommended evidence-based strategies [as the most promising evidence-based strategies to target problem drinking (159)]. A few recent literature reviews have summarized existing evidence of the effectiveness of randomized controlled trials of these treatments for binge and other problem drinking for adolescents and college students [see Ref. (160–164) for reviews]. Briefly, interventions that incorporate skills-building, motivational, and personalized normative feedback components have been successful in reducing BD and other problem alcohol use. One limitation noted in these literature reviews and based on the present literature search is the lack of studies' reports of findings across gender. Thus, in the next sections, we highlight gender considerations in BD intervention and prevention based on findings from the literature discussed previously and other important findings for gender considerations in substance use treatment more broadly (see **Table 3** for overview of studies and findings).

Tailoring Treatment

Despite advances in tailoring treatments to address comorbid psychiatric and substance use issues (34), less research has focused on developing gender-specific treatment approaches or identifying gender differences in evidence-based treatments for substance use (176, 177). Over the past few decades, there have been efforts to develop gender-specific treatment programs and focus on issues among adult women; however, less research has focused on adolescent girls in particular (177, 178). Furthermore, many studies do not assess for or report on gender differences in treatment effectiveness (177, 178), and as noted previously, few studies focus intervention for BD specifically. Thus, in the following section, we highlight findings from literature on adolescent substance use treatment more broadly and discuss the potential utility of these findings to inform treatment considerations for BD.

There have been some substance use programs developed to target female adolescents in particular, and these gender-specific programs have been based on social learning and behavior theories (165, 177), which is consistent with the previous discussion that adolescent girls may be more vulnerable to social influences on BD (24). For example, programs focused on social skills training, including teaching assertiveness skills and refusal skills to combat peer pressure, how to develop positive peer networks, and challenge perceptions of the prevalence of alcohol use among peers (e.g., "everyone's doing it"), are most effective in reducing adolescent girls' problem alcohol use (166, 177). Furthermore, small group settings may be particularly beneficial for girls, as girls may benefit more from sharing experiences and expressing opinions with others (179). In addition, given girls' proneness to internalizing symptoms and heightened sensitivity to stress, programs focusing on teaching coping skills and stress and tension reduction techniques may be particularly beneficial (167). For example, the coping skills component of CBT-based treatments are likely particularly beneficial for girls as this may help them to learn healthy and adaptive coping skills to manage stress, negative mood, and other internalizing symptoms that trigger BD.

For boys, given their externalizing risk phenotype, they may benefit more from contingency management techniques that reinforce and reward prosocial behaviors as well as expectancy challenge techniques that challenge their beliefs about the positive effects of drinking (168). Furthermore, the personalized feedback component of MET may be particularly beneficial for boys, given that adolescent boys may be more likely to be "in competition" with or trying to keep up with male peers, given that heavy drinking is seen as more socially acceptable for males and sometimes encouraged, such as in college settings (147). Adolescent boys are more prone to overestimate their peers' drinking and, thus, challenging these perceptions, such as using personalized feedback, could influence males' behavior (155). In addition, although gender differences in medication treatment effectiveness among adolescents are unknown (180), among adults, men have better treatment outcomes to pharmacologic treatment for alcohol use than women (181–183). Thus, if these gender differences are similar in adolescents, adolescent males may particularly benefit from pharmacological treatment compared to females.

With respect to gender and parental involvement in treatment, findings are mixed, with some evidence showing more effectiveness of parent involvement in treatment for girls (167) and others showing more effectiveness in boys (169). Among adolescents in residential treatment for substance use, parental involvement in treatment had a significant effect on abstinence at 6-month post-treatment status among boys only; however, treatment characteristics were unknown (169). It may be that the type of parental involvement and family support targeted in treatment should be gender-specific. For example, addressing discipline and

TABLE 3 | Overview of studies highlighting gender differences in substance use prevention and intervention.

Study	Sample	Binge drinking (BD) measure	Intervention	Main finding
Todd and Mullan (165)	122 F college students (aged 17–25, M = 19.0)	Past 2-week BDE frequency	Mere measurement model (MME, *n* = 40) vs. prototype willingness model (PWM, *n* = 40) vs. control (*n* = 40)	MME group less alcohol vs. control group PWM no effect on BD
Longshore et al. (166)	608 F, 774 M seventh graders (T1)/ninth graders (T2)	Weekly alcohol use	Project ALERT Plus school-based prevention program (*n* = 370) vs. ALERT (*n* = 457) vs. control (*n* = 556)	F: ALERT Plus group decrease in weekly alcohol use at T2 vs. control group M: no difference across ALERT Plus or ALERT vs. control in alcohol use at T2
Schinke et al. (167)	202 daughter–mother dyads community sample (age M = 12.2, SD = 0.95)	Alcohol use frequency in past week, month, year	Mother–daughter computer-based intervention vs. control	Intervention group showed improved alcohol-refusal skills, healthier beliefs about drinking, increased self-efficacy to avoid drinking Intervention group less alcohol use over past week, month, and year
Dunn et al. (168)	19 F, 19 M college students (aged 18–28, M = 21.03)	TLFB 30-day alcohol quantity and frequency	Alcohol expectancy challenge pre and post test	M: decreased alcohol use 30 days following intervention F: no change in alcohol use M only: showed changes in expectancy activation
Hsieh and Hollister (169)	1,462 M, 855 F enrolled in SU treatment as part of Comprehensive Assessment and Treatment Outcome Research (CATOR) sample (aged 12–19)	Measurement of abstinence at follow-up	Non-specific 12-step-based interventions from 24 different residential treatment programs part of CATOR	F: better aftercare and self-help group attendance at 6-month follow-up; more likely to be abstinent at 6-month follow-up M: parental involvement linked to better treatment outcomes
D'Amico (170)	693 M, 813 F middle school students (aged 11–14, M = 12.0)	Past month frequency BDE	–	F: stronger interest in alcohol prevention services M = F past month BDE related to lower intentions to use alcohol prevention services
Stevens et al. (171)	941 M, 266 F from 7 SU treatment programs (age M = 15.75)	Substance frequency and problem index	Non-specific drug treatment programs (*n* = 4 outpatient, 3 residential) across US	F more severe SU and comorbid MH diagnoses at intake M faster rate of change in SU across treatment
Hawke et al. (172)	145 F, 301 M post-SU treatment (aged 12–19)	–	Non-specific "therapeutic community" residential SU treatments across Canada/US	F > M: experience physical and sexual abuse pre and post-treatment M > F: criminal involvement post-treatment
Farabee et al. (173)	805 M, 362 F enrolled in SU treatment as part of Drug Abuse Treatment Outcome Studies for Adolescents sample (aged 11–18, M = 15.7)	–	Non-specific U.S. community-based SU treatment programs (*n* = 6 short-term inpatient, *n* = 8 residential, *n* = 9 outpatient)	M: more likely to enter drug treatment under criminal justice system
Grella et al. (174)	684 M, 308 F enrolled in SU treatment (aged 1–18, M = 15.7)	DSM-III-R AUD criteria	Non-specific U.S. community-based SU treatment programs (*n* = 6 short-term inpatient, *n* = 8 residential, *n* = 9 outpatient)	M = F: adolescents with comorbid disorders more likely to meet criteria for AUD and earlier alcohol initiation vs. adolescents without comorbid diagnoses
Godley et al. (175)	1,550 M, 591 F enrolled in SU treatment (75% aged 15–17)	% days abstinent from alcohol over 90 days	Adolescent community reinforcement approach across 33 U.S. sites	M > F: treatment satisfaction F: higher% days abstinent and more likely to be in recovery at 6-month follow-up M and F: equal gains in recovery

Only studies highlighting gender differences are presented. BDE = binge drinking episodes, defined as 4/5 or more drinks for females/males per occasion.

rewarding and reinforcing prosocial behaviors may be important for boys given their externalizing risk profile, while for girls, better communication and emotional understanding and support might better target their internalizing risk profile.

Gender Differences in Seeking Treatment

There are also important gender differences in treatment seeking. In 2008, only 30% of adolescents who sought substance use treatment were girls (35); however, one study found that girls reported higher intentions to seek treatment for alcohol-related problems (170). One reason for this could be related to treatment referrals. Among adolescents, many substance use treatment referrals come from the juvenile justice system (171). Importantly, boys are more likely to get referred for substance use treatment due to a legal issue (171, 172) or to enter treatment under criminal justice supervision (171, 173). Thus, girls are often not identified as early as boys for needing treatment since the criminal justice system is more likely to identify boys. Girls may be more likely

to get referred for treatment or identified from another issue in which BD may be secondary. For example, females seeking substance use treatment in general are twice as likely to be diagnosed with depression (174). Still, girls entering treatment have more severe alcohol problems and higher rates of mental health problems, sexual abuse (171), general health problems (63) and family-related stress (169), while males have more school and legal problems [see Ref. (175) for discussion]. Therefore, girls may also have more severe problems before being identified for treatment which could be detrimental to treatment success. In addition, while not studied in adolescents, among adults, women are less likely to seek treatment due to social stigma, and thus, girls may be less likely to seek treatment due to social stigma as well (28). Due to these differences, further work may need to be done to train and educate health care providers to more effectively screen for and identify BD and other substance use problems in adolescents (184).

Treatment Outcomes

There have been mixed findings on treatment outcomes for alcohol and substance use treatment among adolescents. There is some evidence that boys were more likely to become non-drinkers compared to girls following non-specific alcohol use treatment (185), but another study found that girls were more likely to become non-drinkers compared to boys (171). However, one limitation is that these results are based on non-specific treatment across multiple treatment sites (171), thus limiting understanding of specific factors influencing results. One study using data from multiple treatment sites implementing adolescent community reinforcement approach (175) showed similar change rates in substance use problems across boys and girls in treatment but unique course of treatment. Specifically, boys showed quicker improvement in mental health symptoms while girls had more abstinent days from alcohol and were more likely to be in recovery at 6-month follow-up (175). There is also evidence that girls are more likely to utilize social resources and attend after-care and self-help groups such as Alcoholics Anonymous (186), which may lead to better long-term treatment outcomes (169). One consistent finding is that across all adolescents, peer affiliation, school engagement, and parental supervision influence successful treatment in changing adolescents in treatment from binge drinkers to non-binge drinkers (175). Taken together, these mixed findings emphasize the need for further research to determine treatment components that contribute to potential gender differences in outcomes (24, 25). Furthermore, these findings do not address BD in particular, and thus, it is unknown whether these considerations also apply in BD treatment.

Based on the literature review, it is clear that adolescents are a unique, vulnerable population at risk for BD, and that there are important gender differences to consider in treatment. While literature on risk factors and consequences of BD in particular has increased, there is still a gap in the literature on unique considerations in prevention and intervention techniques for BD, as well as in how to effectively target unique differences in psychiatric comorbidity and risks across girls and boy in treatment.

CONCLUSION

The review sought to highlight gender differences in risk for BD, focusing on gender differences in (1) adolescent neurobiological development, (2) psychiatric symptoms and the relationship between psychiatric disorders and BD, and (3) social-related risk factors in BD, as well as considerations of these gender differences in BD prevention and intervention. The literature highlights unique vulnerabilities for BD among girls and boys. Developmentally, there are unique risks among boys and girls in relation to BD due to differences in rates of neurobiological changes as well as gender differences in alcohol sensitivity that influence risk for BD. Furthermore, many of these sex-specific neurobiological changes that occur during adolescence also influence differential risk for psychiatric issues among males and females which also influence risk for BD. Notably, while males may be more drawn to BD due to higher levels of sensation seeking and lower inhibitory control, females may be more prone to BD due to their heightened stress reactivity and vulnerability to internalizing symptoms. With respect to social development in adolescence, while development of peer relationships is important for both girls and boys during this developmental period, adolescent girls in particular may be more vulnerable to BD due to social influences. For boys, while peer influence may not be as strong, boys may be at greater risk for BD due to the social gender role norms that it is more socially acceptable and even can be rewarding for boys to drink in excess. These social norms may in turn actually serve as a protective factor in girls as BD does not necessarily align with the feminine stereotype.

These differential risk factors in turn provide important considerations for targeting BD intervention and prevention for females and males. Females may benefit from intervention and prevention that focuses on coping skills training and stress reduction, while males may benefit more from impulse control training and engagement in prosocial activities that fulfill the need for sensation seeking. Regarding social risk factors, while both male and female adolescents would benefit from social skills training, challenging social norms may be more effective for boys while assertiveness skills may be more effective for girls in preventing BD.

FUTURE DIRECTIONS

This systematic review highlights two important areas that are in need of further consideration in the literature. The first area is in regard to the necessity of further research on gender-specific risk factors for BD in order to better target at-risk adolescents and also inform prevention for BD. Extensive literature has identified gender differences in the effects of BD on biopsychosocial functioning in adolescents; however, less research has identified risk factors for BD.

There is also extensive literature on theories of adolescent neurobiological development that explain adolescents' heightened risk for engaging in risk-taking and substance use more generally; however, literature on risk for BD vs. other substance use is lacking. Given evidence that BD is a unique alcohol use typology, more research understanding different mechanisms in

the risk process for BD vs. other problem alcohol use vs. other substance use is warranted. Furthermore, given that BD is a hazardous, yet prevalent, developmental phenomenon, more research is needed to better target adolescents that are at risk of developing more severe alcohol use or substance use problems. For example, literature has highlighted the phenomenon of telescoping in women; however, more research on adolescent females and BD is needed.

The second area is the necessity of further research on gender differences in treating and preventing BD among adolescents. For one, many of the randomized controlled trials of BD interventions have focused on college populations, which are a unique group. More research on other adolescent samples, such as younger adolescents, as well as non-college older adolescents, is needed. More importantly, few studies report treatment effects by gender, thus, it is unknown whether there are gender differences in the effectiveness of BD treatment or whether there are gender differences in treatment course or outcomes. Given the increase in BD among adolescent females, as well as the more deleterious effects of alcohol on females, more research in this area is warranted.

AUTHOR CONTRIBUTIONS

AD: manuscript concept, writing content across all sections, editing all sections, and references. RB: writing content for introduction, biological developmental risk section, and editing content. ZA: writing content for trauma and binge drinking section, and intervention section. LH: manuscript concept, writing content for biological developmental risk section, editing content across all sections.

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Binge Eating, But Not Other Disordered Eating Symptoms, Is a Significant Contributor of Binge Drinking Severity: Findings from a Cross-Sectional Study among French Students

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Many studies have suggested the co-occurrence of eating disorders and alcohol use disorders but in which extent binge eating (BE) and other disordered eating symptoms (DES) are associated with the severity of binge drinking (BD) remains unknown. We conducted a online cross-sectional study among 1,872 French students. Participants were asked their age, gender, tobacco and cannabis use status. They completed the Alcohol Use Questionnaire (AUQ), Eating Disorder Examination Questionnaire (EDE-Q), and UPPS impulsive behavior questionnaire. BD score was calculated using the AUQ. Three items of the EDE-Q were used to construct a BE score. The predictors of the BD score were determined using a linear regression model. Our results showed that the BE score was correlated with the BD score ($\beta_0 = 0.051 \pm 0.022$; $p = 0.019$), but no other DES was associated with BD, including purging behaviors. The severity of BD was also correlated with younger age, male gender, tobacco and cannabis use, and with the 'positive urgency,' 'premeditation,' and 'sensation seeking' UPPS subscores (R^2 of the model: 25%). Within DES, BE appeared as an independent determinant of the BD severity. This is in line with the recent hypothesis that BE is not a subtype of DES, but more a general vulnerability factor of emotional dysregulation, which could be shared by different behavioral and addictive disorders.

Keywords: binge drinking, binge eating, binge-eating disorder, alcohol drinking, adolescent

INTRODUCTION

Alcohol use disorders (AUDs) (alcohol abuse and addiction) often co-occur with eating disorders. Bulimia nervosa and bulimic behaviors, binge eating (BE), purging, anorexia nervosa and atypical eating disorders have been associated with AUDs in women in a meta-analysis study (Gadalla and Piran, 2007; Baker et al., 2010; Root et al., 2010).

Binge drinking (BD) consists of episodic heavy alcohol drinking, and is often associated with drunkenness-oriented alcohol use[1]. Similarly, BE has been defined in the DSM-5 as abnormal eating episodes, which comprise eating much more rapidly or much larger amounts of food than normal, eating alone because of being embarrassed by how much one is eating, and feeling disgusted with oneself, depressed, or guilty after overeating.

Common cognitive and behavioral features have been described, and common integrative models have been proposed, with regard to BD and BE (Ferriter and Ray, 2011). BD and BE may share several features, such as repetitive engagement in the behavior despite evidence negative consequences (physical problems and poor academic performance), personality correlate such as neuroticism, and affected characteristics such as elevated levels of negative affect (impulsivity, anxiety, and depression). Concerning the common explanatory models of BD and BE, existing research proposed several key models such as the basic functional model, the motivational model, the expectancies model and the craving model (Ferriter and Ray, 2011).

Nevertheless, the possible interrelationships between BD and BE have only started to be explored. A couple of previous studies found frequent prevalence association between BE and BD, especially in women (Luce et al., 2007; Khaylis et al., 2009). However, though a characterized BE disorder has been defined by the DSM-5, BD remains a very heterogeneous set of drinking behaviors, with multiple and sometimes-questioned official definitions (Courtney and Polich, 2009). In many epidemiological studies, BD is frequently investigated by delineating populations using a cut-off drinking threshold (Courtney and Polich, 2009), which mixes BD subjects into a same group, and makes hard to address severity factors. For example, according to the World Health Organization (WHO), BD is defined as consuming at least 60 g of alcohol per drinking episode but some subjects drink at levels far beyond this binge threshold making difficult the study of severity aspects. That is why some authors have proposed using BD severity scores (Townshend and Duka, 2005). The BD score founded on patterns of drinking, rather than only quantities of alcohol consumed, may be more relevant of BD behavior.

In a more than 1800-subject sample of French students, we scored both BE and BD, as well as other DES, and we analyzed in which extent the BD score was determined by the scores of BE and other DES. It has never been assessed whether BE, as well as other disordered eating symptoms (DES), were associated with BD, not in terms of co-occurrence frequency, but as a specific severity factor of BD. In addition, since impulsivity has been consistently linked to the development and expression of BE and BD behaviors we assessed impulsivity behavior that may represent a common vulnerability factor.

[1]National Institute on Alcohol Abuse and Alcoholism (NIAAA). Drinking Levels Defined n.d. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking (accessed August 8, 2016).

MATERIALS AND METHODS

Study Design and Participants

The study was an online anonymous survey conducted among all the students attending the French University of Rennes 1 in year 2012. 29,000 Students were invited to complete the questionnaire via their individual university email address. Students of Rennes 1 university are distributed as follows: 39% law, economy, management and human sciences, 28% health, 33% sciences, engineering and technologies. The link into the study could be activated only once, to avoid multiple participations in the survey. The identity of the participants completing the anonymous questionnaire was unknown to the researcher. No written informed consent was asked to the participants and the researcher's contact information was indicated in the questionnaire. Students were able to continue with the survey only if they stated that they do consent to participate by ticking the consent button after reading the consent form (purpose of research, participation, procedure, confidentiality, and researcher's contact information). Raw data were stored on a computer not connected to an internet network and were destroyed at the end of the study. The protocol was approved by the regional ethics committee (Comité de Protection des Personnes Nord-Ouest II).

Questionnaire and Type of Data Collected

Participants were asked to provide their age, gender, weight, height, current tobacco smoking status, and current cannabis use status. They were also invited to complete online versions of the Alcohol Use Questionnaire (AUQ) (Mehrabian and Russell, 1978), the Eating Disorder Examination Questionnaire (EDE-Q) (Fairburn and Beglin, 1994), and the 20-item Urgency – Premeditation – Perseverance – Sensation seeking (UPPS) impulsive behavior questionnaire (Billieux et al., 2012).

Score Construction

A BD score was calculated on the basis of three items of the AUQ, as previously validated (Townshend and Duka, 2005). The BD score was calculated for all participants on the basis of the information given in items 10, 11, and 12 of the AUQ [Speed of drinking (average drinks per hour); number of times being drunk in the previous 6 months; percentage of times getting drunk when drinking (average)]. The BD score is calculated as follows [4 × (Item 10) + Item 11 + 0.2 × (Item 12)]. This score gives a picture of the drinking patterns of the participants rather than just a measure of alcohol intake. Using the UPPS questionnaire, scores of 'negative urgency,' 'positive urgency,' 'lack of premeditation,' 'lack of perseverance,' and 'sensation seeking' were calculated for each participant (Billieux et al., 2012). Moreover, the Body Mass Index (BMI) of respondents was calculated on the basis of their reported weight and height. Using the EDE-Q questionnaire, scores of 'dietary restraint,' 'eating concern,' 'shape concern,' and 'weight concern' were calculated as defined by the authors of the questionnaire (Fairburn and Beglin, 1994). In addition, a BE score was calculated by summing

the subscores of the items 13, 14, and 15, of the EDE-Q, while a 'purging behaviors' score was obtained by summing the specific questions of the EDE-Q, i.e., questions 16 and 17. Moreover, categorical BMI groups were constructed. All the subjects with a BMI of less than 18.5 were defined as the 'underweight' group. The '≥18.5 to <25' group was defined as 'normal,' while the '≥25 group' was defined as the 'overweight' group.

Statistical Analysis

Categorical variables are provided as the number and percentage (n; %). Quantitative variables are provided as the mean and standard deviation, and median and interquartile range (mean ± SD; med [IQR]). For both the BD and BE scores, bivariate analyses were conducted to explore the association with the other parameters explored. Comparisons between two quantitative measures were performed using the Spearman's ρ test, whereas comparisons between quantitative and categorical variables were performed using Mann–Whitney or Kruskal–Wallis tests.

Furthermore, a multivariable linear regression modeling was built, with the BD score as the dependent variable, and other variables as the explanatory variables. The standardized coefficients of the model are provided with their standard deviation (β_0 value ± SD). The significance threshold was fixed at 0.05 for all tests. Analyses were conducted using the XLSTAT2014 software[2].

RESULTS

Of the 29,000 students who were invited to complete the online questionnaire, 1,872 accepted to participate (mean age = 21.1 ± 2.44 years; median age = 21 [20–23]); 57.4% females; 21.4% tobacco smokers; 29.6% cannabis users).

Results of the bivariate comparisons of the BD and BE scores with other variables provided in the **Table 1**.

The BD score was significantly associated with the BE score ($\rho = 0.12$; $p < 0.0001$), but not with other EDE-Q subscores. The BD score was also significantly associated with male gender ($p < 0.0001$), tobacco smoking status ($p < 0.0001$), and cannabis use status ($p < 0.0001$). It was also significantly correlated with every UPPS subscore ($p < 0.0001$ for each), and negatively associated with age ($\rho = -0.14$; $p < 0.0001$). Consequently, all these parameters were integrated in the multivariable linear regression model, which is provided in the **Table 2**.

In the multivariable modeling, the BE score remained significantly correlated with the BD score (β_0–value = 0.051 ± 0.022; $p = 0.019$), whereas the scores of other DES were not significantly associated with the BD score. Male gender, younger age, tobacco smoking status, and cannabis use status, were all significant contributors of the BD score ($p < 0.0001$ for each parameter). In addition, only the 'positive urgency' ($p > 0.0001$), 'lack of perseverance' ($p < 0.0001$), and 'sensation seeking' ($p = 0.004$) subscores of the UPPS scale were significantly associated with the BD score. The overall goodness of fit of the model was $R^2 = 25\%$.

DISCUSSION

The main objective of the study was to assess in which extent the different DES were significant contributors of the severity of BD in a population of French students. In this respect, we found that only the severity of BE, and not other dimensions of disordered eating, was significantly correlated to the BD score. Moreover, the BE score appeared also significantly correlated with all other EDE-Q subscores and with the BMI, whereas these different quantitative parameters were not correlated with the BD score.

These findings are consistent with some recent hypotheses, according to which BE should not be viewed as a subcategory of DES, but as the more general expression of an impaired emotion regulation, which would constitute a common vulnerability factor for eating disorders, as well as other addictive behaviors (Stojek et al., 2014; Leehr et al., 2015; Eichen et al., 2016). Impulsivity has been regularly, though inconstantly, associated with this BE-related emotional dysregulation (Schag et al., 2013; Stojek et al., 2014; Eichen et al., 2016). Consequently, it was important to adjust our analyses using impulsivity traits assessment to explore the severity of BD. However, this did not change our main results. Moreover, differentiating between BE and purging behaviors was never previously addressed in previous research on eating behaviors. In this regard, we found that purging behaviors, though highly associated with BE, were not associated with BD. To our knowledge, this is a second original finding.

Furthermore, our results are in line with several previous findings. 'Positive urgency' and 'sensation seeking' were both associated with substance use (Billieux et al., 2012), whereas 'negative urgency' was more associated with substance dependence (Verdejo-García et al., 2007). In our study, which did not focus on dependent subjects, we found a significant association between the BD score and the 'positive urgency' and 'sensation seeking' subscores of the UPPS. Moreover, previous investigations reported an association between BE and either 'negative urgency' (Bardone-Cone et al., 2016), or both 'negative' and 'positive' urgency dimensions (Stojek et al., 2014). In our study, we confirmed these associations, as, among all the UPPS subscores, both urgency subscores were those which showed the strongest association with the BE score.

Several limitations should also be acknowledged regarding this study. First and foremost, the response rate was only about 6.4% and can be partially explained by the fact that the majority of students do not use the email address provided by the university [but is not very low compared to that of similar studies (Tavolacci et al., 2016)]. We cannot exclude that the more involved or problematic individuals refused to participate and the lack of psychiatric interview is also an important limitation here since we did not detect the presence of psychiatric diagnosis

[2]https://www.xlstat.com/en/

TABLE 1 | Bivariable comparisons for the BE and BD scores.

	BE score	*p*-value	BD score	*p*-value
Age	$\rho = -0.03$	0.28	$\rho = -0.14$	<0.0001
Females (vs. males)	0 [0–3] vs. 1 [0.2]	0.9	11 [6–21] vs. 17 [8–30]	<0.0001
Tobacco smokers (vs. non-smokers)	1 [0–3] vs. 1 [0–2]	0.025	21 [12–36] vs. 11 [4–21]	<0.0001
Cannabis users (vs. non-users)	1 [0–3] vs. 0 [0–2]	0.049	23 [14–36] vs. 10 [4–19]	<0.0001
BD score	$\rho = 0.12$	<0.0001	–	–
BE score	–	–	$\rho = 0.12$	<0.0001
EDE-Q – purging behaviors	$\rho = 0.17$	<0.0001	$\rho = 0.03$	0.18
EDE-Q – dietary restraint	$\rho = 0.19$	<0.0001	$\rho = 0.03$	0.18
EDE-Q – eating concern	$\rho = 0.36$	<0.0001	$\rho = 0.006$	0.78
EDE-Q – shape concern	$\rho = 0.28$	<0.0001	$\rho = 0.012$	0.60
EDE-Q – weigh concern	$\rho = 0.26$	<0.0001	$\rho = 0.009$	0.70
BMI (quantitative)	$\rho = 0.17$	<0.0001	$\rho = 0.02$	0.38
BMI ([<18.5] vs. [18.5–25])	0 [0–1] vs. 1 [0–2]	0.095	12 [4–22] vs. 14 [7–24]	0.11
BMI ([>25) vs. [18.5–25])	2 [0–3] vs. 1 [0–2]	0.002	12 [6–17] vs. 14 [7–24]	0.11
UPPS – negative urgency	$\rho = 0.18$	<0.0001	$\rho = 0.09$	<0.0001
UPPS – positive urgency	$\rho = 0.21$	<0.0001	$\rho = 0.22$	<0.0001
UPPS – lack of premeditation	$\rho = 0.08$	0.001	$\rho = 0.21$	<0.0001
UPPS – lack of perseverance	$\rho = 0.06$	0.007	$\rho = 0.13$	<0.0001
UPPS – sensation seeking	$\rho = 0.08$	0.001	$\rho = 0.22$	<0.0001

Comparisons between quantitative variables were performed using the Spearman's correlation test (ρ). Comparisons between categorical and quantitative variables were conducted using the Mann–Whitney test, and are provided as the median and the interquartile range (med [IQR]). BD, binge drinking; BE, binge eating; EDE-Q, Eating Disorder Examination Questionnaire; UPPS, 'urgency – premeditation – perseverance – sensation seeking' impulsive behavior scale.

in our sample. The entirely self-report dimension of the data analyzed may have impacted the reliability of the data despite the large sample size recruited and it has been already shown that for alcohol consumption, it may be underestimated by the use of retrospective questionnaire (Townshend and Duka, 2002), the self-report ascertainment of cannabis use may also be affected by the fact that some cannabis users may deny using cannabis.

TABLE 2 | Results of the multivariable linear regression modeling of the BD score (β_0 = normalized coefficients; $R^2 = 25\%$).

	β_0_ value ± SD	*p*-value
Age	−0.104 ± 0.021	<0.0001
Female gender	−0.175 ± 0.023	<0.0001
Tobacco smoker	0.129 ± 0.022	<0.0001
Cannabis user	0.257 ± 0.023	<0.0001
BE score	0.051 ± 0.022	0.019
EDE-Q – purging behaviors	−0.009 ± 0.021	0.680
EDE-Q – dietary restraint	0.042 ± 0.028	0.140
EDE-Q – eating concern	−0.034 ± 0.031	0.270
EDE-Q – shape concern	0.010 ± 0.055	0.857
EDE-Q – weigh concern	0.032 ± 0.055	0.565
Body mass index	−0.042 ± 0.023	0.069
UPPS – Negative Urgency	−0.016 ± 0.024	0.494
UPPS – positive urgency	0.104 ± 0.025	<0.0001
UPPS – lack of premeditation	0.105 ± 0.024	<0.0001
UPPS – lack of perseverance	0.023 ± 0.023	0.328
UPPS – sensation seeking	0.064 ± 0.022	0.004

BD, binge drinking; BE, binge eating; CI95%, confidence interval 95%; EDE-Q, Eating Disorder Examination Questionnaire; SD, standard deviation; UPPS, 'urgency – premeditation – perseverance – sensation seeking' impulsive behavior scale.

The building of the BD score followed a validated procedure (Townshend and Duka, 2005) while the way the BE and purging scores were constructed was not based on previous studies. The global EDE-Q score has shown good psychometric properties to measure BE (Vander Wal et al., 2011), but no specific study has ever demonstrated the validity of the items we selected to, respectively, score the BE and purging behaviors. However, these items specifically focus on BE or purging symptoms. It is noteworthy that 'purging behavior' is not only defined by vomiting and laxative misuse (as highlighted in the EDE-Q) but also by other behaviors such as misuse of diuretics, infusions and sugar-free candies. Another possible limitation of the study is that no association was found between the female gender and the BE score, whereas BE is usually much more frequent among females (Allen et al., 2014). However, in the present study, we did not use a frequency but a severity assessment, which is not similar. The lack of between-gender difference would be questionable if BE would have been more severe among women, and not only more frequent. To our knowledge, this has not been demonstrated yet.

CONCLUSION

Overall, we found that the BE severity was correlated with the BD severity, contrary to other DES. These results suggest that BE could consist of a general vulnerability factor, underlying elements of emotional dysregulation that remain to be more understood. This common vulnerability could link different types

of behaviors and mental disorders, which may elsewhere be poorly interrelated, like, in our study, BD and DES.

AUTHOR CONTRIBUTIONS

MN and JA developed the study. All authors contributed to the study design. Data collection was conducted by CD and JA and data analyses were performed in collaboration with all authors (BR, MN, CD, HH, FG, and JA). BR drafted the paper under the supervision of MN, while HH, FG, and JA provided critical revisions. All authors approved the final version of the paper.

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Preserved Crossmodal Integration of Emotional Signals in Binge Drinking

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Binge drinking is an alcohol consumption pattern with various psychological and cognitive consequences. As binge drinking showed qualitatively comparable cognitive impairments to those reported in alcohol-dependence, a continuum hypothesis suggests that this habit would be a first step toward alcohol-related disorders. Besides these cognitive impairments, alcohol-dependence is also characterized by large-scale deficits in emotional processing, particularly in crossmodal contexts, and these abilities have scarcely been explored in binge drinking. Emotional decoding, most often based on multiple modalities (e.g., facial expression, prosody or gesture), yet represents a crucial ability for efficient interpersonal communication and social integration. The present study is the first exploration of crossmodal emotional processing in binge drinking, in order to test whether binge drinkers already present the emotional impairments described among alcohol-dependent patients, in line with the continuum hypothesis. Twenty binge drinkers and 20 matched controls performed an experimental task requiring the identification of two emotions (happiness or anger) presented in two modalities (visual or auditory) within three conditions (unimodal, crossmodal congruent or crossmodal incongruent). In accordance with previous research in binge drinking and alcohol-dependence, this study was based on two main hypotheses. First, binge drinkers would present a reduced facilitation effect (i.e., classically indexed in healthy populations by faster reaction times when two congruent modalities are presented simultaneously). Second, binge drinkers would have higher difficulties to inhibit interference in incongruent modalities. Results showed no significant difference between groups in emotional decoding ability, whatever the modality or condition. Control participants, however, appeared slower than binge drinkers in recognizing facial expressions, also leading to a stronger facilitation effect when the two modalities were presented simultaneously. However, findings did not show a disrupted facilitation effect in binge drinkers, whom also presented preserved performance to inhibit incongruence during emotional decoding. The current results thus suggest that binge drinkers do not demonstrate a deficit for emotional processing, both in unimodal and crossmodal contexts. These results imply that binge drinking might not be characterized by impairments for the identification of primary emotions, which could also indicate that these emotional processing abilities are well-preserved at early stages of excessive alcohol consumption.

Keywords: heavy drinking, emotion, facial expression, prosody, alcohol-dependence

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INTRODUCTION

Excessive alcohol consumption represents a major public health problem, directly involved in 4% of deaths worldwide (Rehm et al., 2009), and is also considered as a major concern in adolescents and young adults. Indeed, binge drinking, defined as the consumption of at least 4 (for women) or 5 (for men) drinks within 2 hours (i.e., representing a blood concentration of 0.08 g/dl) (National Institute of Alcohol Abuse and Alcoholism [NIAAA], 2004) has become widespread in this population. While this NIAAA definition is the most reported in the exploration of binge drinking habits, studies currently use various ways to identify binge drinkers. To date, the main categorizations are the self-reported number of alcohol drinks consumed per occasion (e.g., Keller et al., 2007), with different levels of frequency, and the computation of a binge drinking score based on the self-described consumption speed and drunkenness episodes (Townshend and Duka, 2005). As a whole, this topic has recently led to increasing research showing that binge drinking is associated with a large range of consequences. First, at short term, binge drinkers are exposed to higher dangerous issues, such as hypothermia, or risks for falling or drowning (Hingson et al., 2009). Importantly, from a cognitive view and in a longer term perspective, binge drinking is also characterized by reduced performance in memory, executive or attentional abilities. Several subcomponents of memory, like spatial, declarative, episodic, and prospective memory, appear impaired in binge drinkers (e.g., Hartley et al., 2004; Heffernan et al., 2010; Heffernan and O'Neill, 2012). Concerning executive functions, findings indicated slower planning (Hartley et al., 2004), disadvantageous decision-making (e.g., Goudriaan et al., 2007), as well as impaired post-error slowing effect and inhibitory control (e.g., VanderVeen et al., 2013; Bø et al., 2016), particularly when alcohol-related stimuli were presented (Czapla et al., 2015). Eventually, binge drinkers also demonstrated impairments in sustained attention (Hartley et al., 2004), alerting, and attentional control (Lannoy et al., 2017a). This pattern of cognitive deficits gives support to the continuum hypothesis (e.g., Enoch, 2006; Maurage et al., 2013a), globally suggesting a linear worsening of cognitive dysfunctions in the spectrum of alcohol-related disorders. In this perspective, binge drinking could be considered as a first step toward alcohol-dependence. It has moreover been shown that a subgroup of binge drinkers already had hazardous alcohol consumption associated with negative consequences, identifying them as more likely to develop alcohol-use disorders (Lannoy et al., 2017b). This proposal has been further supported by studies indicating premature brain and cognitive aging in binge drinkers (Sanhueza et al., 2011). Nevertheless, alcohol-dependence is also characterized, beyond cognitive impairments, by large-scale interpersonal and emotional deficits (see Donadon and Osório, 2014 for a review), for which studies are strongly lacking in binge drinking. Understanding emotional information is, however, an essential ability in humans, as it notably allows efficient interpersonal life and social integration. Therefore, this paucity of research and data about emotional processing in binge drinking hampers to have an exhaustive picture of the deficits related to this alcohol consumption pattern and of the continuum hypothesis extension toward non-cognitive factors.

To date, emotional processing has been deeply investigated in alcohol-dependence, showing difficulties in the identification of emotional stimuli from others' face (Kornreich et al., 2001; Maurage et al., 2008; D'Hondt et al., 2015), voice (Monnot et al., 2002) or body posture (Maurage et al., 2009). This impaired emotional processing among alcohol-dependent individuals seems particularly related to a difficulty for decoding the emotions expressed by others, mainly for negative states (D'Hondt et al., 2014) and with an overestimation of fear (Townshend and Duka, 2003). These emotional deficits are directly associated with difficulties in social interaction, explaining their pivotal role in the emergence and maintenance of alcohol-dependence (Thoma et al., 2013; Oscar-Berman et al., 2014) as emotional-interpersonal problems are an important cause of relapse after detoxification (Zywiak et al., 2003). However, in everyday life, emotional signals are most frequently presented in a crossmodal way (i.e., via the simultaneous presentation of visual and auditory stimuli). Crossmodal integration, defined as the ability to efficiently perceive and integrate sensory signals coming from different modalities in a joint representation, allows the suitable understanding of social and perceptual environment and the generation of an appropriated response (Maurage and Campanella, 2014). In alcohol-dependence, an impaired crossmodal processing of emotions has been identified (Maurage et al., 2007a, 2013b), notably reflected by a disrupted facilitation effect. The facilitation effect is described by a faster processing of congruent crossmodal stimulations compared to unimodal ones, and is classically observed among healthy populations in crossmodal situations (Maurage et al., 2007a). Moreover, this effect is considered as a reliable marker of crossmodal integration in the neurocognitive literature (Calvert et al., 2001). This result thus means that alcohol-dependent patients did not take advantage of the cross-modality to perform emotional decoding. Beyond their impairment for unimodal emotion processing, alcohol-dependent individuals thus present massive deficits in crossmodal ecological situations.

In binge drinking, emotions have scarcely been investigated. Some studies have been interested in the impact of negative emotions on future binge consumption and showed depressive symptoms as a vulnerability factor (Mushquash et al., 2013; Pape and Norström, 2016). Moreover, the co-existence of these two disorders (i.e., binge drinking and depression) leads to more pronounced cognitive deficits (e.g., Hermens et al., 2013b) and specific changes in electrophysiological activity when identifying emotional faces (Connell et al., 2015). Beyond this co-occurrence, some authors have also proposed that this pattern of alternation between excessive alcohol intake and withdrawal episodes induce abnormal neuronal plasticity, in the same way to what is observed in alcohol-dependent patients, and thus would also lead to emotional impairments (Stephens and Duka, 2008). For example, an impaired fear conditioning was observed in student binge drinkers (Stephens et al., 2005) and suggests a reduced ability to adapt behavior in response to aversive events as well as an increased emotional reactivity in situations under which it is

not required (e.g., overestimation of negative emotions), as it was previously documented in alcohol-dependence. Impairments for the identification of emotional expressions are furthermore associated with cerebral changes, particularly in the amygdala (Morris et al., 1998). In this perspective, functional modifications in the amygdala are evidenced in binge drinking (Xiao et al., 2013; Campanella et al., 2016). These cerebral impairments could thus further indicate difficulties in the processing of emotional stimuli among binge drinkers. Finally, very few research has investigated emotional processing *per se* in binge drinking. To our knowledge, only one study has examined the behavioral and brain correlates of emotional processing by using vocal stimuli morphed on a continuum between angry and fearful emotions (Maurage et al., 2013a). Results showed that binge drinkers had an impaired identification of emotions together with a reorganization of brain activity (i.e., reduced activation of bilateral superior temporal gyrus and increased activation of right middle frontal gyrus). Overall, these results suggest that binge drinking might also be characterized by impairments in emotional processing. As this research field appears almost unexplored, an in-depth investigation of emotional deficits in binge drinking is needed. This should be made with a more ecological paradigm using crossmodal stimuli, which are the rule rather than the exception in real life social interactions.

The aim of this study was thus twofold: first, to determine whether emotional processing, an essential ability for everyday life social interactions, was altered among student binge drinkers; second, to explore whether the continuum hypothesis, supported for cognitive performance, could be extended toward affective abilities. The current study proposed the exploration of the behavioral performance of binge drinkers and control participants in an emotion detection task implying (a) two emotions differing in their valence (happiness and anger), (b) two modalities of emotional processing (visual and auditory), and (c) the crossmodal integration, further investigated by the facilitation effect. Moreover, as binge drinking was previously associated with inhibition deficits, this study also evaluated the crossmodal inhibition effect, by using an incongruent condition (i.e., requiring to inhibit the interference presented in one of the two modalities). Regarding the continuum perspective, we hypothesized a specific impairment for the facilitation effect in binge drinkers as well as a reduced ability to inhibit non-pertinent modality in incongruent crossmodal situations.

MATERIALS AND METHODS

Participants and Procedure

Participants were recruited through a preliminary anonymous screening, sent by email to all students from the Université catholique de Louvain (Belgium) and 3014 answers were collected. The first part assessed sociodemographic (age, gender, education level, and native language) and psychological variables. The previous or current presence of several disorders (i.e., medical, psychological, neurological, substances consumption, family history of alcohol-dependence) was measured by dichotomous choices (Yes/No) and participants had to specify their response in an open question only if they answered "yes" to the initial item. Second, alcohol consumption in the last 6 months was evaluated by the mean number of alcohol units per drinking occasion, the mean number of drinking occasions per week, the consumption speed (the number of alcohol units consumed per hour), the mean number of alcohol units per week, the drunkenness frequency (by stating that drunkenness refers to loss of coordination, nausea, and/or inability to speak clearly), and the percentage of drunkenness episodes [i.e., (number of drunkenness episodes/total number of drinking occasions)*100]; an alcohol unit corresponding to 10 g of pure ethanol. Finally, drinking motives were measured by targeting four motivations to drink alcohol (i.e., social order, referring to social context; enhancement, referring to the entertaining sensations provoked by alcohol; coping, referring to negative affect regulation; and conformity, referring to others' negative judgments avoidance; Grant et al., 2007). Participants selected for the study fulfilled the following criteria: native or fluent French speakers, at least 18 years old, no alcohol-dependence and no family history of alcohol-dependence, no positive psychological or neurological disorders, no current medication, no major medical problems, corrected-to-normal visual abilities, normal auditory abilities, total absence of past or current drug consumption (except alcohol and tobacco). On this basis, 120 undergraduate students were contacted, and 40 accepted to take part in the study: 20 Binge Drinkers, recruited according to a binge drinking score (Townshend and Duka, 2005) focusing on the consumption speed and drunkenness frequency (BD; score $\geq$ 16), and 20 Control Participants (CP; score $\leq$ 12). The group selection was first conducted according to the binge drinking score because, beyond its frequent use in the literature (e.g., Czapla et al., 2015), it allows targeting the specific binge drinking characteristics (e.g., drink quickly to become rapidly intoxicated). However, to ensure a correct classification of binge drinkers and non-binge drinkers, group comparisons were also performed on all alcohol variables (**Table 1**), which clearly supported the distinction between groups regarding alcohol consumption and binge drinking pattern. All participants (22 women) were aged between 18 and 23 years old ($M = 19.73$, $SD = 1.74$). Before the experiment, participants filled in questionnaires assessing state-trait anxiety (State-Trait Anxiety Inventory, STAI; Spielberger et al., 1983), depression (Beck Depression Inventory, BDI-II; Beck et al., 1996), and alcohol-related disorders (Alcohol Use Disorder Identification Test, AUDIT; Babor et al., 2001). The AUDIT is a 10-item questionnaire, developed by the World Health Organization, evaluating the general harmfulness of alcohol consumption. This test is widely used in the alcohol field and is also considered as a good measure of hazardous alcohol habits in university students (Kokotailo et al., 2004). Participants received a compensation of 10€ for their participation. The study protocol was approved by the ethics committee of the Université catholique de Louvain, and carried out according to the Declaration of Helsinki.

Stimuli and Task Description

The emotional crossmodal task assessed emotional detection from emotional facial and vocal stimuli, in separate (unimodal) or simultaneous (crossmodal) ways, the crossmodal conditions

TABLE 1 | Demographic and psychological measures for Binge Drinkers (BD) and Control Participants (CP): mean (*SD*).

Variable	BD ($n = 20$)	CP ($n = 20$)
Demographic measures		
Age^{ns}	19.65 (1.79)	19.80 (1.74)
Gender ratio (female/male)^{ns}	11/9	11/9
Psychological measures		
Beck depression inventory^{ns}	4.35 (3.23)	5.35 (3.54)
STAI state anxiety inventory^{ns}	29.65 (6.44)	33.80 (8.36)
STAI trait anxiety inventory^{ns}	34.90 (6.91)	38.05 (8.67)
Alcohol consumption measures		
Alcohol Use Disorder Identification Test*	16.90 (5.05)	1.10 (2.25)
Total alcohol units per week*	26.60 (12.12)	1.30 (5.13)
Number of occasions per week*	3.15 (0.99)	0.30 (0.92)
Number of alcohol units per occasion*	8.16 (3.54)	0.44 (1.34)
Consumption speed (units per hour)*	3.35 (1.09)	0.60 (0.54)
Drinking motives		
Enhancement*	16.25 (3.40)	6.26 (1.99)
Social order*	17.40 (3.36)	8.74 (3.98)
Conformity^{ns}	6.05 (1.39)	6.21 (3.11)
Coping*	10.10 (3.31)	6.84 (0.50)

^{ns} = *Non-significant;* $*p < 0.001$.

presenting identical (crossmodal congruent; e.g., a happy face with a happy voice) or opposite (crossmodal incongruent; e.g., a happy face with an angry voice) emotions. Participants were in a quiet room and placed at 60 cm from the screen. They had to decide as quickly and accurately as possible the emotional content displayed by pressing the appropriate response key with their dominant hand (i.e., 1 for happiness and 2 for anger).

Visual stimuli represented facial expressions of happiness and anger and were selected from the Radboud Faces Database (RaFD; Langner et al., 2010). Vocal stimuli produced vocalizations without semantic content (i.e., the onomatopoeia ≪ Ah ≫) and were selected from a battery of vocal emotional expressions (Maurage et al., 2007b). As visual stimuli led to faster reaction times (RT) than auditory ones (e.g., Joassin et al., 2004), a morphing strategy (i.e., morph between happiness and anger; Morph 2.5., Gryphon Software Corp.) was used in order to obtain similar difficulty in the two unimodal conditions (face and voice), which is a necessary requisite to observe a facilitation effect in the crossmodal congruent condition. Based on a pretest phase ($n = 11$), the morphing level 40–60 was chosen because it led to similar RT in visual and auditory conditions, both for happiness [$t(10) = 0.67, p = 0.517$] and anger [$t(10) = 0.57, p = 0.583$]. The morphing level was thus set at 60% happiness – 40% anger for happiness faces and 40% happiness – 60% anger for anger faces. The task finally included five men and five women faces as well as five male and five female voices, both depicting happiness and anger.

The task comprised 200 unimodal trials (i.e., 100 faces, 100 voices), 200 crossmodal congruent trials (i.e., 100 where the instruction was to focus on the face to answer, 100 where the instruction was to focus on the voice), and 200 crossmodal incongruent trials (i.e., 100 where the instruction was to focus on the face to answer, 100 where the instruction was to focus on the voice). The experimental paradigm was distributed in 3 conditions (unimodal, crossmodal congruent, crossmodal incongruent) × 2 modalities (face, voice) × 2 emotions (happiness, anger) (**Figure 1**). A total of 600 trials were displayed into three blocks (i.e., face unimodal, voice unimodal, and crossmodal), the two first blocks being presented with pseudo-randomized order across participants whereas the experiment always ended with the crossmodal condition. Each trial started with a fixation cross presented for 500 ms, then the stimulus was presented (face, voice, or both) for another 500 ms and followed by a blank screen for 2000 ms. From the stimulus onset, participants thus had 2500 ms to answer. Accuracy Scores (AS; percentage of correct responses) and RT were recorded. Only correct responses were considered for the RT analyses.

Statistical Analyses

All statistical analyses were performed using SPSS software package (version 21.0) and the significance was set at an alpha level of 0.05. Comparisons between groups were first performed on demographic, psychological, and alcohol consumption characteristics. Then, performance in the emotion detection task were compared via 2 × 2 × 2 × 3 repeated measures analyses of variance (ANOVAs) with Group (CP and BD) as between-subjects factor and Emotion (Happiness and Anger), Modality (Face and Voice), and Condition (Unimodal, Crossmodal Congruent, and Crossmodal Incongruent) as within-subjects factors, computed separately for AS and RT. Finally, bivariate correlations analyses, corrected for multiple comparisons (i.e., Bonferroni's correction), were performed between task performance and alcohol-related variables (i.e., binge drinking score, AUDIT score, and drinking motives), separately for BD and CP.

RESULTS

Demographic and Psychological Measures

Characteristics of each group are reported in **Table 1**. No significant group differences were found for age [$t(38) = 0.27$, $p = 0.789$], gender [$\chi^2(1, N = 40) = 0$, $p = 1$], depressive symptoms [$t(38) = 0.93$, $p = 0.357$], and anxiety (state: [$t(38) = 1.76, p = 0.087$], trait: [$t(38) = 1.27, p = 0.211$]). Groups, however, significantly differed on all alcohol-related variables, including three of the four drinking motives (i.e., enhancement, social order, and coping).

Behavioral Analyses

Mean performance and RT for each experimental condition are reported in **Table 2**.

Accuracy Score

Three main effects were identified: Emotion [$F(1,38) = 7.39$, $p = 0.010$, $\eta_p^2 = 0.163$], happiness leading to higher accuracies than anger; Modality [$F(1,38) = 194.90$, $p < 0.001$, $\eta_p^2 = 0.837$], voices leading to better performance than faces; Condition

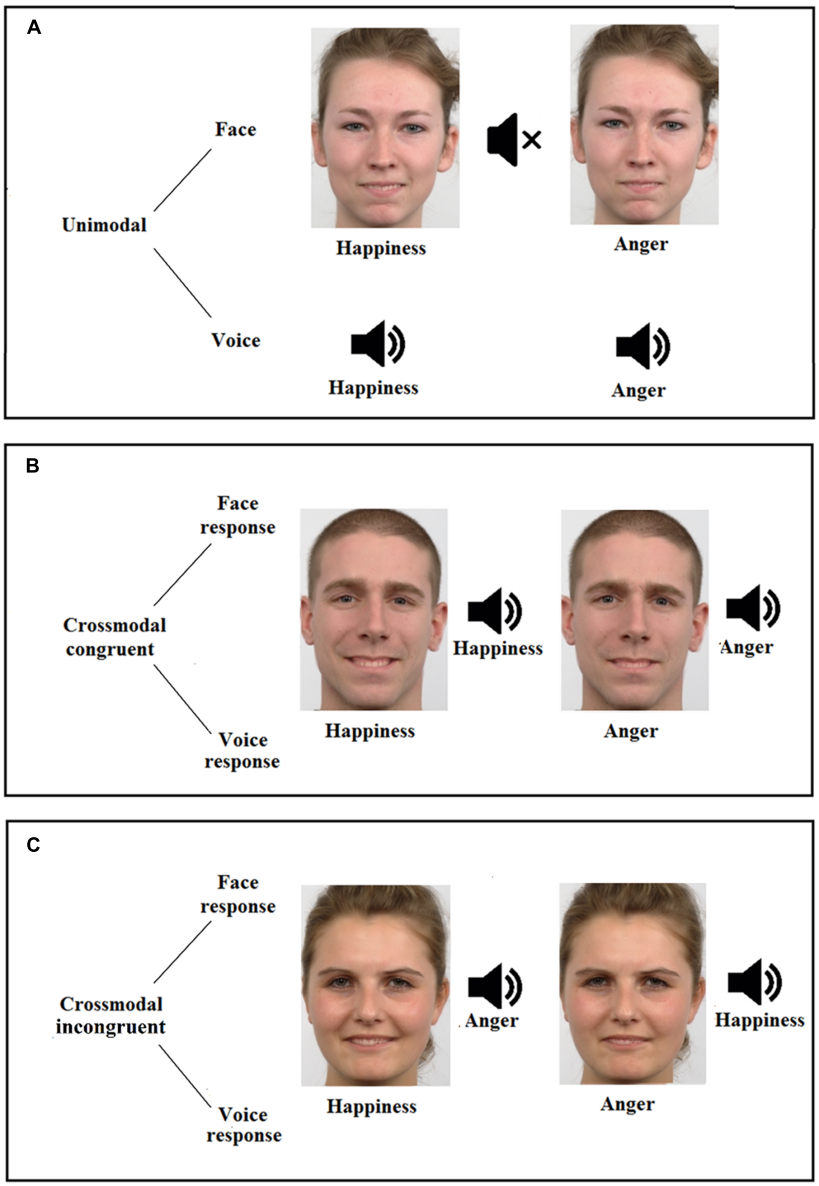

FIGURE 1 | Description of the emotion detection task, displaying the three possible conditions (**A**, unimodal; **B**, crossmodal congruent; and **C**, crossmodal incongruent), the two modalities (face and voice) and the two emotions (happiness and anger). Figure also illustrates two examples of female faces (conditions **A,C**) and an example of male face (condition **B**), for both happiness (morphed with 60% of happiness and 40% of anger, Left) and anger (morphed with 60% of anger and 40% of happiness, Right) faces.

$[F(2,76) = 21.86, p < 0.001, \eta_p^2 = 0.365]$, unimodal trials leading to better accuracies than crossmodal congruent $[t(39) = 2.79, p = 0.008]$ and crossmodal incongruent $[t(39) = 6.27, p < 0.001]$ ones, and crossmodal congruent trials leading to better accuracies than incongruent trials $[t(39) = 5.28, p < 0.001]$. An interaction between Emotion and Modality $[F(1,38) = 29.92, p < 0.001, \eta_p^2 = 0.440]$ was also found. These effects were qualified by a triple interaction between Emotion, Modality, and Condition $[F(2,76) = 17.34, p < 0.001, \eta_p^2 = 0.313]$. In the unimodal Condition, there was no difference in the identification of happiness and anger, both for face $[t(39) = 1.92, p = 0.063]$ and voice $[t(39) = 0.76, p = 0.443]$ modalities. In the crossmodal congruent Condition, happiness was better identified than anger in the face Modality $[t(39) = 3.79, p = 0.001]$ but not in the voice Modality $[t(39) = 1.33, p = 0.191]$. In the crossmodal incongruent Condition, happiness was better recognized than anger in the face Modality $[t(39) = 5.82, p < 0.001]$ but anger was better identified in the voice Modality $[t(39) = 2.95, p = 0.005]$. There was no interaction effect between Emotion and Condition $[F(2,76) = 2.88, p = 0.062, \eta_p^2 = 0.070]$ or Modality and Condition $[F(2,76) = 2.74, p = 0.071, \eta_p^2 = 0.067]$. Moreover, and centrally, there was no main Group effect $[F(1,38) = 0.49,$

TABLE 2 | Accuracy Scores (AS; percentage of correct answers) and Reaction Times (RT; in milliseconds) for Binge Drinkers (BD) and Control Participants (CP) in each experimental condition (i.e., emotions, modalities, and conditions) of the crossmodal emotional identification task: mean (*SD*).

				Conditions		
Emotion	**Modality**	**Variable**	**Group**	**Unimodal**	**Crossmodal congruent**	**Crossmodal incongruent**
Happiness						
	Face	AS	BD	79.10 (12.39)	82.10 (13.05)	78.80 (13.05)
			CP	82.10 (10.89)	79.60 (14.62)	79.20 (13.79)
		RT	BD	873.39 (240.28)	450.96 (113.97)	463 (139.39)
			CP	1057.96 (289.98)	422.62 (100.35)	441.50 (101.64)
	Voice	AS	BD	95.40 (6.30)	91.10 (12.15)	87.50 (8.70)
			CP	95.20 (5.75)	89.10 (10.98)	86.10 (10.89)
		RT	BD	456.55 (182.97)	457.66 (145.82)	465.27 (101.15)
			CP	467.74 (115.73)	432.34 (112.09)	483.59 (150.92)
Anger						
	Face	AS	BD	76.10 (10.47)	71.30 (12.64)	66.50 (12.29)
			CP	74.20 (10.58)	68.90 (16.22)	58.70 (15.73)
		RT	BD	873.65 (238.25)	479.56 (138.96)	477.98 (116.86)
			CP	1096.81 (288.57)	470.34 (119.97)	457.28 (88.44)
	Voice	AS	BD	95.90 (5.13)	92.30 (7.32)	92.10 (8.01)
			CP	96.60 (4.41)	91.70 (8.09)	91.30 (8.34)
		RT	BD	467.29 (146.95)	457.98 (89.33)	476.53 (107.07)
			CP	468.46 (104.40)	441.95 (89.54)	446.51 (104.97)

$p = 0.490$, $\eta_p^2 = 0.013$] nor any interaction between Emotion and Group [$F(1,38) = 0.31$, $p = 0.584$, $\eta_p^2 = 0.008$]; Modality and Group [$F(1,38) = 0.22$, $p = 0.645$, $\eta_p^2 = 0.006$]; Condition and Group [$F(2,76) = 1.05$, $p = 0.356$, $\eta_p^2 = 0.027$]; Emotion, Modality, and Group [$F(1,38) = 1.16$, $p = 0.288$, $\eta_p^2 = 0.030$]; Emotion, Condition, and Group [$F(1,76) = 1.21$, $p = 0.303$, $\eta_p^2 = 0.031$]; Modality, Condition, and Group [$F(2,76) = 0.62$, $p = 0.542$, $\eta_p^2 = 0.016$]; as well as Emotion, Modality, Condition, and Group [$F(2,76) = 1.10$, $p = 0.337$, $\eta_p^2 = 0.028$].

Reaction Times

While there was no main effect of Emotion [$F(1,38) = 3.53$, $p = 0.068$, $\eta_p^2 = 0.085$], results showed a main effect of Modality [$F(1,38) = 117.70$, $p < 0.001$, $\eta_p^2 = 0.756$], voices leading to faster processing than faces and a main effect of Condition [$F(2,76) = 116.12$, $p < 0.001$, $\eta_p^2 = 0.753$], crossmodal congruent trials leading to faster processing than crossmodal incongruent [$t(39) = 2.37$, $p = 0.023$] and unimodal [$t(39) = 10.27$, $p < 0.001$] trials, and crossmodal incongruent trials leading to faster processing than unimodal trials [$t(39) = 10.16$, $p < 0.001$]. These effects were qualified by two interactions between Condition and Group [$F(2,76) = 6.24$, $p = 0.003$, $\eta_p^2 = 0.141$], and between Modality, Condition, and Group [$F(2,76) = 6.88$, $p = 0.002$, $\eta_p^2 = 0.153$]. First, conditions comparison showed no significant difference between groups (all $p \geq 0.062$); in both groups, crossmodal Condition led to faster RT than unimodal ones, but this difference was larger in CP than in BD [i.e., for congruent trials, $t(19) = 2.46$, $p = 0.024$, and for incongruent trials, $t(19) = 2.50$, $p = 0.022$]. Second, the triple interaction showed a faster processing of face unimodal trials in BD compared to CP [$t(38) = 2.47$, $p = 0.018$] (**Figure 2**). An interaction was also found between Emotion and Modality [$F(1,38) = 4.97$, $p = 0.032$, $\eta_p^2 = 0.116$], showing that happiness processing was faster than anger processing for faces [$t(39) = 2.95$, $p = 0.005$] while no significant difference was found for voices [$t(39) = 0.85$, $p = 0.932$]. Finally, an interaction between Modality and Condition [$F(2,76) = 170.86$, $p < 0.001$, $\eta_p^2 = 0.818$] showed that voice processing was faster than face processing in unimodal Conditions [$t(39) = 13$, $p < 0.001$]. However, there was no significant difference for crossmodal congruent [$t(39) = 0.55$, $p = 0.583$] and incongruent [$t(39) = 0.58$, $p = 0.565$] conditions. No main group effect was found [$F(1,38) = 0.52$, $p = 0.477$, $\eta_p^2 = 0.013$] nor any interaction between Emotion and Group [$F(1,38) = 0.02$, $p = 0.901$, $\eta_p^2 = 0$]; Modality and Group [$F(1,38) = 3.83$, $p = 0.058$, $\eta_p^2 = 0.092$]; Emotion and Condition [$F(2,76) = 1.62$, $p = 0.205$, $\eta_p^2 = 0.041$]; Emotion, Modality, and Condition [$F(2,76) = 0.32$, $p = 0.730$, $\eta_p^2 = 0.008$]; Emotion, Modality, and Group [$F(1,38) = 2.54$, $p = 0.120$, $\eta_p^2 = 0.063$]; Emotion, Condition, and Group [$F(2,76) = 1.88$, $p = 0.160$, $\eta_p^2 = 0.047$]; as well as Emotion, Modality, Condition, and Group [$F(2,76) = 0.40$, $p = 0.675$, $\eta_p^2 = 0.010$].

Correlational Analyses

First, correlations analyses conducted between emotional processing abilities (AS and RT) and alcohol consumption characteristics, using binge drinking and AUDIT scores, showed no significant relationship (all $p > 0.05$). Second, correlations between emotional processing abilities and drinking motives were not significant for social order, conformity, and coping motives (all $p > 0.05$). However, significant correlations were

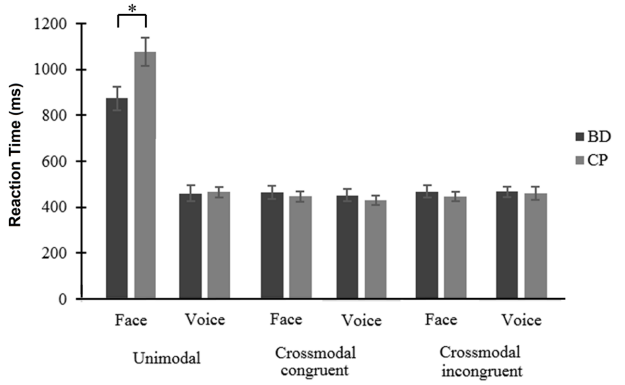

FIGURE 2 | Reaction times (in milliseconds) for the two modalities (face and voice) of emotional processing, within the three possible conditions (unimodal, crossmodal congruent, and crossmodal incongruent) among Binge Drinkers (BD) and Control Participants (CP). $*p < 0.05$. Bars represent the mean value for each condition and whiskers represent the standard error.

found in BD group between enhancement motive and the percentage of correct anger identification in face crossmodal congruent trials ($r = 0.77$, $p = 0.003$) and face crossmodal incongruent trials ($r = 0.70$, $p = 0.048$). The presented p-values were adjusted after Bonferroni correction.

DISCUSSION

The aims of this study were to evaluate emotional processing among binge drinkers and to explore the extension of the continuum hypothesis toward affective abilities. Indeed, while earlier studies have underlined a wide range of interpersonal and emotional impairments in alcohol-dependence (notably for crossmodal processing), no available data using more ecological paradigms allowed determining whether binge drinking, potentially considered as a first step toward alcohol-dependence, was also characterized by emotional impairments. For this purpose, the performance of binge drinkers and controls was compared during an emotion detection task using crossmodal stimuli which are characteristic of the everyday life interactions, particularly in emotional context.

On the one hand, this study reveals that BD are not impaired for the processing of emotional stimuli, centrally showing that the emotional difficulties widely described in alcohol-dependence do not constitute a central deficit at the early stages of alcohol-related disorders. Actually, BD even appeared faster than CP for the detection of emotional facial expressions in unimodal condition. A hypothesis to understand this finding could be made through the perception of social context in undergraduate students. Research focusing on emotions has indeed largely underlined that emotions are innately social (van Kleef et al., 2016). Indeed, emotional expression is based on the perception of other's emotions or social context and thus appears as a response to other people or social norms (Fischer and van Kleef, 2010). Therefore, it has been shown that social factors influence (e.g., Stamkou et al., 2016) and even improve (Bublatzky et al., 2014) the recognition and interpretation of facial emotional expressions. Besides, regarding alcohol consumption in youth, longitudinal study targeting people from adolescence to adulthood showed greater social acceptance and social integration in alcohol users, including binge drinkers (Pedersen and von Soest, 2015). Taken together, these results suggest that a more efficient social environment in BD might be related to the faster emotional detection observed in this group in the current study. This social context can be understood by the specific motivations related to alcohol in young drinkers (e.g., because it is fun or exciting) and notably by the motivations associated with social interactions (e.g., to feel more relax). These motivations involve alcohol expectancies and drinking motives, both being strongly relevant in binge drinking (e.g., Van Tyne et al., 2012). In this respect, the current study showed that BD had significantly greater drinking motives associated to enhancement, social order, and coping. Especially, among BD, a positive relationship was found between enhancement and the correct anger identification in face crossmodal conditions. In other words, it suggests that the more BD drink alcohol for positive reinforcement and agreeable sensations, which is frequently related to social context in undergraduates, the more they are effective to recognize emotional facial expressions of anger in crossmodal condition. It could thus be hypothesized that student BD with higher enhancement motives and drinking alcohol for positive reinforcement, notably in social situations, improve their ability to recognize others' emotions through a repeated and prolonged involvement in social context in comparison to students being less socially involved. Moreover, these findings highlight that social environment is very different in binge drinking than in alcohol-dependence, rather described as a disorder related to social isolation, which suggest that the continuum hypothesis could not be applied to emotional processing. However, it is also important to underline that binge drinking is not defined as a unitary group, also implying that the BD who could evolve toward alcohol-dependence represent a specific subgroup (e.g., Lannoy et al., 2017b). Hazardous BD, characterized by greater alcohol consumption associated with strong negative consequences, could therefore present impaired emotional processing, while more recreational BD (characterized by heavy alcohol use but less negative consequences including in self-reported control abilities) could present preserved emotional abilities.

On the other hand, the classical effects found in crossmodal tasks were observed in this study. First, results indicate a facilitation effect in both groups, characterized by a faster processing of crossmodal congruent than unimodal trials. This effect was more pronounced in the control group, however, as CP was slower than BD to identify facial expressions in unimodal condition, the current results cannot suggest an impaired facilitation effect among BD. Indeed, this greater difference between unimodal and crossmodal congruent trials in CP could be rather explained by a slower processing of face unimodal condition. These results are thus in line with the discussed hypothesis concerning social context, as the facilitation effect is typically related to the correct integration of social

environment in different modalities. Second, an interference effect was also shown in both groups, indexed by better AS and faster RT in crossmodal congruent than incongruent trials. Moreover, findings put forward that this effect was similar in CP and BD, suggesting that BD correctly inhibit the interference from the incongruent modality. Therefore, while inhibition of interference has been identified as a reliable predictor of binge drinking (Paz et al., 2016) and found to be impaired in this population using tasks probing attentional networks (Lannoy et al., 2017a), the paradigm used in this study required to focus on one modality (and therefore inhibit the other) during a half block with no instruction change. It thus appears easier than classical inhibition tasks and could explain the good performance of BD.

Finally, this study presents some limitations. First, even if previous studies have asserted that face stimuli should be modified to have the same complexity than voice stimuli (e.g., Joassin et al., 2004), and whereas the current pretest phase highlighted an optimal morphing level at 40–60, as it was also used in previous studies (e.g., Maurage et al., 2007a), voice unimodal trials led to faster processing and better accuracies than faces, suggesting that future studies should confirm the use of this morphing level and potentially determine a more efficient level of complexity. Second, some variables used in this study to assess alcohol consumption appear quite subjective (e.g., the drunkenness). While group selection and statistical analyses support the consistency between all alcohol measures (those used to compute binge drinking score and those used to evaluate the number of drinks consumed), it should be underlined and taken into account in future studies.

This first exploration of emotional processing in binge drinking did not allow to highlight group differences and thus suggests preserved emotional detection and crossmodal integration among BD. In previous studies, the abnormal cerebral activity leading to emotional processing impairments was identified as the result of numerous withdrawals (Duka et al., 2004) and relapses in alcohol-dependent patients. This argument led to the proposal that binge drinking pattern, especially characterized by the alternation between intense intake and abstinence periods, would also be associated with emotional impairments (Stephens and Duka, 2008). The current study, however, conveys that basic emotional processing is preserved at the first stages of alcohol-related disorders and that these impairments could rather appear in the transition between binge drinking and alcohol-dependence. Indeed, the earlier identification of impaired emotional detection (Maurage et al., 2013a) used more complex vocal stimuli presenting different morphing levels between angry and fearful rather than one positive and one negative emotional content, always presented with the same complexity. Nevertheless, considering the main advantages of crossmodal explorations (Maurage and Campanella, 2014), the identification of specific brain correlates dedicated to crossmodal integration (Maurage et al., 2013b), and the results found in alcohol-dependence, neuroscientific approaches could be useful to highlight possible cerebral alterations during crossmodal processing in binge drinking. Neuroscience studies indeed allow for underlining cerebral changes before the emergence of behavioral deficits, and have brought valuable contributions to the binge drinking research field (see Hermens et al., 2013a; Maurage et al., 2013c for reviews). It might be hypothesized that the preserved behavioral performance observed here actually masks underlying subtle brain modifications.

CONCLUSION

While this preliminary investigation of emotional processing in binge drinking did not emphasize difficulty for emotional detection or crossmodal integration, it bares central perspectives for future studies. Indeed, as one previous study had identified emotional deficits at the behavioral and brain levels in binge drinking, it suggests that emotional abilities are not totally preserved when complex emotional decoding is requested (Maurage et al., 2013a). The current study thus contributes to specifying that the impairments presented by BD depend on the nature and the complexity of the evaluation. Moreover, the ecological design using crossmodal stimuli brings light to the potential beneficial features associated with binge drinking (e.g., positive motivations and social integration), underlining its main distinction with alcohol-dependence, as BD appears preserved in close to real life crossmodal situations. Primary emotional detection thus seems to be preserved, indicating that BD would be undermined only in more complicated situations. Finally, these results suggest that the continuum hypothesis cannot be generalized toward the broad field of emotions processing, and urge future studies to deepen the exploration of emotional and cognitive abilities in binge drinking. A precise description of the impaired versus preserved abilities characterizing this alcohol consumption pattern is needed to have a clearer view of the extent and limits of the continuum hypothesis.

AUTHOR CONTRIBUTIONS

SL, MB, and PM developed the study. All authors contributed to the study design. Data collection was conducted by SL and data analyses were performed in collaboration with all authors (SL, VD, MB, JB, and PM). SL drafted the paper under the supervision of PM, while VD, MB, and JB provided critical revisions. All authors approved the final version of the paper.

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Distress Response to the Failure to an Insoluble Anagrams Task: Maladaptive Emotion Regulation Strategies in Binge Drinking Students

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Background: Emotion regulation refers to the attempt to influence the latency, magnitude, and duration of an emotion, and to modify the experiential, behavioral, or physiological components of the emotional response. In situations of personal failure, individuals, and in particular those who present a tendency to self-focus, may experience intense emotional distress. Individuals who lack proper adaptive emotion regulation strategies may engage in activities leading to immediate pleasure, such as alcohol drinking, in order to escape the self-relevance of emotional experiences. This self-awareness theory of drinking has been shown explain relapses in self-focused alcohol-dependent individuals in situations of personal failure, after detoxification. Such relapses support the existence of maladaptive emotion regulation strategies in alcohol dependence. As binge drinking may be considered as an early stage of alcohol-use-disorder, the aim of this study was to explore the relationship between emotional distress, self-regulation and self-consciousness in binge drinkers (BD).

Methods: Fifty-five students (32 BD and 23 controls) completed different questionnaires related to the self (self-consciousness and self-regulation questionnaires) and were exposed to a situation of self-failure (insoluble anagrams).

Results: The distress induced by the anagrams task was more related to self-blame, ruminations and maladaptive emotion regulation strategies in BD than in controls. Emotional distress was related to less positive refocusing, refocusing on planning, and adaptive emotion regulation strategies among the control group with less public self-consciousness. Emotional distress was related to more positive refocusing, positive reappraisal, refocusing on planning, and adaptive emotion regulation strategies among control participants with higher public self-consciousness. Low self-conscious BD who experienced anagram distress used less acceptance and less refocusing on planning strategies. Conversely, high self-conscious BD used more refocusing on planning strategies when experiencing anagram distress.

Conclusion: This study suggests a relationship between emotional distress and self-regulation, in BD only. Moreover, public self-consciousness appears to be a disposition that motivates non-BD to improve actions and attitudes to meet self-standards. Finally,

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this study suggests a minor role of self-consciousness in the relationship between self-regulation and emotional distress in BD. Finally, low private/public self-consciousness in the binge drinking group may also be related to more maladaptive emotion regulation strategies.

Keywords: binge drinking, self-failure, self-regulation, self-consciousness, self-related sensitivity

INTRODUCTION

Emotion regulation refers to the attempt to influence the latency, magnitude, and duration of an emotion, and to modify the experiential, behavioral, or physiological components of the emotional response (Gross, 2014). In his process model, Gross (2014) highlights five emotion regulation processes: (1) situation selection, (2) situation modification, (3) attentional deployment, (4) cognitive change, and (5) response modulation. The purpose of the first two processes is to directly or indirectly change the environment that has induced the emotion (Gross, 2014; Martins et al., 2016). Attention deployment can be defined as the redirection of attention in a given situation to modify one's emotions. Cognitive change involves the reappraisal of a situation to influence its emotional significance. The final process of response modulation consists in modifying experiential, behavioral or physiological components of the emotional response (e.g., by using relaxation, drugs, etc.) (Gross, 2014).

The cognitive emotion regulation questionnaire (CERQ) was designed to assess the type of cognitive emotion regulation strategies that an individual uses in response to an unpleasant event of daily life (Jermann et al., 2006). This measure assesses four maladaptive and five adaptive cognitive emotion regulation strategies. Self-blame refers to blaming oneself for when experiencing an unpleasant situation. Blaming others refers to holding others responsible when you experience an unpleasant situation. Rumination refers to thinking about the feelings and

TABLE 1 | Multiple regression analyses predicting maladaptive emotion regulation strategies as a function of group (BD and C), distress and their interaction.

Model	β	*t*	*p*	R^2	f^2	*F*	*p*	Bootstrap CI (95%)
Self-blame				0.17	0.20	3.49	0.02	
Group	−1.09	−1.03	0.31					[−3.18; 0.96]
Distress	−0.16	−0.61	0.55					[−0.76; 0.51]
Distress × group	1.04	2.68	0.01	0.12	0.14	7.16	0.01	[0.21; 1.8]
Condition effect of distress on Rumination for each group:								
C (=0)	−0.16	−0.61	0.55					[−3.18; 0.96]
BD (=1)	0.88	3.04	0.003					[−2.15; 2.05]
Rumination				0.10	0.11	1.99	0.13	
Group	−0.17	−0.19	0.85					[−2; 1.58]
Distress	−0.18	−0.82	0.42					[−0.63; 0.29]
Distress × group	0.75	2.26	0.03	0.09	0.10	5.11	0.03	[−0.08; 1.40]
Condition effect of distress on Rumination for each group:								
C (=0)	−0.18	−0.82	0.42					[−2; 1.58]
BD (= 1)	0.57	2.30	0.03					[−1.44; 2.4]
Blaming others				0.10	0.11	1.87	0.15	
Group	−0.01	−0.10	0.92					[−0.29; 0.23]
Distress	0.03	0.85	0.40					[−0.05; 0.08]
Distress × group	0.05	1.09	0.28	0.02	0.02	1.18	0.28	[−0.03; 0.14]
Catastrophizing				0.29	0.41	0.50	0.68	
Group	−0.12	−0.92	0.36					[−0.42; 0.16]
Distress	−0.01	−0.31	0.76					[−0.09; 0.09]
Distress × group	0.04	0.78	0.44	0.01	0.01	0.61	0.44	[−0.08; 0.14]
Maladaptive strategies				0.19	0.23	3.88	0.01	
Group	−2.27	−0.99	0.32					[−7.33; 2.33]
Distress	−0.26	−0.47	0.64					[−1.57; 1.18]
Distress × group	2.30	2.75	0.008	0.12	0.14	7.58	0.008	[0.54; 3.90]
Condition effect of distress on Rumination for each group:								
C (=0)	−0.26	−0.47	0.64					[−7.33; 2.33]
BD (=1)	2.04	3.27	0.002					[−5.11; 4.41]

All β coefficients are unstandardized.

TABLE 2 | Multiple regression analyses predicting adaptive emotion regulation strategies as a function of group (BD and C), distress and their interaction.

Model	β	*t*	*p*	R^2	f^2	*F*	*p*	Bootstrap CI (95%)
Acceptance				0.13	0.15	2.50	0.07	
Group	−2.26	−2.48	0.02					[−3.93; −0.41]
Distress	−0.01	−0.05	0.96					[−0.5; 0.47]
Distress × group	−0.25	−0.75	0.46	0.009	0.009	0.56	0.46	[−1.03; 0.42]
Positive refocusing				0.06	0.06	1.14	0.34	
Group	−1.85	−1.78	0.08					[−3.90; 0.32]
Distress	0.10	−0.39	0.70					[−0.39; 0.65]
Distress × group	0.03	0.08	0.93	0.001	0.001	0.007	0.93	[−0.68; 0.67]
Positive reappraisal				0.05	0.05	0.97	0.41	
Group	−0.66	−0.53	0.60					[−3.08; 1.90]
Distress	0.49	0.30	0.11					[−0.30; 1.19]
Distress × group	−0.59	−1.31	0.20	0.03	0.03	1.72	0.20	[−1.63; 0.32]
Putting into perspective				0.009	0.009	0.15	0.93	
Group	−0.11	−0.11	0.92					[−2.25; 2.09]
Distress	0.16	0.61	0.55					[−0.65; 0.87]
Distress × group	−0.23	−0.59	0.56	0.007	0.007	0.35	0.56	[−1.13; 0.68]
Refocus on planning				0.008	0.008	0.15	0.93	
Group	−0.19	−0.18	0.85					[−2.11; 1.86]
Distress	−0.05	0.25	0.85					[−0.67; 0.61]
Distress × group	−0.12	−0.32	0.75	0.002	0.002	0.10	0.75	[−1.08; 0.71]
Adaptive strategies				0.04	0.04	0.78	0.51	
Group	−5.06	−1.29	0.20					[−13; 3.23]
Distress	0.68	0.72	0.47					[−1.74; 2.85]
distress × group	−1.16	−0.81	0.42	0.01	0.01	0.65	0.42	[−4.52; 1.77]

All β coefficients are unstandardized.

thoughts associated with unpleasant situations. Catastrophizing refers to having thoughts that emphasize the negativity of the situation. Putting into perspective refers to comparing the unpleasant situation to another situation. Positive refocusing refers to thinking about joyful and pleasant issues instead of thinking about the unpleasant situation. Positive reappraisal refers to thinking about the positive personal growth resulting from an unpleasant situation. Acceptance means accepting the reality of an unpleasant situation that is experienced. Finally, refocusing on planning refers to thinking about how to cope with an unpleasant situation. The CERQ is in line with the cognitive aspects of Gross's model of emotion regulation (Martins et al., 2016). Indeed, the adaptive emotion regulation strategies assessed by the CERQ correspond either to attentional deployment (e.g., positive refocusing, refocusing on planning) or to cognitive change processes (e.g., positive reappraisal, putting into perspective) (Martins et al., 2016).

The relevance of the cognitive emotion regulation strategies assessed by CERQ was recently demonstrated in the domain of psychopathology (Martins et al., 2016; Potthoff et al., 2016). These authors observed an association between maladaptive cognitive emotion regulation strategies and symptoms of psychopathology (e.g., somatization, depression, and anxiety), while adaptive strategies seemed to be protective factors. Aldao and Nolen-Hoeksema (2010) even observed that the presence of maladaptive cognitive emotion regulation strategies had more damaging effects on psychological health than the relative lack of adaptive strategies. Response modulation consists mainly in inhibiting emotion expression, and has regularly been associated with negative affect and psychological distress (Lynch et al., 2001; Veilleux et al., 2014), and deficits in adaptive emotional regulation strategies (Veilleux et al., 2014). Individuals who lack proper adaptive emotion regulation strategies tend to use activities leading to immediate pleasure to alleviate negative emotions, but that may be harmful to the self and/or others. These activities may range from alcohol consumption (Baumeister et al., 2007; Merrill and Thomas, 2013; Veilleux et al., 2014), compulsive eating (Davis and Carter, 2009), unsafe sexual activities (Tice et al., 2001; Brawner et al., 2017), or cigarette smoking (Johnson and McLeish, 2016). In such instances, cognitive emotion regulation deficits lead to intense emotional distress from which the individual tries to obtain immediate relief, and also prevent him from making adaptive choices relevant for long-term personal goals (Tice et al., 2001). In other words, the unhealthy behaviors are a maladaptive emotional strategy motivated by the desire to escape the unpleasant awareness of one's own emotional distress (Baumeister et al., 2007).

As a consequence of this tendency, it can be suggested that emotion regulation is tightly related to self-consciousness (SC), i.e., the persistent tendency of individuals to focus attention on the self (Baumeister et al., 2007; Fenigstein, 2009). Indeed, emotion regulation can indeed hardly take place

TABLE 3 | Multiple regression analyses predicting maladaptive emotion regulation strategies as a function of private SC, distress and their interaction in the binge drinking group.

Model	β	*t*	*p*	R^2	f^2	*F*	*p*	Bootstrap CI (95%)
Self-blame				0.40	0.67	6.15	0.002	
Private SC	0.25	1.46	0.16					[−0.08; 0.49]
Distress	0.80	3.25	0.003					[0.39; 1.37]
Distress × private SC	0.08	1.30	0.20	0.03	0.03	1.69	0.20	[−0.02; 0.19]
Rumination				0.25	0.33	3.07	0.04	
Private SC	0.17	0.99	0.33					[−0.28; 0.57]
Distress	0.51	2.11	0.04					[−0.27; 0.96]
Distress × private SC	0.07	1.22	0.23	0.04	0.04	1.49	0.23	[−0.07; 0.28]
Blame to others				0.31	0.45	4.29	0.01	
Private SC	0.003	0.13	0.90					[−0.03; 0.06]
Distress	0.08	2.73	0.01					[0.009; 0.14]
Distress × private SC	−0.02	−2.43	0.02	0.14	0.16	5.90	0.02	[−0.04; −0.002]
Johnson–Neyman significance region								
Value SC	% below		% above					
1.07	46.88		52.13					
Catastrophizing				0.30	0.42	4.07	0.02	
Private SC	0.05	3.06	0.005					[0.01; 0.08]
Distress	0.02	0.76	0.45					[−0.04; 0.07]
Distress × private SC	0.0009	0.15	0.88	0.0006	0.0006	0.02	0.88	[−0.01; 0.02]
Maladaptive strategies				0.50	1	9.18	0.0002	
Private SC	0.67	2.17	0.04					[−0.05; 1.30]
Distress	1.90	4.26	0.0002					[0.67; 2.62]
Distress × private SC	0.05	0.48	0.63	0.004	0.004	0.23	0.63	[−0.14; 0.38]

All β coefficients are unstandardized.

without paying attention to the self (Scheier and Carver, 1977). Fenigstein et al. (1975) proposed a tridimensional construct of SC including private and public SC that refer, respectively, to the tendency to pay attention to internal aspects of oneself (e.g., thoughts, feelings, etc.) and the sensitivity to others' opinion of oneself. Fenigstein et al. (1975) also added a third dimension, which is social anxiety. In his self-awareness model of alcohol consumption, Hull (1981) suggested that alcohol is frequently used as a means to reduce unpleasant awareness elicited by the experience of personal failure. In support of this theory, he observed that alcohol-dependent individuals (AD) scoring high in SC demonstrated a tendency to relapse rapidly after detoxification when they experienced situations of personal failure (Hull et al., 1983, 1986). Consistent with Hull's theory, de Timary et al. (2013) observed that depression symptoms were strongly related to alcohol craving in ADs scoring high on SC, while no such relationship was observed in those with low SC scores. The role of self-related distress in highly self-conscious AD subjects was confirmed by the observation that self-discrepancy, i.e., the difference between the actual self and the ideal self (Higgins, 1987), was related to greater depressive symptoms, alcohol craving and alcohol consumption (Poncin et al., 2015), but also to less adaptive emotion regulation strategies, as measured by the CERQ. Self-consciousness moderated the relationship between the distress related to self-discrepancy and emotion regulation.

These observations support, for the AD population, Hull's self-awareness theory of drinking (1981). However, Hull's theory is not restricted to the AD population and it would be worth testing whether these dimensions also play a role in binge drinking, a milder form of excessive drinking, that is frequently observed at a younger age. Binge drinking is an alcohol consumption pattern defined by alternating episodes of intense alcohol intake and abstinence (Crego et al., 2009). According to National Institute of Alcohol Abuse and Alcoholism [NIAAA] (2004), a binge drinking episode is characterized by drinking four or more drinks for women and five or more drinks for men within a 2-h period. This alcohol pattern, which is widespread among undergraduate students, has damaging consequences such as cerebral and cognitive impact (Field et al., 2008). Binge drinking can also be considered as a risk factor for alcohol-dependence. Approximately 40% of AD individuals exhibit binge drinking habits during late adolescence (Bonomo et al., 2004; Jennison, 2004; Enoch, 2006). Furthermore, Maurage et al. (2012) proposed that binge drinking and alcohol-dependence were two stages of the same phenomenon, as they observed a similar pattern of cognitive impairment between binge drinkers (BD) and alcohol-dependent subjects. In the same vein, we believe it essential to investigate the relationship between emotional distress, SC, and emotion regulation in binge drinking, to identify whether BD also exhibit self-related sensitivity, as observed in the alcohol-dependent population.

TABLE 4 | Multiple regression analyses predicting adaptive emotion regulation strategies as a function of private SC, distress and their interaction in the binge drinking group.

Model	β	*t*	*p*	R^2	f^2	F	*p*	Bootstrap CI (95%)
Acceptance				0.14	0.16	1.47	0.24	
Private SC	−0.17	−1.06	0.30					[−0.61; 0.16]
Distress	−0.26	−1.12	0.27					[−1.06; 0.38]
Distress × private SC	0.10	1.70	0.10	0.09	0.10	2.89	0.10	[−0.10; 0.29]
Positive refocusing				0.02	0.02	0.23	0.87	
Private SC	−0.13	−0.66	0.52					[−0.74; 0.16]
Distress	0.14	0.51	0.61					[−0.57; 0.75]
Distress × private SC	0.03	0.40	0.69	0.006	0.006	0.16	0.69	[−0.10; 0.25]
Positive reappraisal				0.005	0.005	0.05	0.99	
Private SC	0.02	0.10	0.92					[−0.42; 0.46]
Distress	−0.11	−0.34	0.74					[−1.13; 0.46]
Distress × private SC	−0.01	−0.15	0.88	0.0008	0.0008	0.02	0.88	[−0.23; 0.17]
Putting into perspective				0.14	0.16	1.50	0.24	
Private SC	−0.33	−2.09	0.05					[−0.65; 0.01]
Distress	−0.03	−0.13	0.90					[−0.70; 0.45]
Distress × private SC	0.04	0.77	0.45	0.02	0.02	0.59	0.45	[−0.11; 0.17]
Refocus on planning				0.16	0.19	1.78	0.17	
Private SC	0.03	0.18	0.86					[−0.29; 0.42]
Distress	−0.22	−0.88	0.39					[−1.07; 0.22]
Distress × private SC	0.12	2.03	0.05	0.12	0.14	4.10	0.05	[−0.05; 0.24]
Johnson–Neyman significance region								
Value SC	% below		% above					
−4.55	9.38		90.63					
Adaptive strategies				0.06	0.06	0.60	0.62	
Private SC	−0.58	−0.84	0.41					[−2.35; 0.85]
Distress	−0.47	−0.48	0.64					[−4.01; 1.53]
Distress × private SC	0.28	1.15	0.26	0.04	0.04	1.32	0.26	[−0.40; 1.08]

All β coefficients are unstandardized.

Because, contrary to what is observed in the AD population, BD are not always exposed to ethanol consumption and do not exhibit persistent distress, we decided to investigate the relationship between cognitive emotion regulation strategies (using the CERQ), SC and emotional distress that was experimentally provoked in BD and control individuals. For this purpose, an anagram task where part of the task is unsolvable was chosen, because it allows an experience of failure and emotional distress to be induced (Miller, 2010). Whereas a lack of emotion regulation skills may lead individuals to experience greater emotional distress, we first postulated a positive relationship between the intensity of the emotional distress elicited by the anagram task and alterations in emotion regulation strategies in daily life, as measured by a self-rated questionnaire. If binge drinking may be considered as an unhealthy behavior to alleviate negative emotion because individuals lack skills to cope otherwise, we expected that the use of maladaptive emotion regulation strategies in daily life would be more related to distress in the anagram task among BD than in the control group. Finally, the third hypothesis was that SC moderates the relationship between emotional distress after failure in the anagram task and emotion regulation strategies in both groups.

MATERIALS AND METHODS

Participants

A total of 3162 undergraduate students from the Université catholique de Louvain (Belgium) were screened with an online questionnaire assessing binge drinking habits. Among these students, 254 individuals meeting the criteria of control group and 246 individuals meeting recognized criteria characterizing moderate to intense binge drinking habits (Keller et al., 2007; Maurage et al., 2012) were recontacted by email. In order to participate in this research, students had to accept a fasting blood test that was conducted in the early morning to assess their inflammatory status but this issue is beyond the scope of this paper. Although students were financially incentivized to participate in the study, blood sample and early awakening were two reasons that have dampened their desire of participating in this study. Two groups of undergraduate students took part in this study (55 in total). The first group was composed of 32 students (19 men) having moderate to intense binge drinking habits that met the following criteria: (1) drinking 7 or more alcohol units per occasion, where a unit corresponds with 10 g of pure ethanol, (2) having 2 or more drinking occasion per week, (3) having a consumption speed of 3 or more units per hour.

TABLE 5 | Multiple regression analyses predicting maladaptive emotion regulation strategies as a function of public SC, distress and their interaction in the binge drinking group.

Model	β	*t*	*p*	R^2	f^2	*F*	*p*	Bootstrap CI (95%)
Self-blame				0.31	0.45	4.17	0.01	
Public SC	0.13	0.96	0.35					[−0.13; 0.36]
Distress	0.89	3.34	0.002					[0.44; 1.45]
Distress × public SC	0.06	0.79	0.43	0.02	0.02	0.63	0.43	[−0.14; 0.19]
Rumination				0.30	0.43	4.17	0.01	
Public SC	0.30	2.51	0.02					[0.003; 0.55]
Distress	0.62	2.64	0.01					[−0.03; 1.03]
Distress × public SC	0.007	0.11	0.91	0.0003	0.0003	0.01	0.91	[−0.14; 0.18]
Blaming others				0.18	0.22	2.09	0.12	
Public SC	−0.008	−0.46	0.65					[−0.04; 0.04]
Distress	0.08	2.35	0.03					[−0.007; 0.13]
Distress × public SC	−0.008	−0.86	0.40	0.02	0.02	0.74	0.40	[−0.03; 0.02]
Catastrophizing				.07	.08	.70	.56	
Public SC	0.008	0.58	0.57					[−0.02; 0.04]
Distress	0.03	0.98	0.34					[−0.04; 0.09]
Distress × public SC	0.007	0.94	0.35	0.03	0.03	0.89	0.35	[−0.01; 0.03]
Maladaptive strategies				0.44	0.79	7.37	0.0009	
Public SC	0.41	1.71	0.10					[−0.07; 0.83]
Distress	2.09	4.46	0.0001					[0.10; 2.88]
Distress × public SC	0.05	0.40	0.69	0.003	0.003	0.16	0.69	[−0.21; 0.33]

All β coefficients are unstandardized.

The second group consisted of 23 control individuals (9 men) who (1) drank fewer than 2 alcohol units per occasion, (2) had fewer than 0.5 drinking occasion per week, (3) drank less than 1 unit per hour, and (4) drank, on average, fewer than 2 units of alcohol per week. The average age was 20.88 ($SD = 2.17$) for BD and 21.78 ($SD = 2.91$) for the control group. None of the participants reported any personal or family history of substance dependence. No group difference was observed for age [$F(1,53) = 1.763$, $p = 0.19$, $d = 0.36$] nor gender [$\chi^2(1, N = 55) = 2.195$, $p = 0.14$]. This study protocol was approved by the Ethical Committee of the Hospital and the Medical Faculty of the Université catholique de Louvain. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Measures

Procedure

Participants accomplished the anagram solution task (MacLeod et al., 2002; Watkins et al., 2008; Wemm et al., 2010) that consisted of 15 soluble and 15 insoluble anagrams, each five or six letters long. Each letter string from the anagram was displayed on a screen, in a random order, individually during 20 s. Then, a countdown of 10 s began and participants could type their answer. Feedback was given to the participant: "correct" for solved anagrams or "incorrect" for unsolved anagrams. Before starting, participants were instructed that on average 50–60% of anagrams were correctly solved and that their performance at this task would be a good indicator of future academic and career success. In other words, the instructor induced negative affect by providing a standard that students cannot reach. The anagram task was followed by a visual analog scale assessing distress experienced by participants (0 = not at all to 10 = extremely). After the anagram task, participants completed questionnaires assessing cognitive emotion regulation (CERQ) and SC (revised self-consciousness scale). On average, the experiment lasted about 25 min. At the end of the experiment, participants were debriefed about the goal of the anagram task, and no participant indicated that they were aware that it was impossible to reach the anagram standard given.

The Revised Self-Consciousness Scale (RSCS)

The self-consciousness trait was evaluated using Fenigstein et al.'s RSCS (Fenigstein et al., 1975; Scheier and Carver, 1985) that includes 22-items rated on a 4-point Likert scale (0 = extremely uncharacteristic to 3 = extremely characteristic). This measure is comprised of three subscales of *private self-consciousness* (i.e., attention to one's inner feeling and thoughts), *public self-consciousness* (i.e., awareness of the self as a social object), *social anxiety* (i.e., discomfort in the presence of others). The items "I'm always trying to figure myself out," "I care a lot about how I present myself to others," and "It takes me time to get over my shyness in new situations" are some examples of private SC, public SC, and social anxiety, respectively. The internal reliability of the different subscales was acceptable to good, as shown by the Cronbach's alphas: 0.69, 0.65, 0.82 for private SC, public SC, and social anxiety, respectively.

Cognitive Emotion Regulation Questionnaire (CERQ)

The objective of the CERQ is to evaluate how an individual generally copes with unpleasant situations. Thus, it measures

TABLE 6 | Multiple regression analyses predicting adaptive emotion regulation strategies as a function of public SC, distress and their interaction in the binge drinking group.

Model	β	*t*	*p*	R^2	f^2	*F*	*p*	Bootstrap CI (95%)
Acceptance				0.21	0.27	2.47	0.08	
Public SC	0.02	0.16	0.88					[−0.24; 0.28]
Distress	−0.30	−1.33	0.19					[−0.85; 0.17]
Distress × public SC	0.15	2.45	0.02	0.17	0.20	6.02	0.02	[−0.01; 0.28]
Johnson–Neyman significance region								
Value SC	% below		% above					
−1.34	50		50					
Positive refocusing				0.04	0.04	0.36	0.78	
Public SC	−0.05	−0.37	0.71					[−0.44; 0.34]
Distress	0.11	0.38	0.70					[−0.40; 0.67]
Distress × public SC	0.06	0.78	0.44	0.02	0.02	0.60	0.44	[−0.09; 0.25]
Positive reappraisal				0.05	0.05	0.53	0.66	
Public SC	−0.18	−1.15	0.26					[−0.52; 0.08]
Distress	−0.14	−0.46	0.65					[−0.93; 0.40]
Distress × public SC	0.02	0.20	0.84	0.001	0.001	0.04	0.84	[−0.18; 0.18]
Putting into perspective				0.01	0.01	0.09	0.96	
Public SC	−0.02	−0.18	0.86					[−0.26; 0.20]
Distress	−0.08	−0.34	0.73					[−0.64; 0.38]
Distress × public SC	0.02	0.37	0.72	0.005	0.005	0.14	0.72	[−0.09; 0.14]
Refocus on planning				0.16	0.19	1.81	0.17	
Public SC	−0.11	−0.90	0.37					[−0.37; 0.09]
Distress	−0.22	−0.89	0.38					[−0.88; 0.29]
Distress × public SC	0.12	1.87	0.07	0.10	0.11	3.48	0.07	[−0.03; 0.30]
Adaptive strategies				0.10	0.11	1.05	0.38	
Public SC	−0.35	−0.71	0.48					[−1.54; 0.70]
Distress	−0.63	−0.65	0.52					[−3.16; 1.17]
Distress × public SC	0.37	1.42	0.17	0.06	0.06	2.02	0.17	[−0.21; 0.98]

All β coefficients are unstandardized.

cognitive aspects of emotion regulation and consists of 36-items, each of which is rated on a 5-point Likert scale ranging from 1 = almost never to 5 = almost always. This questionnaire comprises nine subscales: self-blame, blaming others, rumination, catastrophizing, putting into perspective, positive refocusing, positive reappraisal, acceptance and refocusing on planning. The first four subscales refer to maladaptive emotion regulation strategies, while the last five ones refer to more adaptive strategies (Garnefski et al., 2001; Jermann et al., 2006). The internal reliability of the different subscales was acceptable to excellent, as shown by the Cronbach's alphas: 0.90, 0.70, 0.60, 0.83, 0.83 for self-blame, rumination, catastrophizing, blaming others and maladaptive strategies, respectively and 0.67, 0.82, 0.84, 0.86, 0.79, 0.90 for acceptance, positive refocusing, refocus on planning, positive reappraisal, putting into perspective and adaptive strategies, respectively.

Statistical Analyses

Firstly, we conducted chi-squared tests and *t*-tests to compare groups on anagram distress, SC and emotion regulation strategies. We conducted regression analyses with anagram distress as the independent variable and emotion regulation strategies as the dependent variable. As the aim of this study was to determine whether binge drinking acts as a dichotomous moderator of the effect of anagram distress on emotion regulation strategies, a moderation analysis was employed. The PROCESS macro for SPSS developed by Hayes (2013) was used to examine moderation analyses. Dummy variables were created with '0' representing the control group and '1' representing the binge drinking group. The second interest of this study was to observe the influence of private and public SC on the relationship between anagram distress and emotion regulation strategies. We conducted moderation analyses using Hayes' PROCESS macro. Private and public SC were considered to be the continuous moderators of the relationship between anagram distress and emotion regulation strategies. The Johnson–Neyman method allows determining the threshold values at which a moderator factor is responsible for a significant relationship between two variables (Hayes, 2013). Bootstrap confidence intervals were generated for regression coefficients in all tables. Considering that no options were available to calculate bootstrap inference for moderation analysis, we used Hayes' hacking method to generate bootstrap confidence intervals (Hayes, 2013; Hayes, unpublished). It is worth mentioning that there were no missing data for all analyses.

TABLE 7 | Multiple regression analyses predicting maladaptive emotion regulation strategies as a function of private SC, distress and their interaction in the control group.

Model	β	*t*	*p*	R^2	f^2	*F*	*p*	Bootstrap CI (95%)
Self-blame				0.06	0.06	0.42	0.74	
Private SC	0.11	0.67	0.51					[−0.23; 0.47]
Distress	−0.16	−0.52	0.61					[−0.84; 0.62]
Distress × private SC	−0.03	−0.67	0.51	0.02	0.02	0.46	0.51	[−0.17; 0.09]
Rumination				0.29	0.41	2.56	0.09	
Private SC	0.28	2.49	0.02					[0.10; 0.59]
Distress	−0.16	−0.82	0.42					[−0.68; 0.32]
Distress × private SC	−0.02	−0.59	0.56	0.01	0.01	0.35	0.56	[−0.14; 0.06]
Blaming others				0.08	0.09	0.52	0.67	
Private SC	0.01	0.62	0.54					[−0.04; 0.07]
Distress	0.03	0.75	0.46					[−0.07; 0.09]
Distress × private SC	−0.004	−0.73	0.48	0.03	0.03	0.53	0.48	[−0.02; 0.006]
Catastrophizing				0.12	0.14	0.89	0.46	
Private SC	0.04	1.58	0.13					[−0.006; 0.09]
Distress	−0.008	−0.19	0.85					[−0.09; 0.11]
Distress × private SC	−0.002	−0.21	0.84	0.002	0.002	0.04	0.84	[−0.02; 0.02]
Maladaptive strategies				0.18	0.22	1.43	0.27	
Private SC	0.70	1.83	0.08					[−0.09; 1.85]
Distress	−0.23	−0.34	0.74					[−1.71; 1.41]
Distress × private SC	−0.08	−0.73	0.47	0.02	0.02	0.54	0.47	[−0.44; 0.20]

All β coefficients are unstandardized.

TABLE 8 | Multiple regression analyses predicting adaptive emotion regulation strategies as a function of private SC, distress and their interaction in the control group.

Model	β	*t*	*p*	R^2	f^2	*F*	*p*	Bootstrap CI (95%)
Acceptance				0.01	0.01	0.07	0.97	
Private SC	−0.05	−0.35	0.73					[−0.31; 0.35]
Distress	−0.02	−0.08	0.94					[−0.61; 0.41]
Distress × private SC	−0.01	−0.33	0.74	0.006	0.006	0.11	0.74	[−0.14; 0.12]
Positive refocusing				0.03	0.03	0.16	0.92	
Private SC	−0.09	−0.60	0.56					[−0.52; 0.18]
Distress	0.09	0.32	0.75					[−0.49; 0.71]
Distress × private SC	−0.005	−0.11	0.92	0.0006	0.0006	0.01	0.92	[−0.13; 0.11]
Positive reappraisal				0.09	0.10	0.63	0.60	
Private SC	−0.05	−0.22	0.83					[−0.52; 0.35]
Distress	0.48	1.34	0.20					[−0.55; 1.13]
Distress × private SC	−0.007	−0.11	0.91	0.0006	0.0006	0.01	0.91	[−0.19; 0.18]
Putting into perspective				0.15	0.18	1.08	0.38	
Private SC	−0.18	−1.00	0.33					[−0.55; 0.19]
Distress	0.16	0.52	0.61					[−0.83; 0.77]
Distress × private SC	0.07	1.32	0.20	0.08	0.09	1.75	0.20	[−0.08; 0.22]
Refocus on planning				0.02	0.02	0.10	0.96	
Private SC	0.03	0.21	0.84					[−0.42; 0.29]
Distress	−0.05	−0.18	0.86					[−0.74; 0.70]
Distress × private SC	−0.02	−0.46	0.65	0.01	0.01	0.21	0.65	[−0.13; 0.13]
Adaptive strategies				0.03	0.03	0.23	0.88	
Private SC	−0.33	−0.52	0.61					[−1.78; 0.84]
Distress	0.66	0.60	0.56					[−2.45; 2.82]
Distress × private SC	0.02	0.11	0.91	0.0007	0.0007	0.01	0.91	[−0.44; 0.55]

All β coefficients are unstandardized.

TABLE 9 | Multiple regression analyses predicting maladaptive emotion regulation strategies as a function of public SC, distress and their interaction in the control group.

Model	β	*t*	*p*	R^2	f^2	*F*	*p*	Bootstrap CI (95%)
Self-blame				0.05	0.05	0.34	0.80	
Public SC	−0.09	−0.43	0.67					[−0.52; 0.42]
Distress	−0.21	−0.66	0.52					[−0.80; 0.59]
Distress × public SC	0.07	0.80	0.44	0.03	0.03	0.63	0.44	[−0.12; 0.21]
Rumination				0.06	0.06	0.43	0.73	
Public SC	0.14	0.80	0.43					[−0.17; 0.54]
Distress	−0.21	−0.86	0.40					[−0.67; 0.31]
Distress × public SC	0.002	0.03	0.98	0.00	0.00	0.0006	0.98	[−0.22; 0.09]
Blaming others				0.11	0.12	0.82	0.50	
Public SC	−0.004	−0.14	0.89					[−0.05; 0.05]
Distress	0.04	1.11	0.28					[−0.05; 0.10]
Distress × public SC	−0.01	−1.33	0.20	0.08	0.09	1.77	0.20	[−0.03; 0.01]
Catastrophizing				0.02	0.02	0.13	0.94	
Public SC	0.02	0.57	0.58					[−0.04; 0.08]
Distress	−0.01	−0.31	0.76					[−0.12; 0.10]
Distress × public SC	0.0007	0.06	0.95	0.0002	0.0002	0.004	0.95	[−0.04; 0.02]
Maladaptive strategies				0.009	0.009	0.06	0.98	
Public SC	0.11	0.20	0.85					[−0.62; 1.10]
Distress	−0.29	−0.38	0.71					[−1.75; 1.46]
Distress × public SC	0.01	0.06	0.96	0.0002	0.0002	0.003	0.96	[−0.44; 0.25]

All β coefficients are unstandardized.

RESULTS

Description of Subject Population

There were no differences between binge drinking and control groups concerning the scores for anagram distress [$t(53) = -0.520$, $p = 0.61$, $d = 0.14$], public SC [$t(53) = 0.109$, $p = 0.28$, $d = 0.30$], private SC [$t(53) = -0.91$, $p = 0.37$, $d = 0.24$], self-blame [$t(53) = 0.865$, $p = 0.40$, $d = 0.24$], rumination [$t(53) = 0.125$, $p = 0.90$, $d = 0.03$], catastrophizing [$t(53) = 0.846$, $p = 0.40$, $d = 0.24$], Blaming others [$t(53) = -0.044$, $p = 0.97$, $d = 0.01$], maladaptive strategies [$t(53) = 0.804$, $p = 0.43$, $d = 0.21$], putting into perspective [$t(53) = 0.08$, $p = 0.94$, $d = 0.02$], positive refocusing [$t(53) = 1.77$, $p = 0.08$, $d = 0.48$], positive reappraisal [$t(53) = 0.451$, $p = 0.65$, $d = 0.12$], refocusing on planning [$t(53) = 0.225$, $p = 0.82$, $d = 0.06$] and adaptive strategies [$t(53) = 1.288$, $p = 0.20$, $d = 0.21$]. The control group used more acceptance strategies than the binge drinking group [$t(53) = 2.557$, $p = 0.01$, $d = 0.69$].

Relationship between Anagram Induced Distress and Emotion Regulation across Subjects

Regression analysis revealed that anagram induced distress was significantly and positively related to blaming others only, $\beta = 0.279$, $t(53) = 2.12$, $p = 0.04$. The predictor explained 8% of the variance [$R^2 = 0.08$, $F(1,53) = 4.483$, $p = 0.04$, $f^2 = 0.09$]. In others words, the participants who exhibited higher distress when exposed to the anagram task were more likely to blame another person when they experienced an unpleasant situation. Conversely, the anagram induced distress was neither a predictor of maladaptive emotion regulation strategies [$R^2 = 0.05$, $F(1,53) = 2.731$, $p = 0.10$, $f^2 = 0.05$] nor of adaptive strategies [$R^2 = 0.00$, $F(1,53) = 0.023$, $p = 0.88$, $f^2 = 0.00$] across participants.

Distress and Emotion Regulation in the BD and Control Groups

To examine the interactive effects of group variable and anagram distress on each emotion regulation strategy, moderation analyses were conducted using Hayes' PROCESS macro. Analyses revealed that the effect of anagram distress variable on self-blame, rumination, and maladaptive emotion regulation strategies was different in the binge drinking and the control groups (**Tables 1**, **2**). In the BD group only, the anagram induced distress was related to more maladaptive emotion regulation strategies, rumination and self-blame.

Relationship between Anagram Elicited Distress, Emotion Regulation, and Private or Public Self-Consciousness in the BD and C Groups

To investigate the influence of private and public SC on the relationship between anagram distress and emotion regulation strategies, moderation analysis was conducted with Hayes' PROCESS macro. The effect of anagram induced distress on blaming others and refocusing on planning strategies depended on private SC in BD (**Tables 3**, **4**). Compared to high self-conscious BD, low self-conscious BD who felt distress in response to the anagram task were more likely to blame others and refocus less on planning. Moreover, public SC moderated the relationship between anagram distress and acceptance: anagram distress was related to less acceptance among low self-conscious

TABLE 10 | Multiple regression analyses predicting adaptive emotion regulation strategies as a function of public SC, distress and their interaction in the control group.

Model	β	*t*	*p*	R^2	f^2	*F*	*p*	Bootstrap CI (95%)
Acceptance				0.14	0.16	1.07	0.38	
Public SC	−0.06	−0.34	0.74					[−0.31; 0.40]
Distress	−0.11	−0.48	0.64					[−0.62; 0.45]
Distress × public SC	0.11	1.79	0.09	0.14	0.16	3.2	0.09	[−0.06; 0.21]
Positive refocusing				0.38	0.61	3.86	0.03	
Public SC	−0.08	−0.49	0.63					[−0.42; 0.40]
Distress	−0.09	−0.41	0.69					[−0.50; 0.48]
Distress × public SC	0.21	3.37	0.003	0.37	0.59	11.37	0.003	[0.02; 0.37]
Johnson–Neyman significance region								
Value SC	% below		% above					
−2.78	21.74		78.26					
3.09	65.22		34.78					
Positive reappraisal				0.37	0.59	3.77	0.03	
Public SC	−0.38	−1.73	0.10					[−0.80; 0.01]
Distress	0.34	1.10	0.29					[−0.48; 1.02]
Distress × public SC	0.21	2.58	0.02	0.22	0.28	6.68	0.02	[0.06; 0.37]
Johnson–Neyman significance region								
Value SC	% below		% above					
1.38	52.17		47.83					
Putting into perspective				0.06	0.06	0.39	0.76	
Public SC	−0.14	−0.61	0.55					[−0.59; 0.48]
Distress	0.11	0.32	0.75					[−0.74; 0.99]
Distress × public SC	0.07	0.83	0.42	0.03	0.03	0.69	0.42	[−0.14; 0.26]
Refocus on planning				0.24	0.32	1.98	0.15	
Public SC	−0.06	−0.30	0.77					[−0.40; 0.42]
Distress	−0.21	−0.79	0.44					[0.87; 0.57]
Distress × public SC	0.17	2.43	0.03	0.24	0.32	5.88	0.03	[−0.02; 0.29]
Johnson–Neyman significance region								
Value SC	% below		% above					
−4.26	13.04		86.96					
8.38	95.65		4.35					
Adaptive strategies				0.36	0.56	3.60	0.03	
Public SC	−0.71	−1.08	0.29					[−1.93; 1.04]
Distress	0.03	0.04	0.97					[−2.29; 2.53]
Distress × public SC	0.77	3.12	0.006	0.33	0.49	9.75	0.006	[0.13; 1.23]
Johnson–Neyman significance region								
Value SC	% below		% above					
−4.36	13.04		86.96					
2.67	65.22		34.78					

All β coefficients are unstandardized.

BD (**Tables 5**, **6**). No influence of private SC on the relation between anagram distress and emotion regulation strategies has been observed among the control group (**Tables 7**, **8**). Public SC moderated the relationship between anagram distress and adaptive emotion regulation strategies among the control group only (**Tables 9**, **10**). Anagram distress was related to more positive refocusing, positive reappraisal, refocusing on planning and adaptive strategies among high self-conscious participants in the control group. Conversely, anagram distress was related to less positive refocusing, refocusing on planning and adaptive strategies among low self-conscious control participants. **Table 11** shows the different correlations between all investigated variables.

DISCUSSION

The main objective of this study was to investigate the relationship between emotional distress, emotional regulation and SC in binge drinking. Individuals scoring high on SC and exhibiting poor emotion regulation skills are likely to experience unpleasant awareness of their emotional distress, and to thus use activities to relieve negative emotion. In an alcohol-dependent population, Hull et al. (1986) has already observed that subjects with high in SC used alcohol as a means of reducing awareness of personal failure and are more likely to relapse when they experience such failure. According to the continuum hypothesis suggesting that binge drinking and alcohol-dependence are two

TABLE 11 | Correlations between all investigated variables.

	Anagram distress	Self-blame	Acceptance	Rumination	Positive refocusing	Refocusing on planning	Positive reappraisal	Putting into perspective	Catastrophizing	Blame to others	Adaptive strategies	Maladaptive strategies	Public SC	Private SC
Anagram distress	1													
Self-blame	0.191	1												
Acceptance	−0.119	0.009	1											
Rumination	0.119	0.440***	0.041	1										
Positive refocusing	0.064	−0.109	0.337*	−0.121	1									
Refocusing on planning	−0.077	−0.132	0.294*	0.064	0.374**	1								
Positive reappraisal	0.132	−0.263†	0.374**	−0.035	0.375**	0.665***	1							
Putting into perspective	0.039	−0.354**	0.327*	−0.233 †	0.362**	0.435***	0.699***	1						
Catastrophizing	0.029	0.504***	0.133	0.544***	−0.046	−0.062	−0.298*	−0.528***	1					
Blame to others	0.279*	0.073	−0.229 †	0.065	−0.147	−0.118	−0.129	−0.076	−0.013	1				
Adaptive strategies	0.021	−0.239†	0.614***	−0.079	0.660***	0.754***	0.865***	0.776***	−0.232	−0.186	1			
Maladaptive strategies	0.221	0.801***	0.001	0.766***	−0.149	−0.093	−0.264	−0.431***	0.744***	0.359**	−0.262	1		
Public SC	0.005	0.035	0.026	0.286*	−0.020	−0.107	−0.200	−0.065	0.108	−0.070	−0.107	0.130	1	
Private SC	0.030	0.229	−0.127	0.377**	−0.141	0.088	−0.042	−0.280*	0.392**	0.049	−0.134	0.378**	0.141	1

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; †$0.05 < p < 0.10$.

stages of the same process (Enoch, 2006; Maurage et al., 2012), it is important to explore in the BD population the potential Self-sensitivity for which activities leading to immediate pleasure (e.g., alcohol consumption) may be used as a means to relieve self-related emotional distress.

It is important to note that there were no differences between the BD and control groups regarding the overall scores of distress on the anagram task, SC and any cognitive emotion regulation strategies, except for acceptance, which was higher in the control group. The question that is raised by this study is, therefore, whether emotional regulation strategies and SC do relate in a specific way to experimentally induced emotional distress, and whether such a relationship might be specific to the BD group. We also examined the potential moderating impact of SC on the relationship between emotional distress and emotion regulation strategies.

The first objective of this study was to examine the relationship between emotional distress associated with the anagram task and emotion regulation strategies. As mentioned above, the anagram task concerned preoccupation with academic achievement (Miller, 2010), which is a central preoccupation in students. It is therefore an appropriate situation for evaluating sensitivity to self-threatening situations. In the overall group, anagram distress was positively related blaming others in unpleasant situations that participants experienced. Besides this relationship, we failed to observe any other relationship between emotional distress and emotion regulation strategies in the overall group. Duval and Silvia (2002) suggest that individuals who note a discrepancy between themselves and an ideal standard and who are unable to improve themselves, have the tendency to attribute their failure to external sources: this seems to be the case for a substantial proportion of the subjects irrespective of their drinking habits.

However, this does not rule out the existence of specific relationships between emotional distress and emotion regulation strategies in the BD or control groups and of a possible influence of SC, which were the subject of our second and third objectives, respectively. The main differences that we observed between the two groups in our data may be summarized in the following manner: (1) In the binge drinking population, greater distress induced by the anagram task was related to more self-blame, to more rumination and to more maladaptive emotion regulation strategies. Hence, binge drinking individuals who experience more distress when exposed to difficult situations are also those that describe a higher tendency for maladaptive strategies, and in particular, strategies that are related to a negative self-perception. This is an indirect observation that supports the role of self-related elements in binge drinking. (2) In control participants with higher levels of SC, greater distress induced by the anagram task was related to more adaptive strategies, and in particular, by more positive refocusing, more positive reappraisal and more refocusing on planning. Such a relationship was not observed in the binge drinking population. A possible explanation for this observation is that in non-binge drinking participants, higher levels of public SC are related to more active modes of coping, such as positive refocusing and reappraisal or refocusing on planning when exposed to negative events.

Overall, these observations support different modes of coping in response to a self-threatening situation among BD and non-binge-drinkers. Silvia and Duval (2001) suggested that different attitudes may be observed when a subject is exposed to situations where he/she does not measure up to their target standards: their first impulse may be to change their actions and attitudes in an attempt to measure up to the expected standards. We believe that this might be the case for the non-binge-drinking individuals that are high in public SC. SC hence appears to be a disposition that motivates them to improve actions and attitudes to meet self-standards. Conversely, some individuals may be overwhelmed by the self-discrepancy induced by the situation of failure, which may lead to maladaptive emotion regulation strategies, such as self-blame or rumination. This trend was observed in the binge drinking population. Considering that self-blame and rumination are regarded as the most self-contained cognitive strategies (Bornas et al., 2013), the observation that BD who express distress related to the self are also more likely to pay attention to the self and to use maladaptive, self-contained emotion regulation strategies in keeping with self-sensitivity in BD. Moreover, rumination and self-blame describe the tendency to focus on the causes, meanings and consequences of distressing situations and to attribute the causality of these situations internally, respectively, which in turn exacerbates psychological distress (Jermann et al., 2006; Moberly and Watkins, 2008). This could highlight a sensitivity to self-stressors in some BD. These results are in line with the observation that ADs are more likely to drink or relapse if they are more self-conscious (Hull et al., 1986; de Timary et al., 2013), and extend Hull's self-awareness theory of alcohol-drinking to part of the BD population (Hull, 1981). These data are also consistent with Poncin et al.'s (2015) results suggesting that the sensitivity toward self-discrepancies is related to less adaptive emotion regulation strategies in the AD population. These results are suggestive of the importance of the sensitivity to self-stressors of a subgroup of BD, but does not allow us to ascertain whether this leads to alcohol consumption. However, Lannoy et al. (2017), suggest the existence of several binge drinking profiles, including an emotional profile for which alcohol is used as a maladaptive regulation strategy. This subgroup of BD could be more sensitive to stressful situations related to the Self and could use alcohol to relieve emotional distress.

Two other differences were also observed between BD and controls. BD, who had below average levels of private SC and who experienced distress from the anagram task, were less likely to refocus on planning and more likely to blame others. BD with low public SC and who experienced anagram distress used fewer acceptance strategies. These two observations suggest that low private/public SC in the binge drinking group may also be related to more maladaptive or less adaptive emotion regulation strategies. Decreasing self-consciousness might be a maladaptive way to escape self-stressors in some BD individuals.

This study is among the first to examine the relationship between self-regulation and SC in binge drinking. A limitation of this study was the small sample size. Field (2007) indicates that the sample size also depends on the effect size. For a regression with three predictors (as in this study), he recommends having a sample size of 40 for a large effect size. If the effect size is medium and small, the sample size should be 80 and 600, respectively. Considering the 3 parameters and the small sample size, regression models might be overfitting. It is thus important to be cautious about the results of this study that may not reflect the overall population. It is therefore necessary to repeat this study in a larger sample in order to increase statistical power and to be even more representative of alcohol consumption in student population. Moreover, to increase the variability of students' consumption behaviors, it may be important to consider alcohol consumption habits as a continuous variable. Townshend and Duka (2002) propose a scoring method based on an alcohol use questionnaire in binge drinking. This score is calculated based on the number of drinks per week, the speed of drinking, number of times one was drunk in the previous 6 months and percentage of time being drunk when drinking. Moreover, another limitation of this study is that there was no manipulation check of emotional distress. Therefore, further studies should pay attention to check participants' emotional state before the task inducing emotional distress. Finally, it could be interesting to distinguish investigate the effect of gender in further studies because there may be gender differences in emotion regulation strategies.

CONCLUSION

This study supports the hypothesis of a difference in the relationship between self-regulation and emotional distress among BD and non-BD. Emotional distress was related to more self-blame, rumination and maladaptive regulation strategies in BD only. A sensitivity to self-stressors with difficulties of emotion regulation was also observed in BD. Moreover, this study suggests that public SC may motivate individuals to improve actions and attitudes to meet target standards among non-binge-drinkers. It is important to continue the careful exploration of the self-related elements model of alcohol consumption in alcohol-dependence and binge drinking, as the identification of shared self-related sensitivity in binge drinking and alcohol-dependence may inform preventative interventions.

AUTHOR CONTRIBUTIONS

All authors developed the study design. MP contributed to the data collection, performed the statistical analysis and wrote the original paper. PdT and NV oversaw the writing of the paper. All authors contributed to and have approved the final version of the manuscript.

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Behavioral Control and Reward Sensitivity in Adolescents' Risk Taking Behavior: A Longitudinal TRAILS Study

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Neurodevelopmental theories of risk behavior hypothesize that low behavioral control in combination with high reward sensitivity explains adolescents' risk behavior. However, empirical studies examining this hypothesis while including actual risk taking behavior in adolescence are lacking. In this study we tested whether the imbalance between behavioral control and reward sensitivity underlies risk taking behavior in adolescence, using a nationally representative longitudinal sample of 715 adolescents, of which 66% revealed an increased risk for mental health problems. To assess behavioral control at age 11 we used both self-report (effortful control) as well as behavioral measures of cognitive control (i.e., working memory and response inhibition). Reward sensitivity was assessed with the Bangor Gambling Task. The main finding of this study was that effortful control at age 11 was the best predictor of risk taking behavior (alcohol and cannabis use) at age 16, particularly among adolescents who were more reward sensitive. Risk taking behavior in adolescents might be explained by relatively weak behavioral control functioning combined with high sensitivity for reward.

Keywords: behavioral control, reward sensitivity, risk taking, substance use, adolescence

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INTRODUCTION

The peak in risk taking behavior, assumed to occur in mid adolescence (14–17 years), has received much attention from different fields of research. Recently, neurodevelopmental studies using fMRI techniques have observed developmental disparities in brain regions associated with behavioral control and reward sensitivity, possibly explaining the peak in risk behavior which is typical for mid adolescence (15–17 years, Galvan et al., 2006; Giedd, 2008; Somerville et al., 2011). The results suggest that brain regions associated with reward and cognitive control follow a different developmental trajectory, resulting in fully developed and relatively hypersensitive reward systems (e.g., affective processing) while control systems are still developing until late adolescence (>18–21 years). Although these differences in neurobiological substrates have been found in several studies (Ernst et al., 2005; Galvan et al., 2006, 2007; Silverman et al., 2015) and used to explain the peak in risk taking behavior characteristic of the mid adolescence period (Spear, 2000; Casey et al., 2008), empirical evidence on the assumed interaction effect of behavioral control and reward sensitivity on the actual risk taking behavior of adolescents is scarce. Adolescents who have difficulties in controlling their behavior and are reward sensitive might be more likely to engage in risk behavior,

as the motivation to engage in risk behavior might be relatively high while the ability to regulate impulses might be relatively low among these adolescents. In the present longitudinal study, we examined the predictive role of behavioral control and studied the differential effect of reward sensitivity on risk taking behavior in a sample of young adolescents. To the best of our knowledge this is one of the first empirical studies examining the development of risk taking behavior in real life in relation to behavioral control and reward sensitivity.

Behavioral Control and Risk Behavior

During adolescence, several neurobiological alterations take place, to some extent driven by pubertal changes and hormones (Giedd, 2008; Blakemore et al., 2010; Peters et al., 2015). While some brain areas, such as the visual cortex and motor cortex, are already fully developed in childhood (Gazzaniga et al., 2002), the fine-tuning of other brain regions, such as the prefrontal cortex, is still in progress during adolescence (Luna et al., 2004; Blakemore and Choudhury, 2006). The prefrontal cortex plays a major role in the regulation of behavior. In the present study, we assessed elements of behavioral control including cognitions that are assumed to be involved in the regulation of behavior (Moffitt et al., 2011), such as the inhibition of responses (e.g., response inhibition) and delay of gratification (Krueger et al., 1996), as well as traits and personality characteristics, such as acting without thinking (Barratt, 1983; Evenden, 1999). We assessed two elements of behavioral control; self-reported behavioral control (i.e., effortful control) and cognitive control (i.e., response inhibition and working memory, Peeters et al., 2015).

Several studies from different disciplines (cf. Verdejo-García et al., 2008) have ascertained the role of behavioral control in the onset and continuation of risk behavior. The use of substances among adolescents, for instance, has been linked to problems with delay of responses (Romer et al., 2010), inhibition problems (Fernie et al., 2013), self-reported impulsivity (Krank et al., 2011; White et al., 2011), and effortful control in particular (Piehler et al., 2012). Behavioral control appears to play a vital role in initiating alcohol use (Squeglia et al., 2014; Peeters et al., 2015) and the development of problematic drinking behavior in adolescents (Nigg et al., 2006). Problems with inhibition, both assessed on a cognitive as well as on a behavioral level increase the chance of early initiating of alcohol use and problem drinking in adolescents. Whelan et al. (2012) found reduced activity in brain regions important for cognitive control even among adolescents who just initiated alcohol use, suggesting that vulnerabilities in neural circuits underlying cognitive control might precede the initiation of drinking behavior in adolescents (Wetherill et al., 2013).

Altogether, these results suggest that relatively early weaknesses in behavioral control might place adolescents at risk for early initiation of risk behavior and the development of related problems. Adolescents with behavioral control problems are more likely to act without thinking and less likely delay response, receiving decreased attention for the negative consequences of behavior and increasing their involvement in risk behavior. This reasoning is in line with Krueger et al. (1996) and Tarter et al. (2003) who assumed that early weaknesses in behavioral control underlie the development of externalizing psychopathology later in life.

Reward Sensitivity and Risk Behavior

Adolescent risk taking behavior is sometimes conceptualized as irrational and impulsive; however, studies suggest little to no differences in risk evaluation and perception between adults and adolescents (Gerrard et al., 1996; Steinberg and Cauffman, 1996; Spear, 2000). This suggests that adolescents, just like adults, are aware of the consequences involved in risk taking behavior. One possible explanation for the observed difference in risk taking behavior among adolescents and adults might thus be that the expected rewarding value of (some) risk behaviors is greater for adolescents than for adults (Van Leijenhorst et al., 2010a,b; Spear, 2011). The gains might simply be much higher for adolescents than for adults when engaging in risky behaviors (Crone and Dahl, 2012). In addition, adolescents might be more sensitive to rewards than adults. Indeed, Chein et al. (2011) found increased activity in reward related brain systems in adolescents while performing a risk taking task; however, this increase was only observed when adolescents completed the task in the presence of peers. This reward sensitization was present not only at a neurocognitive level (e.g., neural activation), but also at a behavioral level (e.g., task performance), resulting in more risk taking behavior by adolescents, as observed by peers. Adults did not reveal this heightened activity or increased risk taking while performing the task with peers (Chein et al., 2011). This study suggested that the peer presence increased the reward for engaging in risky behaviors among adolescents, but not for adults. It seems that the presence of peers changes the perception with respect to the anticipated reward when engaging in risk behavior (Spear, 2011), a change only observed in adolescents but not in adults.

Besides differences in reward perception, the neurological response observed among adults and adolescents is different when faced with the same rewarding stimuli (Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2010a,b). Van Leijenhorst et al. (2010a), for instance, found that adolescents compared to adults and children revealed a heightened neurological response toward rewards in a decision making task. Participants could choose either a low-risk gamble (lower risk and lower reward) or a high-risk gamble (higher risk and higher reward). While performing the task, brain activation was assessed using fMRI techniques. The results indicated that during adolescence, reward related systems show a peak in activation in response to risky decisions, with a possible high rewarding outcome.

With respect to risk taking behavior in real life like substance use, individual variability among adolescents in reward sensitivity either due to heightened neurological responses or higher expected rewarding value of engagement in these risk behaviors might explain why some adolescents more than others engage in risky behaviors like substance use. Taking risk might be more rewarding for some individuals in certain situations compared to different individuals in different situations (Dawe et al., 2004; Galvan et al., 2007). Heightened reward sensitivity might contribute to more risk taking behaviors in reward sensitive

adolescents, as shown in a study by van Hemel-Ruiter et al. (2015) who found that adolescents (12–18 years) who scored high on reward sensitivity drank more heavily compared to adolescents who were less sensitive to reward. Moreover, Xiao et al. (2013) found differences in reward sensitivity assessed with the Iowa Gambling Task (IGT; a measure assumed to assess variation in reward sensitivity, Franken and Muris, 2005; Cauffman et al., 2010) between adolescent binge drinking and abstainers, such that binge drinkers were more sensitive for reward than the abstainers. Altogether, these results suggest that individual differences in reward sensitivity are directly associated with risk behaviors, such as alcohol use. Moreover, the increased sensitivity to reward observed in adolescents relative to adults and children affects the level at which behavioral control must be deployed (Somerville et al., 2011).

Present Study

Neurodevelopmental models suggest that the peak in risk behavior in mid adolescence can be explained by the interplay between not yet fully developed cognitive control functions and increased neural responses toward reward (e.g., dual system models/imbalance model, cf. Spear, 2000; Galvan et al., 2006; Casey et al., 2008; Giedd, 2008; Somerville et al., 2011; Smith et al., 2013; Silverman et al., 2015). To this end it is hypothesized that adolescents with relatively weak behavioral control at age 11 and high reward sensitivity at age 16 are at the greatest risk for risk behaviors at age 16, such as alcohol use, cannabis use, and smoking. To the best of our knowledge, this is the first longitudinal study that examined this interaction looking at both self-reported behavioral control as well as cognitive control. Although these measures all tap in the same underlying construct, namely behavioral control, they might be differently related to specific risky behaviors like substance use (Verdejo-García et al., 2008; Janssen et al., 2015) and interact differently with reward sensitivity.

MATERIALS AND METHODS

Participants

Participants in the present study were selected from a larger longitudinal population study that included 2230 Dutch adolescents who enrolled the study at age 11, and they were followed at least to age 25. For a detailed description of the inclusion criteria and selection process, please see de Winter et al. (2005) and Huisman et al. (2008). Mean age of the population sample was 11.09 years at baseline ($SD = 0.59$, 50.8% girls), 13.56 years at T2 ($SD = 0.53$), and 16.13 years at T3 ($SD = 0.73$). Response rates were 2149 (96.3, 51.2% girls) at T2 and 1816 (81.6, 52.3%) at T3 for the population sample.

At the third wave, a focus sample of 744 adolescents was selected and invited to participate in a number of laboratory tasks. In total, 715 (96.1%) adolescents (49.1% boys) agreed to participate in this experimental session (Mean age T1 = 11.10, $SD = 0.55$, T3 = 16.11, $SD = 0.59$). Adolescents with increased risk for mental health problems (e.g., high frustration/fearfulness and low effortful control, and family risk parental depression, anxiety, addiction, psychoses, antisocial behavior, single parent household) were oversampled in this focus cohort, resulting in a group of 66% adolescents being at risk and 34% adolescents being randomly selected from the population sample ($N = 715$). Information on mental health problems assessed with the Youth Self-Report Scale for the focus sample and for the total TRAILS sample (including simple *t*-test) are provided in **Table 1**. Adolescents in the focus cohort scored significantly higher on Attentional Deficit Hyperactivity Disorder (ADHD) and Oppositional Disorders, in line with Krueger et al. (1996) and Tarter et al. (2003). Due to a strong overlap between these subscales of the YSR and aspects of behavioral control (e.g., ADHD and effortful control Pearson correlation = −0.48, $p < 0.001$; oppositional problems and effortful control Pearson correlation = −0.34, $p < 0.001$) we decided not to include these subscales as confounding variables. The experimental protocol was approved by the Central Committee on Research Involving Human subjects (CCMO). Written informed consent was obtained from the participants. Assessment took place under the guidance of a TRAILS research assistant who received extensive training to ensure a standardized procedure for all participants. Assessment took place at different locations (depending on the residence of the participants). At each location, the experimental room was sound proof, and it had blinded windows (for a detailed description of the procedure of the experimental session, see Bouma et al., 2009).

In this study, we used a focus cohort, which provided the possibility to include additional measures that might be relevant for this specific group and age. This resulted in varying availability of measures. Measures of behavioral control for instance were available at wave 1, however, not at wave 3, while measures of reward sensitivity were only assessed within the focus cohort and therefore only available at wave 3.

Measures

Risk Behavior

Alcohol use

To select the drinking adolescents from the non-drinking adolescents at the first wave, adolescents were asked to indicate whether they ever consumed alcohol in their lives. Adolescents

TABLE 1 | Mental health scores and mean differences on subscales of the Youth Self-Report Scale for the total sample and the at-risk sample.

	Mean (SD) risk sample ($N = 715$)	Mean (SD) population Sample ($N = 2191$)	*t*-test
Affective problems	0.300 (0.244)	0.292 (0.247)	−1.595
Anxiety problems	0.354 (0.305)	0.346 (0.305)	−1.131
Somatic problems	0.460 (0.323)	0.458 (0.332)	−0.237
Attentional Deficit Hyperactivity Problems	**0.625 (0.359)**	**0.588 (0.358)**	**−4.822**
Oppositional problems	**0.465 (0.343)**	**0.445 (0.348)**	**−2.660**
Conduct problems	0.241 (0.202)	0.235 (0.197)	−1.465

Numbers in bold significantly differ from each other.

could select from five categories ranging from "never" to "7 times or more." Depending on their answers to this item, adolescents were selected for the final analyses in which only non-drinkers at wave 1 were included (see also the analyzing strategy). At the third wave, alcohol use was assessed with the quantity by frequency measure (Sobell and Sobell, 1995). Participants indicated on how many days during the week (Monday to Thursday) and weekend (Friday to Sunday, two items) they consumed alcohol on average. In addition, participants were asked to indicate the average number of drinks they consumed on a regular weekend or weekday (two items). The drinking weekdays were multiplied by the number of drinks consumed on a weekday, and the drinking weekend days by the number of drinks on a regular weekend day. A sum score was specified by adding these two numbers together.

Cannabis use

At the first wave, adolescents were asked to indicate whether they had ever smoked cannabis in their lives. Adolescents could select from five categories ranging from "never" to "7 times or more." Depending on their answers to this item, adolescents were selected for the final analyses in which only non-cannabis users at wave 1 were included (see also the analyzing strategy). At the third wave, cannabis use was assessed by the number of occasions (e.g., party, at home, going out) on which cannabis was consumed in the last month. Possible answer categories ranged from 0 to 40 times or more (0–10; 11–19; 20–39; 40 *or more*).

Smoking behavior

At the first wave, adolescents were asked to indicate whether they had ever smoked a cigarette in their lives. Adolescents could select from five categories ranging from "never" to "7 times or more." Depending on their answer to this item, adolescents were selected for the final analyses in which only non-smokers at wave 1 were included (see also the analyzing strategy). At the third wave, adolescents were asked to indicate the amount of cigarettes they smoked per day in the last 4 weeks. Response categories ranged from "never smoked" to "more than 20 cigarettes a day," with the other categories distinguishing between occasional (e.g., once a week/one per day) and daily smokers (e.g., 2–20 cigarettes per day).

Effortful Control

At the first wave (age 11), effortful control was assessed using the child version of the Early Adolescent Temperament Questionnaire revised (EATQ-r; Putnam et al., 2001). This revised version of the EATQ was developed to improve assessment of self-regulation and executive functioning (Putnam et al., 2001). Items loading on the "effortful control" factor were selected to measure self-reported behavioral control. This part of the questionnaire comprises 11 items with response categories ranging from "almost never true" to "almost always true" (e.g., I tend to get in the middle of one thing, then go off and do something else). A Dutch translated version was used (Oldehinkel et al., 2004). The internal consistency of the scale was acceptable ($\alpha = 0.69$). Higher scores indicate better effortful control.

Cognitive Control

At the first wave (age 11), cognitive control was assessed using the Amsterdam Neuropsychology Task (ANT, de Sonneville, 1999). Both working memory and response inhibition, that is, executive functions involved in cognitive control, were assessed with the ANT. In the working memory task, participants have to indicate whether certain letters are presented in the square presented on the computer screen. In the first part (40 trials), the working memory load was low, and participants only needed to indicate whether a certain letter ('k') is presented in the square (i.e., yes or no). In the second part (96 trials), the working memory load was high, and the participants needed to indicate whether one of the three letters ('k, r, s') are presented on the screen. The median reaction time of the correct trials on the low load (part 1) was subtracted from the median reaction time of the correct trials on the high load (part 3), with higher scores indicating poorer working memory performance. In the response inhibition task, participants received the instruction to indicate on which side the target is located (right or left) by using the corresponding arrows on the keyboard. In the first part (40 trials), the compatible condition, all targets were green, and the participants had to respond congruent with direction of the target. In the second part (40 trials), the incompatible condition, some targets were red, and participants needed to respond in the opposite direction (e.g., left when the target jumps to the right and vice versa). In this latter condition, participants needed to inhibit a predominant response. The median RT in the incompatible condition was subtracted from the compatible condition, with higher scores indicating poorer response inhibition. Both final RT scores were divided by 1000 to avoid large covariances between variables.

Reward Sensitivity

In the third wave (age 16), reward sensitivity was assessed using the Bangor Gambling Task (BGT, Bowman and Turnbull, 2004). The BGT is a simplified and alternative version for the IGT (Bechara et al., 1994) assessing responses to reward under arousing circumstances in which real gains and losses can follow behavioral decisions. The BGT uses regular playing cards in which high cards (e.g., jack's, ace) produce gains in money while low number cards (e.g., 2–10) produce losses. Participants received 5.00 euro (and could keep the money they won), and they were instructed to win as much money as possible by choosing either to "gamble" or "not to gamble" (100 trails). Participants were told that cards were not randomly chosen but specifically selected for this gamble task and that when they would choose wisely they would be able to win money. When participants decided not to gamble, there was no gain or loss of money, regardless of the card. When participants chose the gamble option, they either lost or won the money, depending on the face of that card (win or loss high = €0.40, win or loss low = €0.20). As the game progressed, the probabilities of losing money increased. To this end it is expected that as the

risk to lose money increases with successive blocks, the selection of the non-gamble options should increase accordingly in non-clinical populations. Mean block scores indeed revealed such pattern (mean block is non-gamble – gamble option: mean block 1 = −1.14; mean block 5 = 11.05). Contrary to Bowman and Turnbull (2004), the participants in the present study did not receive more money when they had no money left. This resulted in a situation in which some participants lost all their money after playing 71 cards. To ensure that a gambling score for each participant was calculated in the same manner and based on the same number of cards, only the first 71 played cards were used (the total amount of cards that were played by all participants). The percentage of gambling choices was calculated as the number of gambling choices divided by the total cards played (van Leeuwen et al., 2011), and it was used as a measure of reward sensitivity.

Strategy of Analysis

First, descriptive statistics and Pearson correlations among the study variables are provided. Second, simple path analyses were used to examine the unique effects of effortful control, cognitive control, and reward sensitivity on the three risk behaviors. For each risk behavior, we selected adolescents who indicated that they had not used the substance in question at baseline. This resulted in three different data sets, one including only non-drinkers at baseline ($N = 489$), one including only non-cannabis users ($N = 699$), and one including only non-smokers at baseline ($N = 615$). **Table 2** includes an overview of the sample size and demographic information for each data set separately. In the second step, interaction variables were created between reward sensitivity and cognitive control and between reward sensitivity and effortful control using centered variables. Each interaction was entered in a separate model in order to maintain a clear interpretation of each interaction effect. Cannabis use and smoking both revealed a skewed distribution with many zeros; therefore, we used a Zero-Inflated Poisson (ZIP) model as a traditional Poisson model is not sufficient when standard deviations are bigger than the mean (over-dispersion; cf. Peeters et al., 2012). The ZIP model allowed us to interpret the continuous part of the model (adolescents who used cannabis/cigarettes) while accounting for the many zero's. We controlled for gender and used Maximum likelihood with robust standard errors (MLR) as estimation method to account for non-normality of the data in all analysis. FIML was used to deal with missing data. Analyses were completed in Mplus version 7.3 (Muthén and Muthén, 1998). Model fit measures were not informative because all possible paths in the model were estimated (e.g., full model).

RESULTS

Information on Subsamples

For each risk behavior (i.e., alcohol, cannabis, smoking), we selected the non-users at baseline resulting in three different samples with non-users at baseline (either non-drinker, non-cannabis user or non-smoker at wave 1). Measures of behavioral control at wave 1 therefore preceded risk behavior. **Table 2** includes information on mean age, percentage boy/girl, the three measures of behavioral control and for reward sensitivity for the three subsamples separately and for the total sample. We further looked at the use of other substances in the specific subsamples (alcohol, cannabis, and smoking behavior). In the alcohol sample only one adolescent reported cannabis use. Ninety-three percent reported that they never smoked a cigarette (1.5% adolescents indicated cigarette use more than once). In the cannabis subsample, 69.6% reported no alcohol use at baseline (around 15% of the drinkers reported that they only drank alcohol once in their lives). 87.9% reported no smoking behavior (4.5% of the smokers reported cigarette use more than once). In the smoking subsample, 73.8% reported no alcohol use at baseline (around 12% of the drinkers reported that they only drank once in their lives). Only three (0.5%) adolescents reported cannabis use, of whom 1 reported cannabis use more than once at baseline.

Descriptive Statistics

In **Table 3**, descriptive statistics for the three risk behaviors, alcohol, cannabis, and smoking, are presented. All three risk behaviors revealed a positive association with each other. Furthermore, Pearson correlation revealed poorer effortful control, working memory performance, and response inhibition for boys. Alcohol and cannabis use were both higher among boys; however, smoking behavior appeared to be higher among girls. T-test supported this assumption [$t(684) = 2.847$, $p < 0.005$]. In addition, weaker effortful control at T1 was associated with more alcohol use, cannabis use, and smoking behavior at T3. Reward sensitivity at T3 was positively associated with alcohol use at T3, however, no significant correlation was found with cannabis use or smoking. Working memory and response inhibition correlated positively with each other. A negative correlation was found between working memory and effortful control, suggesting poorer working memory functioning is associated with relatively

TABLE 2 | Demographic information and descriptive statistics of study variables for each data set separately.

Data set	N	Mean age wave 1 (*SD*)	% boy	Effortful control T1 Mean (*SD*)	Working memory T1 Mean (*SD*)	Response inhibition T1 Mean (*SD*)	Reward sensitivity T3 Mean (*SD*)
Total sample	715	11.10 (*0.55*)	49.1	3.54 (*0.52*)	0.47 (*0.25*)	0.19 (*0.15*)	0.50 (*0.13*)
Non-alcohol use	486	11.06 (*0.55*)	43.3	3.59 (*0.53*)	0.46 (*0.24*)	0.19 (*0.15*)	0.51 (*0.13*)
Non-cannabis use	699	11.10 (*0.55*)	48.4	3.55 (*0.52*)	0.47 (*0.25*)	0.19 (*0.15*)	0.51 (*0.13*)
Non-smoking behavior	615	11.09 (*0.55*)	47.8	3.59 (*0.52*)	0.46 (*0.26*)	0.20 (*0.16*)	0.50 (*0.14*)

TABLE 3 | Descriptive statistics and Pearson correlations for all study variables for the total sample.

	M *(SD)*	1	2	3	4	5	6	7
(1) Boy (%)	49.1%							
(2) Effortful control T1	3.54 *(0.52)*	−0.11*						
(3) Working memory T1	0.47 *(0.25)*	0.16**	−0.09*					
(4) Response inhibition T1	0.19 *(0.15)*	0.04	0.01	0.14**				
(5) Reward sensitivity T3	0.51 *(0.13)*	−0.01	−0.11*	−0.01	0.04			
(6) QF T3	5.92 *(7.15)*	0.13*	−0.15**	0.01	−0.02	0.14**		
(7) Cannabis use T3	1.40 (*5.73*)	0.15**	−0.15**	0.08*	−0.04	0.01	0.28**	
(8) Smoking T3	1.56 *(2.37)*	−0.12**	−0.12**	−0.01	−0.04	0.08	0.48**	0.31**

*QF, quantity by frequency alcohol use; * = $p < 0.05$, ** = $p < 0.01$. Effortful control, higher scores indicate better control; working memory + inhibition, higher scores indicate worse performance/lower control.*

TABLE 4 | Regression coefficients for main effects, with alcohol use at T3 as outcome measure.

	B	*SE*	*p*-value (2-tailed)
Multivariate main effects			
Sex	0.09	0.05	0.06
Working memory T1	−0.09	0.05	0.87
Response inhibition T1	−0.01	0.04	0.76
Effortful control T1	−0.14	0.05	**<0.01**
Reward sensitivity T3	0.12	0.08	0.13
Interaction effects			
Work × reward	0.33	0.29	0.26
Inhibition × Reward	0.01	0.45	0.97
Effort × Reward	−0.57	0.15	**<0.01**

Work, working memory; Inhibition, response inhibition; Effort, effortful control; Reward, reward sensitivity. Numbers in bold indicate significant effects.

TABLE 5 | Regression coefficients for main effects, with cannabis use (zero inflated) at T3 as outcome measure.

	B	*SE*	*p*-value (2-tailed)
Multivariate main effects			
Sex	0.43	0.18	**0.02**
Working memory T1	0.43	0.15	**<0.01**
Response inhibition T1	−0.44	0.19	**0.02**
Effortful control T1	−0.57	0.12	**<0.01**
Reward sensitivity T3	−0.22	0.18	0.24
Interaction effects			
Work × reward	−0.64	0.45	0.16
Inhibition × Reward	−0.11	1.16	0.92
Effort × Reward	−1.31	0.46	**<0.01**

Work, working memory; Inhibition, response inhibition; Effort, effortful control; Reward, reward sensitivity. Numbers in bold indicate significant effects.

TABLE 6 | Regression coefficients for main effects, with smoking (zero inflated) at T3 as outcome measure.

	B	*SE*	*p*-value (2-tailed)
Multivariate main effects			
Sex	0.07	0.47	0.88
Working memory T1	−0.61	0.36	0.09
Response inhibition T1	−0.34	0.50	0.50
Effortful control T1	−0.44	0.45	0.34
Reward sensitivity T3	0.53	0.44	0.22
Interaction effects			
Work × reward	1.26	1.25	0.31
Inhibition × Reward	2.67	1.28	**0.04**
Effort × Reward	−1.84	2.99	0.54

Work, working memory; Inhibition, response inhibition; Effort, effortful control; Reward, reward sensitivity. Numbers in bold indicate significant effects.

weaker effortful control skills (note that higher scores on inhibition and working memory indicate poorer functioning).

Main Effects

In **Tables 4–6**, the main unique effects of effortful control, cognitive control, and reward sensitivity on risk behavior are presented. We included all three behavioral control measures in the same model to analyze their unique contribution to risk behavior. With respect to alcohol, effortful control at T1 significantly predicted T3 alcohol use ($\beta = -0.15$, $SE = 0.05$). That is, adolescents with relatively poor effortful control at T1 increased stronger in their alcohol use between T1 and T3 compared to adolescents with relatively good effortful control. For reward sensitivity and cognitive control, no main effect on alcohol use was found.

With respect to cannabis use, a similar pattern for effortful control was observed in that effortful control at T1 predicted a stronger increase in cannabis use between 11 and 16 years of age ($\beta = -0.57$, $SE = 0.12$). Weaker effortful control skills at age 11 predicted cannabis use at age 16. In addition, working memory functioning at age 11 predicted cannabis use at age 16 ($\beta = 0.43$, $SE = 0.15$). Adolescents with relatively weaker working memory skills at age 11 used more cannabis use at age 16 (note higher scores on working memory indicate poorer functioning). In contrast to what was expected, response inhibition was a significant predictor of cannabis use, with those having relatively good inhibitions skills progressing more heavily in the use of cannabis compared to those with weaker inhibition skills ($\beta = -0.08$, $SE = 0.03$). Additional analysis revealed that response inhibition was only a significant predictor of cannabis use when controlling for other measures of behavioral control and not when analyzed alone ($\beta = -0.36$, $SE = 0.40$). In addition,

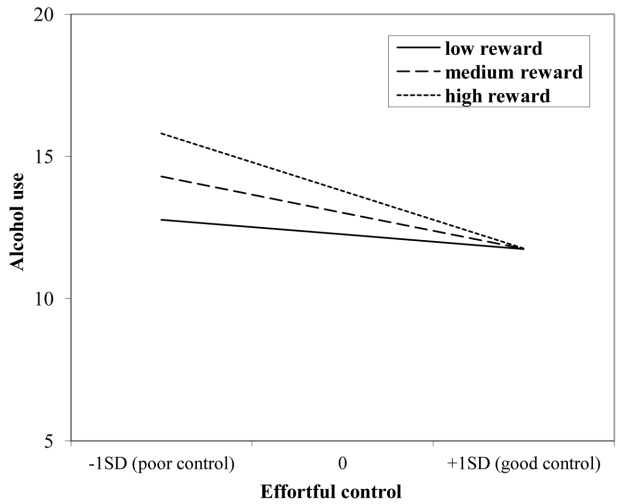

FIGURE 1 | Interaction of reward sensitivity on the relation between effortful control and alcohol use.

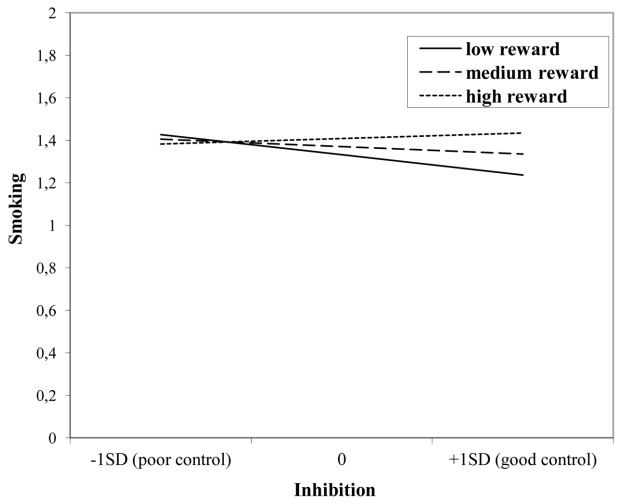

FIGURE 3 | Interaction of reward sensitivity on the relation between response inhibition and smoking.

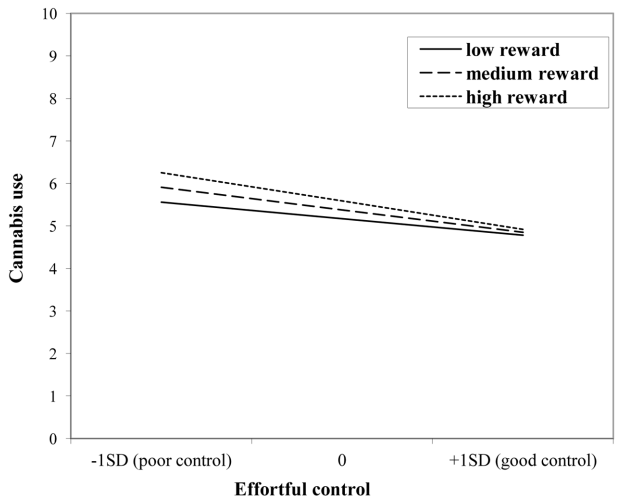

FIGURE 2 | Interaction of reward sensitivity on the relation between effortful control and cannabis use.

gender was a significant predictor of cannabis use at age 16, with boys more likely using cannabis compared to girls.

With respect to smoking behavior, none of the hypothesized main effects were significant. Only gender was a significant unique predictor.

Differential Effects

The interaction effect with reward sensitivity was examined for all three measures of behavioral control (**Tables 4–6**). A significant interaction was found between reward sensitivity and effortful control for alcohol use ($\beta = -0.57$, $SE = 0.15$) and cannabis use ($\beta = -0.28$, $SE = 0.13$). These interaction effects are illustrated in **Figures 1** and **2**. The interaction effect reveals that adolescents with relatively poor effortful control at age 11 and high levels of reward sensitivity at age 16 are the heaviest drinkers and cannabis users at age 16 (controlled for previous use). For adolescents with good effortful control at baseline, the level of reward sensitivity in mid adolescence does not appear to influence the amount of alcohol or cannabis that is consumed in mid adolescence. In contrast, for smoking no main effect of response inhibition on smoking behavior was observed; however, the interaction between response inhibition and reward sensitivity predicting smoking behavior was significant (**Figure 3**; $\beta = 2.67$, $SE = 1.28$). When response inhibition was relatively good, adolescents who were less reward sensitive smoked less at age 16 (reversed effect).

DISCUSSION

This study tested the unique and differential effects of behavioral control and reward sensitivity on risk taking behavior among adolescents. The results indicated that effortful control in early adolescence (age 11) was a significant unique predictor of alcohol and cannabis use in mid adolescence (>4 years later). Adolescents with weak effortful control present before alcohol or cannabis use is initiated, progress more strongly in their use of alcohol and cannabis compared to adolescents with relatively good behavioral control. This effect was strongest among adolescents who were relatively more reward sensitive at age 16. It should be noted, however, that the relation between reward sensitivity and substance use is cross-sectional of nature; both outcomes were assessed at age 16. It is possible that substance use at earlier ages results in more reward sensitivity at age 16, and not otherwise. Though, recent findings of Peeters et al. (2013) suggest that motivational processes such as reward sensitivity, more likely predict increase in substance use than that they increase as a result of substance use. Moreover, the findings are in line with Kim-Spoon et al. (2016) who found that reward sensitivity, was associated with earlier substance use

onset in the group of adolescents with lower behavioral control. Nevertheless, more longitudinal studies in different cultures (see for an overview Duell et al., 2016) are needed before any firm conclusion can be drawn with respect to the nature of this relationship.

Cognitive control as measured with neurocognitive tasks, predicted only cannabis use at age 16. Adolescents with relatively weak working memory functioning at age 11 were more likely to increase in their cannabis use between 11 and 16 years of age. In addition, and in contrast to the other findings, adolescents with better inhibition skills at age 11 were more likely to increase stronger in cannabis use between 11 and 16 years of age. This surprising finding might be explained by the fact that all measures of behavioral control show overlap, as this relation was only significant when controlling for effortful control and working memory, not when examined alone. Working memory remained a significant predictor of cannabis when analyzed in the absence of other behavioral control measures. Nevertheless, the correlations between the measures of behavioral control were not all significant suggesting that other explanations are needed.

These findings are partly in line with research, suggesting that risk behavior is a result of different neurodevelopmental trajectories, underlying processes of reward, and behavioral control (Galvan et al., 2006; Blakemore and Robbins, 2012). Several researchers have suggested that (emotional) decision making develops in mid adolescence; however, not fully developed control systems could exert insufficient influence on affective processes, resulting in hypersensitivity to reward and increased engagement in risk behavior during adolescence (Steinberg, 2007; Casey and Jones, 2010; Spear, 2011; Crone and Dahl, 2012). Surprisingly, we only found this interaction for self-reported effortful control and not for cognitive control as measured with neurocognitive tasks while according to several theoretical studies (Steinberg, 2007; Casey et al., 2008; Spear, 2011) particularly cognitive control systems would reveal immature development and possibly interact with processes involved in reward. The current study revealed only an effect of cognitive control on cannabis use and not on alcohol use or smoking behavior. It should be noted, however, that cognitive control was assessed in early adolescence (11–12 years) and not in mid adolescence (15–16 years), which is assumed to be the period at which risk taking behavior reaches its' peak. It is possible that immature brain development, as indicated by these measures of cognitive control, does not necessarily explain the increased risk behavior among adolescents. Somerville et al. (2011), for instance, found different cognitive control responses toward appetitive stimuli among adolescents compared to adult and children. These appetitive stimuli can be seen as rewarding. The results of Somerville et al. (2011) suggested a kind of context-dependent reduced control observed in adolescents who are faced with rewarding stimuli, which has not been seen in adults and children. Similarly, Botdorf et al. (2016) found that weaker behavioral control under arousing circumstances was associated with (laboratory) risk taking behavior. This might indicate that the situation itself elicits impaired cognitive control responses and that it is not so much a matter of immature cognitive control, but rather temporary weaker control in response to rewarding stimuli. Traditional measures of cognitive control (e.g., inhibition/interference tasks, working memory load tasks) might not be able to assess these temporary impairments, as these measures assess cognitive control in so called "cold situations" (Metcalfe and Mischel, 1999). The effortful control scale (e.g., EATQ-R) includes references to so called "hot situations" (e.g., the more I try to stop myself from doing something I shouldn't, the more likely I am to do it") and for that reason, it might better tap into behavioral control processes under arousing circumstances. Similarly, Romer et al. (2010) suggested that a rise in sensation seeking might explain the increased risk behavior in mid adolescence. Romer found no difference in the importance of behavioral control in explaining risk behavior, despite the age differences in the sample (e.g., 14–22 years). This implies that irrespective of age, behavioral control is an important predictor of risk behavior and according to Romer et al. (2010), the maturation of cognitive control in adolescence might be less important in explaining risk behavior than previously assumed. In addition, Romer et al. (2010) suggested that experience with risk taking behaviors might even increase behavioral control, as the negative consequences of these behaviors may act as a constrain. In other words, experience with risk behaviors might eventually result in increased control over behavior according to negative reinforcement principles. In the present study, we only looked at behavioral control at the age of 11, before the critical period of 16 years during which a peak in risk behavior is observed. To test this hypothesis in more detail, future research should examine possible increases in behavioral control after involvement in risk behavior in a research design with multiple measurement waves over a closer period of time.

In contrast to what was expected, we did not find a main effect of reward or behavioral control on smoking behavior at age 16. An interaction was found, although in a different direction: Adolescents with good inhibition skills who were low in reward sensitivity indicated less cigarette use. A possible explanation may be that adolescents experience craving for and withdrawal symptoms of smoking differently compared to other risk behaviors, such as alcohol use (Chung and Martin, 2005). Accordingly, behavioral control and reward sensitivity might predict experimental use of smoking but are less successful in predicting regular smoking behavior.

Limitations

Bedsides the strengths of the study, such as a large sample size and the use of different measures of control, some limitations should be mentioned. First, both effortful control and cognitive control were assessed only at wave 1 at age 11. This allowed us to look at weaknesses in behavioral control before initiation of alcohol. Yet, it can be argued that levels of behavior control at this stage of live are not indicative of levels of control during mid adolescence when the peak in risk taking is observed. After all, the ongoing maturation of the prefrontal cortex during adolescence is assumed to play a vital role in explaining the risk behavior (Steinberg, 2007; Casey and Jones, 2010). At the same time, recent studies have suggested (Forbes and Dahl, 2010; Peters et al., 2015) that the onset of puberty entails hormonal changes that underlie structural brain maturation and influence cognitive

processing associated with reward, motivation, and risk taking behavior. Moreover, individual differences in cognitive control might already be visible at this early age, reflecting a general pattern of growth that is not age specific (Spear, 2000; Casey et al., 2008). In addition, longitudinal assessment of cognitive control in the TRAILS study does reveal correlation between cognitive control at ages 11 and 19 (Boelema et al., 2015). Nevertheless, for future research, it would be interesting to include measures of cognitive control in mid adolescence when the peak in risk taking behavior is observed.

Second, the measures of cognitive control in the present study were designed to reveal neurocognitive abnormalities in complex cognitive functioning (de Sonneville, 1999). This measure might be particularly relevant for clinical populations, but it might be less sensitive when it involves detecting differences in functioning in a relatively normal sample of adolescents (Boelema et al., 2015). This might explain why no predictive effects of cognitive control on alcohol were found. Other tasks, such as the Self Ordered Pointing Task might be better in detecting working memory difficulties in non-clinical populations (see for instance Peeters et al., 2015). Third, the BGT has been originally developed to assess decision-making behavior under arousing circumstances (reward-based decision-making). It is possible that the BGT task does not assess reward sensitivity but rather decision making in arousing situations. Nevertheless, the IGT, a similar decision-making task as the BGT, assesses the extent to which immediate rewards are weighted in relation to long term consequences (Ernst et al., 2003; Bechara, 2005), which can be interpreted as a measure of sensitivity to reward (e.g., for some, an immediate reward might not outweigh long term consequences while for others, immediate reward is much more appealing). Similar gambling tasks have been used to examine reward processing at a neuropsychological level (Van Leijenhorst et al., 2010a). In addition, relatively poor performance on the IGT (predominantly preference for immediate gains) has been associated with self-reported reward sensitivity (Davis et al., 2007). A limitation related to the BGT is that only the first 71 cards were used instead of all 100 cards as in Bowman and Turnbull (2004). Nevertheless, the gambling ratio in the first and last blocks in our study revealed similar results (more gambling in the first block, and less gambling options in the last block) as the task used in Bowman and Turnbull (2004). Lastly, since temperament and parental psychopathology were selection criteria for this subsample (cf. Bouma et al., 2009), generalizability of results to other adolescent populations might be restricted. It should be noted that 34% of this sample was selected from the normal population, resulting in a sample slightly oversampled with adolescents at risk for behavioral and mental health problems. Simple *t*-test revealed only significant differences for ADHD and Oppositional Disorder assessed with the Youth Self-Report Scale (see **Table 1** for more details).

CONCLUSION

The present study reveals that behavioral control is an important predictor in adolescent risk taking behavior. Adolescents who are reward sensitive and have difficulties in controlling their behavior appear to be most susceptible involvement in risk behavior. The increased susceptibility for reward might encourage some adolescents to explore opportunities and take on challenges, which might be important for the social and emotional development (Forbes and Dahl, 2010; Crone and Dahl, 2012). However, this motivational orientation toward reward might require more control over impulses than present among adolescents who experience problems with behavioral control. As a result, some adolescents might encounter difficulties in regulating their behavior when it involves risk taking behavior while for others, these difficulties might have severe consequences on their (later) health behavior.

AUTHOR CONTRIBUTIONS

MP was responsible for the design, analyses, coordination, and draft of the manuscript; WV and TO participated in the design and interpretation of the data and results. All authors read, revised, and approved the final manuscript.

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Do Executive Functions Predict Binge-Drinking Patterns? Evidence from a Longitudinal Study in Young Adulthood

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Background: Impairments in executive functions (EFs) are related to binge drinking in young adulthood, but research on how EFs influence future binge drinking is lacking. The aim of the current report is therefore to investigate the association between various EFs and later severity of, and change in, binge drinking over a prolonged period during young adulthood.

Methods: At baseline, 121 students reported on their alcohol habits (Alcohol use disorder identification test; Alcohol use questionnaire). Concurrently, EFs [working memory, reversal, set-shifting, response inhibition, response monitoring and decision-making (with ambiguity and implicit risk)] were assessed. Eighteen months later, information on alcohol habits for 103 of the participants were gathered. Data were analyzed by means of multilevel regression modeling.

Results: Future severity of binge drinking was uniquely predicted by performance on the Information sampling task, assessing risky decision-making ($\beta = -1.86$, 95% CI: −3.69, −0.04). None of the study variables predicted severity or change in binge drinking.

Conclusion: Future severity of binge drinking was associated with making risky decisions in the prospect for gain, suggesting reward hypersensitivity. Future studies should aim at clarifying whether there is a causal association between decision-making style and binge drinking. Performance on all executive tasks was unrelated to change in binge drinking patterns; however, the finding was limited by overall small changes, and needs to be confirmed with longer follow-up periods.

Keywords: binge drinking, executive functions, decision-making, young adults, longitudinal study

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Abbreviations: AUD, alcohol use disorder; AUDIT, alcohol use disorder identification test; AUQ, alcohol use questionnaire; BAC, blood alcohol concentration; EFs, executive functions; IGT, Iowa gambling task; IST, information sampling task; LNS, letter number sequencing; PES, post error slowing; PFC, prefrontal cortex; SSD, stop signal delay; SSRT, stop signal reaction time; SST, stop signal task.

INTRODUCTION

Binge drinking is a drinking pattern characterized by repeated episodes of intense alcohol consumption, leading to high levels of inebriation (Courtney and Polich, 2009). The drinking pattern may increase the risk of developing AUD (Olsson et al., 2016), a disorder which is developed in young adulthood by the majority of its sufferers (Kessler et al., 2005). This age period also coincides with the highest prevalence of binge drinking (Plant et al., 2009). Since AUD and binge drinking are associated with severe consequences (Rehm et al., 2010), it is important to identify potential risk factors that could be relevant when developing interventions targeting escalation of troublesome drinking patterns.

In several cross-sectional studies, reduced EFs are identified as risk factors for continued binge drinking among young adults (18–25 years of age) (Townshend and Duka, 2005; Goudriaan et al., 2007, 2011; Parada et al., 2012; Townshend et al., 2014; Bø et al., 2015, 2016; Banca et al., 2016). These studies indicate that young adult binge drinkers have aberrations in risky and ambiguous decision-making, working memory, inhibition, and response monitoring. Whether these aberrations are predispositions or consequences of alcohol use is not yet known. However, prospective studies in adolescent populations have identified aberrations in prefrontal functions, both as a predisposition for, and as a consequence of, initiating heavy alcohol consumption (Squeglia and Gray, 2016).

Executive performance is supported by the PFC (Miller and Cohen, 2001), an area particularly vulnerable to the neurotoxic effect of alcohol (Lyvers, 2000). In order to support self-control and goal-directed behaviors, the PFC orchestrates and maintains patterns of activity that represent goals and the means to achieve them. Many accounts describe what the underlying executive processes are. Some argue for a distinction between "cold" and "hot" EFs (Zelazo and Müller, 2002), referring to mechanistic and logically based processes, and processes requiring regulation of emotion, motivation, and reinforcement, respectively. While cold aspects are associated with the functioning of the dorsolateral PFC, hot aspects are associated with the functioning of the orbitofrontal cortex (Kerr and Zelazo, 2004).

Several attempts have been made to isolate the specific processes of cold prefrontal functions. Miyake et al. (2000) have, by means of a latent variable analysis of commonly used EF tasks, defined three separate, albeit correlated factors of cold EF: working memory (maintain/update), shifting, and inhibition. On the other hand, hot EF tasks trigger the need to monitor the self and the situation, and to regulate affect and motivation accordingly. These processes are, amongst others, captured by decision-making tasks (Damasio, 1994; Bechara et al., 1999), where immediate gains need to be set aside in order to achieve long-term goals. While dissociable, the cold components of EFs are still important to the hot processes (e.g., decision-making), and some errors in the hot EFs are partially traceable to the ineffectiveness of different cold control processes (Billieux et al., 2010; Del Missier et al., 2012).

In order to identify whether EFs are relevant predictors of future binge drinking, longitudinal studies are required. However, at present, studies in young adult populations are scarce. In a rather small sample of predominantly females, facets of inhibition predicted total number of intoxications and hangover days over a 28-day period, but not a composite binge score (Paz et al., 2016). In males, but not females, Goudriaan et al. (2011) found that binge drinking 2 years post testing was associated with disadvantageous, ambiguous decision-making. Aberration in this domain was also characteristic of the high severity binge drinking group at baseline compared to the low severity binge drinkers (Goudriaan et al., 2007). No association between binge drinking and response inhibition was detected for either gender at either time point. In a study investigating the role of intention to drink and EFs in young adult students, Mullan et al. (2011) found that planning and inhibition interacted with intention in predicting binge drinking the following week (defined by 5+ drinks per session). However, EFs (i.e., planning, decision-making, inhibition, set shifting) explained no significant variance. To date, these longitudinal studies are scarce and are mainly characterized by their coverage of only a few EF factors. Hence, at present, we are left with a fragmented picture of the exact relation between EFs and future binge drinking, and risk factors identified in cross-sectional studies (i.e., response monitoring, working memory, risky decision-making) are left unaccounted for as of now.

In contrast to the lack of longitudinal studies conducted in young adulthood, several prospective studies have addressed the relation between future alcohol use and EFs in adolescent populations. Crucially, these studies have shown abnormal brain activation during response inhibition as a consistent marker of transitioning toward alcohol abuse and binge drinking (Norman et al., 2011; Mahmood et al., 2013; Wetherill et al., 2013a,b; Whelan et al., 2014; Squeglia and Gray, 2016). With regard to neuropsychological vulnerabilities, preexisting deficits in working memory and inhibition have been found to predict increased alcohol use and first binge drinking episode in adolescence (Khurana et al., 2013; Peeters et al., 2015; Squeglia and Gray, 2016). Both adolescent groups who progressed into binge drinking and those who continued binge drinking have been reported as suffering from pre-existing poor decision-making skills (Xiao et al., 2009). In high-risk children, poor response inhibition—not set-shifting and working memory—has been emphasized as a risk factor for further problem drinking in adolescence (Nigg et al., 2006). Overall, it thus appears that vulnerabilities in facets of both cold and hot EFs constitute established risk factors for initiating and perpetuating (heavy) alcohol consumption and binge drinking during adolescence.

Though prospective existing studies suggested that performance on executive tasks are important risk factors for future binge drinking, these studies are not readily generalizable to young adult populations. Indeed, during the adolescent years, the prefrontal areas of the brain mature (Casey et al., 2000) and this development is associated with a decrease in risky behavior (Steinberg, 2004; Reyna and Farley, 2006). Therefore, EFs might be differently associated with future binge drinking in young adulthood compared to the association between EFs and the initiation of alcohol use during the adolescent years. Accordingly, onset and sustained binge drinking has been found

to hold different risk factors (Copeland et al., 2012). Clearly, in order to improve the tailoring of prevention efforts in young adulthood, broader studies should be conducted in the young adult population.

Binge drinking is often operationalized in terms of consumption of a certain number of drinks within a limited time period (e.g., NIAAA, 2004), as a proxy for intoxication. However, it has been suggested that asking directly about subjective intoxication (i.e., drunkenness) might provide a better estimate of a heavy drinking episode (i.e., binge drinking), as it takes into account the level of tolerance (Andreasson, 2016) and other individual characteristics known to influence intoxication levels (e.g., metabolism, body composition, and gender). In order to overcome limitations associated with cut off (e.g., no valid cut off available); we decided to operationalize binge drinking as a continuous variable based on subjective drunkenness and speed of drinking.

To tackle the lack of longitudinal studies in the young adult population, we reassessed binge drinking in a sample of young adults 18 months after assessment of executive functioning. In alcohol studies, the EF tasks we employed are commonly used (Day et al., 2015). Thus, the main aim of the present study was to establish whether EFs are: (1) associated with future severity of binge drinking, and (2) associated with change in binge drinking patterns within young adulthood. Several hypotheses can be derived from the few available prospective studies. First, we expect working memory performance to be associated with future binge drinking. Second, based on longitudinal-, prospective-, and cross-sectional studies, we hypothesize that less advantageous and risky decisions will be related to future binge drinking. However, based on the inconsistent or null results obtained from previous studies, we do not expect inhibition and shifting abilities to predict future binge drinking. Association between change in binge drinking patterns and EFs has not previously been studied in a young adult population, and this research is therefore of an exploratory nature.

MATERIALS AND METHODS

Participants and Procedure

One hundred twenty-one students (62 females) self-enrolled to a study of alcohol habits in a student population aged 18–25 (mean = 21.7, $SD = 2.1$). At baseline, they were all screened for serious physical and psychological health conditions, as described in Bø et al. (2015), and all reported regular alcohol consumption (AUDIT $\geq$ 1). They completed an online questionnaire about alcohol habits. Upon arrival at the Department of Psychology at the University of Oslo, all participants received both written and oral information about the project and their right to withdraw at any time. Informed consent was obtained by signature. Participants then underwent a short demographic interview and neuropsychological testing (T1). Upon testing, all self-reported abstinence from caffeine and nicotine for a minimum of 3 h, alcohol for 48 h, and all types of illegal substances for 7 days. At baseline, 119 participants agreed to participate in the follow-up study. Eighteen months later (T2), we contacted the participants by email and SMS, requesting them to complete an online questionnaire about their current drinking pattern. One hundred and three participants (50 females) completed the follow-up (85.1%). Data collection began in June 2013 and follow-up ended in February 2016. The study was conducted in compliance with the Helsinki Declaration and the Ethical principles for Nordic psychologists, as issued by the Norwegian Psychological Association. Upon completing the baseline assessments, participants obtained a gift card worth 250 NOK ($30). See **Table 1** for a description of the sample.

Alcohol Consumption

The last three questions of the AUQ [(10) Number of drinks per hour; (11) Number of times intoxicated by alcohol; (12) Percentage of time drunk when going out drinking] (Mehrabian and Russell, 1978) were used to calculate binge score (Townshend and Duka, 2002, 2005), which gives an estimate of binge drinking severity. The AUQ binge score is a validated (Townshend and Duka, 2002, 2005) and widely used method for exploring binge drinking (e.g., Kessler et al., 2013; Townshend et al., 2014; Czapla et al., 2015). As described previously (Bø et al., 2015, 2016), we employed a continuous approach to binge drinking, which is in line with the view of Enoch (2006). This operationalization is sensitive to an individual's level of intoxication, and has the advantage of separating drinking pattern from overall alcohol consumption (Townshend and Duka, 2002). It is tangent to the NIAAA (2004, p. 3) view, where binge drinking is defined as "a pattern of drinking alcohol that brings BAC to 0.08 gram percent or above." This level of intoxication is not always reached by a predefined number of drinks due to individual differences in metabolism, body composition, tolerance, and lack of specified duration of consumption (Thombs et al., 2003). Thus, self-reported drunkenness (i.e., loss of coordination, nausea and/or inability to speak clearly) overcomes the limitation associated with a predefined number of drinks.

The AUDIT (Saunders et al., 1993), a 10-item self-report questionnaire, was used to assess hazardous alcohol consumption during the last year. Participants also reported weekly alcohol consumption. These variables do not appear in the main analyses, as they do not directly assess binge drinking, but were included to present a detailed description of participants' alcohol habits.

Executive Functions

Working memory was assessed by the LNS task from the Wechsler Adult Intelligence Scale – Fourth edition (Wechsler, 2008). The participants were presented orally with a combination of letters and numbers. The task was to repeat the numbers in ascending order, followed by the letters in alphabetical order (e.g., 9-L-2-A; correct response is 2-9-A-L). The variable of interest was the maximum letter-number sequencing span.

Reversal and set-shifting were assessed by the IED from CANTAB® (Cambridge Cognition, 2006). The task requires participants to learn, via computer assisted feedback, which of two presented stimuli is correct; pink shapes or white lines. After six consecutive, correct responses, the previously correct response is no longer rewarded, thus requiring the

TABLE 1 | Descriptives of the study sample.

	T1 Baseline			T2 18 months follow-up			
	M	*SD*	(Min–max)	*M*	*SD*	(Min–max)	*t*-statistics
Binge score	25.6	17.7	(1.32–99)	21.6	16.6	(1.32–88)	$t(102) = 3.259$, $p = 0.001$, $d = 0.273$
AUDIT	10.0	5.7	(1–27)	9.3	5.4	(0–29)	$t(102) = 1.530$, $p = 0.129$
Weekly alcohol consumption (units)	6.6	6.9	(0–32.5)	5.4	6.0	(0–25)	$t(101) = 3.07$, $p = 0.003$, $d = 0.185$

M, mean; SD, standard deviation; AUDIT, alcohol use disorder identification test.

participants to switch from the old set to a new one. First, the change occurs intra-dimensionally (between pink shapes), then extra-dimensionally (between shapes and lines). The test terminates if the participant fails to reach the criterion of learning after 50 consecutive trails, or when the nine stages are completed. The variables of interest were the number of errors on trials before the extra-dimensional shift (reversal), and the number of errors on trials after the extra-dimensional shift (set-shift).

Decision-making under explicitly presented risk was assessed by the IST from CANTAB® (Cambridge Cognition, 2006). In a series of 10 trials, the participants were required to consecutively open boxes in a 5 × 5 matrix that revealed colored squares, and then subsequently decide which of the two colors lay in the majority. The color of the boxes was changed in every trial. A conflict between reinforcement and certainty was present as the possible gain of 250 points was reduced by 10 for every box opened. To maximize reinforcement, the test taker must tolerate a high degree of uncertainty, because sampling information until a point of high certainty would yield very few points. In case the wrong color was chosen, 100 points were lost irrespective of number of boxes opened. The variable of interest was the mean probability of being correct at the time of decision (see Clark et al., 2006 for a comprehensive description of the computed index).

Pre-potent response inhibition and response monitoring were both assessed by the SST from CANTAB® (Cambridge Cognition, 2006). A practice block of 16 go-trials (right or left facing arrow requiring corresponding response on a press pad) preceded the main task, which consisted of 320 trials. In a minority of these (∼25%), an auditory beep (the stop signal) indicated that the response should be withheld on that particular trial, thereby assessing the ability to inhibit an already initiated motor response (Logan, 1994). The delay ahead of the stop signal (stop signal delay; SSD) was adjusted according to performance. Over time, this tracking procedure stabilized the probability of successful inhibition around 0.5 for each participant. We quantified the pre-potent response inhibition process by computing the SSRT using the so-called 'integration approach.' This method aims to minimize false skewing of the SSRT that may result from continuous slowing on go-trials (Verbruggen et al., 2013). In this approach, reaction times on go-trials are rank-ordered individually for each participant in each of the five blocks. Then we subtracted the mean SSD from the *n*th percentile of the reaction time on go-trials corresponding to the percentage of unsuccessful stop-trials in the particular block, yielding the SSRT for this block. The mean SSRT across all five blocks was the variable of interest. Response monitoring, referring to the ability to evaluate action outcomes and let feedback guide future performance (Thakkar et al., 2014), was investigated by means of PES. PES was calculated by contrasting reaction times for "Go- after-go" trials and "Go-after-failure to stop" trials, as described in Lawrence et al. (2009).

Decision-making under ambiguity and implicitly presented risk was estimated by the computerized version of the IGT (Bechara et al., 1999). The participants were required to draw cards from one out of four decks of cards (A, B, C, and D), and the task instruction was to maximize profit. Unbeknownst to the participant, two of the decks (C and D) resulted in overall gain, whereas the others resulted in overall loss. The task consisted of five blocks of twenty trials. The last forty trials (trials 61–100) were proposed to measure decision-making under implicitly presented risk (because the reinforcement contingences were at least partly known), and the first forty trials (trials 1–40) dealt with decision-making under ambiguity (Brand et al., 2006; Billieux et al., 2010). The variable of interest was the number of advantageous decisions (decks C+D)–(decks A+B) in trials 1–40 (decision under ambiguity) and trials 61–100 (decision under implicitly known risk), respectively.

Please see **Table 2** for overview of study variables. All computerized tests were administrated on a Dell Latitude D610 laptop computer with a 14.1″ LCD screen using 1024 pixels × 768 pixels at 32-bit color quality. Press pad, touch screen, and external speakers were connected. An internal mouse pad was used to obtain responses on the IGT. The EF-tests were administrated in a pre-determined fixed order (corresponding to the order in which the tasks are described in the section "Materials and Methods," see above).

Statistical Analysis

All statistical analyses were performed with IBM SPSS 22 and Stata 14. Due to technical problems, CANTAB®-data for three participants were missing. One male participant, who had previous detailed knowledge about the test, did not perform the IGT. Five participants completed all cards in one deck (60 cards) during the fourth block of the IGT, forcing an unintended change in strategy. The IGT data from these participants were therefore discarded from analysis. Binge scores were logarithmically transformed due to skewed distributions.

Independent sample *t*-tests were conducted for all study variables to detect significant group differences between

TABLE 2 | Overview of study variables.

Task	Variable	Construct measured
Letter number sequencing task	Letter number sequencing span	Working memory; maintain and update
Intra-extra dimensional shift	Errors before extra-dimensional shift	Reversal
	Errors after extra-dimensional shift	Set-shifting
Stop signal task	Stop signal reaction time	Prepotent response inhibition
	Post error slowing	Response monitoring
Information sampling task	*p*(correct)	Decision-making under explicitly presented risk
Iowa gambling task	Advantageous choices trials 1–40	Decision-making under ambiguity
	Advantageous choices trials 61–100	Decision-making under implicitly presented risk

participants taking part at both time points of the study and those participating only at baseline. Pairwise comparisons between alcohol consumption measures at T1 and T2 was calculated. Bivariate correlations were computed to investigate the relation between T1 binge drinking and executive performance, and the relation among predictor variables. Partial correlations between T2 binge drinking and executive performance, controlling for T1 binge drinking, were calculated. Due to the exploratory nature of the present study, corrections for multiple comparisons were not employed. Employing a more stringent criterion for alpha would increase the risk for committing type II errors. Because the aim of the study is to identify risk factors, the cost associated with overlooking potentially important risk factors could be substantial.

Due to the longitudinal data collection, we used a linear multilevel model with a random intercept over participants to allow for dependence in responses within participants. Self-reports of alcohol consumption across time are correlated, and treating them as independent observations could lead to incorrect estimates of standard errors. This model allows for inclusion of participants with missing responses at the second occasion. **Figure 1** illustrates key components of the statistical model. Parameters were estimated according to the maximum likelihood criterion. Our analytical approach proceeded in three steps. First, we estimated a null model without any of the covariates of interest; second, we included main effects of all covariates; finally, we also included interactions allowing all covariate effects to vary between baseline and follow-up. In order to investigate our first aim, that is whether any of the EFs were related to severity in binge drinking at the follow-up, we compared the first and the second model by means of a likelihood ratio test. Using this test, the null hypothesis that all covariate effects were equal to zero was evaluated. To investigate our second aim, which was to test whether any of the EFs were related to change in the binge severity between baseline and follow-up, we compared the second and the third model, testing the null hypothesis that all interaction effects were equal to zero.

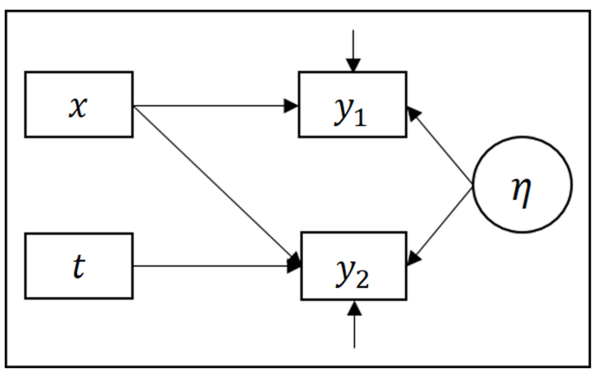

FIGURE 1 | Path diagram illustrating key components of the statistical models. Observed variables are represented by rectangles and latent variables by ovals. y_1 and y_2 represents binge-severity at time-point 1 and 2, respectively. *x* represents all explanatory variables except time, which is represented by t. The arrows represent regression effects.

RESULTS

In **Table 1**, socio-demographic characteristics and alcohol consumption habits of the study sample are reported. A significant decline in binge score and weekly alcohol consumption was detected.

The two participants who refused to be contacted at follow-up differed from those agreeing to be contacted: gender (equal variances not assumed): $t(118) = 11.329$, $p < 0.001$; IED errors after extra-dimensional shift: $t(117) = -2.509$, $p = 0.013$; IGT advantageous choices trials 61–100: $t(113) = 2.324$, $p = 0.022$; IST *p*(correct): $t(115) = 2.111$, $p = 0.037$. Overall, however, participants attending follow-up did not differ from those who only participated at baseline on any demographic [age: $t(119) = -1.131$, $p = 0.260$; gender: $t(119) = 1.419$, $p = 0.158$], drinking [binge score: $t(119) = 0.107$, $p = 0.915$; AUDIT: $t(119) = 0.045$, $p = 0.065$; weekly alcohol consumption: $t(119) = -0.888$, $p = 0.376$], or neuropsychological variables [LNS: $t(119) = 0.418$, $p = 0.677$; IED errors before extra-dimensional shift: $t(117) = 0.439$, $p = 0.66$; IED errors after extra-dimensional shift: $t(117) = 0.219$, $p = 0.827$, SSRT: $t(117) = -0.577$, $p = 0.565$; PES: $t(117) = -0.164$, $p = 0.870$; IGT advantageous choices trials 1–40: $t(117) = -0.715$, $p = 0.476$, IGT advantageous choices trials 61–100: $t(113) = -0.1.202$, $p = 0.232$; IST *p*(correct): $t(115) = -1.540$, $p = 0.126$]. Accordingly, the dropout was non-systematic.

TABLE 3 | Correlations between binge scores and executive functions.

	T1 binge score	T2 binge score
Letter number sequencing span	0.115	0.127
SST stop signal reaction time	−0.029	−.016
SST post error slowing	−0.184*	0.081
IED errors before extra-dimensional shift	−0.036	0.066
IED errors after extra-dimensional shift	0.060	0.062
IST *p*(correct)	−0.196*	−0.111
IGT advantageous choices trials 1–40	0.129	0.105
IGT advantageous choices trials 61–100	−0.044	0.021

*$p < 0.05$. *IED, intra extra dimensional shift; IGT, Iowa gambling task; IST, information sampling task; SST, stop signal task. Partial correlations between binge score at T2 and executive functions, controlling for T1 binge score.*

Bivariate and partial correlations between the predictors and the binge scores at baseline and follow-up are presented in **Table 3**.

Bivariate correlation between the measures of EFs are presented in **Table 4**.

The null model, including only a constant term for the fixed effects, showed substantial correlation (intraclass correlation = 0.63, 95% CI = 0.51, 0.74) in the responses within participants. The likelihood ratio test, comparing the null model with the second model, showed significant improvement in fit after inclusion of all covariates [$\chi^2(10) = 35.00$, $p < 0.01$]. Comparing the second and third model, there were no improvements in fit by inclusion of any interaction terms [$\chi^2(8) = 5.27$, $p = 0.73$]. We therefore proceeded by interpreting the coefficients from the second model. There was significantly higher mean scores at baseline than follow-up ($\beta = 0.22$, 95% CI = 0.09, 0.34). Further, females on average scored lower than males ($\beta = -0.41$, 95% CI = −0.68, −0.14). Risky decision-making under explicitly presented risk (IST) was negatively related to binge drinking severity ($\beta = -1.61$, 95% CI = −3.19, −0.03). None of the other variables of interest were significantly related to binge drinking severity. Please see **Table 5** for a detailed account of the estimated model.

DISCUSSION

The current study investigated the association between EFs and future severity of and change in binge drinking among young adults over a period of 18 months. Results revealed that only decision-making under explicitly presented risks (IST) was associated with *future severity*. Since binge drinking is associated with potentially serious consequences, it is important to identify risk factors that can later be tested for causality in appropriate designs. No other measures of EFs were significantly associated with future severity. The latter result was unexpected, and suggests that findings obtained in adolescent samples are not readily generalizable to adult populations. This might be due to developmental factors affecting the occurrence of risky behavior in various age groups. Alternatively, the lack of significant associations might be due to different factors contributing to initiation vs. sustainment of binge drinking. Of note, some EFs, which have been established as impaired in previous cross-sectional studies on binge drinking, failed to predict future binge drinking in the current study. Although replications are required, our study thus contributed to detecting which specific EFs are the best candidates for specific preventions and early interventions. None of the variables included in this study were associated with *change* in binge drinking over an 18-month period, though this might have been due to the small changes in binge drinking during the period.

In this study, binge drinking was defined by the AUQ binge score; a continuous variable based on self-reported drunkenness and consumption speed. Accordingly, this definition might be better at capturing those at risk of alcohol related harm due to high BACs, compared to more traditional definitions based on number of drinks per occasion. We did not make any cut-off with regard to possible AUD. At follow-up, five participants had AUDIT scores ≥ 20, which is indicative of alcohol dependence (Babor et al., 2001). This proportion is probably quite representative of community samples where the 12-month prevalence rate of severe AUD in the age group 18–29 is 7.1% (Grant et al., 2015). Generally, the current sample consists of healthy, well-functioning, highly educated young adults, and it is not certain that the results will generalize to other samples. Therefore, the study should be replicated in broader populations to ascertain the generalizability of these current results.

Future Severity of Binge Drinking

One of the variables associated with severity of binge drinking at baseline (e.g., Bø et al., 2016), was also associated with future severity of binge drinking. Specifically, decision-making

TABLE 4 | Bivariate correlations between behavioral measures.

	2	3	4	5	6	7	8
(1) Letter number sequencing task	−0.118	−0.110	−0.122	−0.039	0.055	0.138	0.098
(2) IED errors before extra-dimensional shift		0.000	0.029	0.129	0.046	−0.239*	−0.026
(3) IED errors after extra-dimensional shift			−0.026	−0.101	−0.074	−0.172	−0.013
(4) SST stop signal reaction time				0.155	−0.023	−0.002	−0.001
(5) SST post error slowing					0.003	0.077	−0.005
(6) IGT trials 1–40						0.309**	0.054
(7) IGT trials 61–100							0.201*
(8) IST *p*(correct)							

*$p < 0.05$, **$p < 0.001$. *IED, intra extra dimensional shift; IGT, Iowa gambling task; IST, information sampling task; SST, stop signal task.*

TABLE 5 | Results from the multilevel modeling.

Model	Model 1: Main effects		Model 2: Change	
Fixed effects	**β (SE)**	**95% CI**	**β (SE)**	**95 % CI**
Intercept	*3.68 (0.75)*	*2.22, 5.14*	*3.40 (0.87)*	*1.70, 5.10*
Sex	−0.41 (0.14)	−0.67, −0.14	−0.41 (0.14)	−0.68, −0.15
Time	0.22 (0.07)	0.09, 0.34	0.72 (0.77)	−0.80, 2.23
IED errors before extra-dimensional shift	0.01 (0.01)	−0.00, 0.02	0.01 (0.01)	−0.00, 0.03
IED errors after extra-dimensional shift	−0.01 (0.01)	−0.00, 0.02	−0.00 (0.03)	−0.06, 0.06
IST *p*(correct)	−1.61 (0.81)	−3.19, −0.03	−1.86 (0.93)	−3.69, −0.04
Letter number sequencing span	0.08 (0.06)	−0.04, 0.21	0.12 (0.07)	−0.03, 0.26
SST stop signal reaction time	−0.00 (0.00)	−0.00, 0.00	−0.00 (0.00)	−0.00, 0.00
SST post error slowing	−0.00 (0.00)	−0.00, 0.00	−0.00 (0.00)	−0.00, 0.00
IGT advantageous choices 1–40	0.02 (0.01)	−0.01, 0.04	0.02 (0.01)	−0.00, 0.05
IGT advantageous choices 61–100	−0.00 (0.01)	−0.01, 0.01	−0.00 (0.01)	−0.02, 0.01
Time × IED errors before extra-dimensional shift	–	–	−0.01 (0.01)	−0.02, 0.01
Time × IED errors after extra-dimensional shift	–	–	−0.02 (0.03)	−0.07, 0.03
Time × IST *p*(correct)	–	–	0.47 (0.82)	−1.14, 2.08
Time × Letter number sequencing span	–	–	−0.06 (0.07)	−0.19, 0.07
Time × SST stop signal reaction time	–	–	−0.00 (0.00)	−0.00, 0.00
Time × SST post error slowing	–	–	−0.00 (0.00)	−0.01, 0.00
Time × IGT advantageous choices trials 1–40	–	–	−0.01 (0.01)	−0.03, 0.01
Time × IGT advantageous choices trials 61–100	–	–	−0.00 (0.01)	−0.02, 0.01
Variance components				
Intercept	0.31 (0.06)	0.21, 0.45	0.32 (0.06)	0.22, 0.46
Residual	0.22 (0.03)	0.16 – −0.29	0.20 (0.03)	0.15, 0.27
	Log likelihood		**Log likelihood**	
	−209.32		−206.69	

IED, intra extra dimensional shift; IGT, Iowa gambling task; IST, information sampling task; SST, stop signal task.

under explicitly presented risks (IST) was associated with future severity of binge drinking, suggesting that more severe, future binge drinkers are driven by prospect for gain when making decisions. Accordingly, alcohol expectancies are shown to mediate frequency in alcohol consumption among college students, with those having the highest expectancies consuming the most (Brown et al., 1985). A decisional balance characterized by hyperactivation to reward and hypoactivation to punishment have previously been identified among persons with AUD (Shiv et al., 2005). According to the continuum hypothesis (e.g., Enoch, 2006; Lannoy et al., 2014), this type of decisional (im)balance might represent one of the relevant tracks for developing more serious alcohol use among binge drinkers.

In contrast to prior studies, ambiguous decision-making (IGT) was unrelated to future binge drinking. This might be due to the definition of binge drinking employed by Goudriaan et al. (2011), whose definition of binge drinking actually corresponds to heavy consumption rather than the drinking pattern. In addition, since the number of trials differed, and their finding was applicable to men only, strict comparisons across studies are not warranted. The construction of the IGT led to the exclusion of data from five participants. This is a known phenomenon (e.g., Goudriaan et al., 2007), and we have no reason to believe that this has affected the results with regard to ambiguous decision-making.

All cold EF variables were unrelated to future binge drinking. In accordance with previous findings (Goudriaan et al., 2011; Paz et al., 2016), response inhibition (SSRT) did not predict future binge drinking. Moreover, set-shifting (IED), response monitoring (PES), and working memory performance (LNS) were not associated with future binge drinking. These null-findings represents an important addition to the previously inexistent literature. The fact that cold EFs failed to predict future binge drinking in young adulthood contradicts previous findings obtained in adolescent populations. Improvements in reflective functions, associated with prefrontal maturation taking place in the period from adolescence to young adulthood, might be the reason for this difference. However, it is worth mentioning that while previous studies showed that cold EF deficits predict future heavy alcohol consumption and alcohol related problems in adolescence, these have most of the time been identified at the cerebral and not the behavioral level. Thus, future studies combining the use of neuroscience and behavioral measures are required to clarify the relation between EFs and future binge drinking.

Binge drinking has previously been conceptualized in a dual-process framework (Lannoy et al., 2014), suggesting that the behavior might be a product of an imbalance between affective-automatic and reflective processes. The fact that cold EFs failed to predict future binge drinking might imply that increased affective-automatic processes, rather than defective reflective processes, was contributing to an increased risk of engaging in binge drinking in the future. Thus, to understand how the decisional balance tips in favor of immediate gratification and risky behavior, future studies should aim at elucidating the exact nature of reward and punishment (hyper)sensitivity to the development in drinking pattern.

Change in Binge Drinking

Neuropsychological function was not related to change in binge drinking habits in this sample, which could be considered positive, considering the documented negative effect binge drinking has on prefrontal neural functioning (Maurage et al., 2012). At an aggregate level, a significant decline in binge drinking over 18 months was detected. With age, binge drinking frequency is expected to decline (Skretting et al., 2015); however, the effect size was small. Perhaps the ability to change drinking pattern is more heavily reliant on the capacity in EFs when larger changes are required, e.g., due to increased social obligations and responsibilities when ending college. Studies with longer duration of follow-up are needed to clarify this. Moreover, we cannot rule out that the very act of taking part in the study led to the detected reduction in binge drinking.

In the current study, the measure of binge drinking behaviors relied on subjective accounts of drunkenness. However, subjective assessments of drunkenness are known to be potentially inconsistent over time (Kerr et al., 2006). This could perhaps—at least partly—explain the apparent reduction in binge drinking observed at T2 in our study. However, it is unlikely that an important change in definition actually occurred over the two periods of the study, especially because the AUQ provides examples of what drunkenness implies in this context.

Previous research has indeed identified different trajectories for binge drinking in the age period 18–24 (Schulenberg et al., 1996). Nearly 60% of the total sample of 9,945 participants continued binge drinking at the same levels, while trajectories in over 30% of the sample reflected discontinuity. Future studies should acknowledge this variation when investigating changes in drinking pattern, and should ideally include multiple time-points to account for random changes attributable to the selected period.

Limitations

Some limitations should be acknowledged. First, we had a modest sample size, which gives limited statistical power to detect associations. Second, we did not have data on potentially important confounding variables (e.g., genetics, environmental), which may be relevant to drinking pattern development. Third, while the drinking culture in Norway is characterized by lower alcohol consumption compared to other European countries, the drinking pattern is rather hazardous (Rehm et al., 2010). Because drinking to intoxication is quite common, it might not be subject to social sanctions as it would in other cultures. Moreover, perception of drunkenness varies across countries (Muller and Schumann, 2011). In combination with the strict alcohol legislation, generalizations to other countries must be preceded by caution. Fourth, validity and reliability of self-reported alcohol consumption has been found to be at reasonable levels (Del Boca and Darkes, 2003); however, when comparing components of the binge score to diary accounts, the number of times drunk and number of drinks per hour were significantly under- and overestimated, respectively (Townshend and Duka, 2002). Thus, using other measures, like the timeline follow back in combination with AUQ binge score, might be more closely related to real-life consumption (Lake et al., 2015).

CONCLUSION

The current study simultaneously investigated different factors of EFs in future severity and change in binge drinking in young adulthood. While future severity was predicted by decision-making focusing on the prospect for gain, none of the study variables was predictive of change in binge drinking, which could be related to the overall small aggregate change in this allocated period. In order to build preventive efforts aimed at reducing binge drinking, future studies should aim at investigating whether risky decision-making and binge drinking is causally related.

AUTHOR CONTRIBUTIONS

RB, JB, and NL designed the study. RB, LG, and EE analyzed the data. All authors contributed to the interpretation of the data. RB wrote the first draft, and all authors have revised it critically for intellectual content. The final version is approved for publication by all authors.

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Binge Drinking Trajectory and Decision-Making during Late Adolescence: Gender and Developmental Differences

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Objective: Impaired affective decision-making has been consistently related to alcohol dependence. However, less is known about decision-making and binge drinking (BD) in adolescents. The main goal of this longitudinal study was to determine the association between BD and decision-making from late adolescence to early adulthood. A second aim is to assess developmental changes and performance differences in males and females.

Method: An initial sample of 155 1st-year university students, (76 non-BDs, 40 females; and 79 BDs, 39 females), was followed prospectively over a 4-year period. The students were classified as stable non-BDs, stable BDs and ex-BDs according to their scores in item 3 of the AUDIT and the speed of alcohol consumption. Decision-making was assessed by the Iowa Gambling Task (IGT) three times during the study. Dependent variables were net gain and net loss. Results were analyzed using generalized linear mixed models.

Results: A stable BD pattern was not associated with either disadvantageous decision-making or sensitivity to loss frequency. Performance improved significantly in both genders over the study period, especially in the last blocks of the task. Females showed a higher sensitivity to loss frequency than males. No gender-related differences were observed in gains.

Conclusion: Performance in affective decision-making continues to improve in late adolescence, suggesting neuromaturational development in both genders. Females are more sensitive to loss frequency. Stable BD during late adolescence and emerging adulthood is not associated with deficits in decision-making. Poor performance of the IGT may be related to more severe forms of excessive alcohol consumption.

Keywords: binge drinking, adolescents, alcohol, longitudinal, decision-making, IGT, gender, development

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INTRODUCTION

Adolescence is a unique period of neurodevelopment (Spear, 2013) in which the human brain undergoes significant structural and functional changes associated with progressive improvements in cognitive and affective functions (Geier and Luna, 2009; Luna, 2009; Diamond, 2013). Compared to adults, adolescents demonstrate greater reward sensitivity and heightened risk-taking behavior

(Geier, 2013; Crone et al., 2016; van Duijvenvoorde et al., 2016), such as experimenting with drugs. These characteristics may be explained by asynchronous maturation of (or imbalance between) the earlier development of motivational systems and the relatively immature cognitive control (Geier, 2013; Kilford et al., 2016). In addition, as a result of ongoing neuromaturational processes, adolescence is a period of increased vulnerability to the neurotoxic effects of alcohol (Crews et al., 2007). Alcohol use by young adolescents is highly correlated with other suboptimal choices, i.e., unsafe sex (Moure-Rodriguez et al., 2016) and substance use (Windle, 2016). Binge drinking (BD) is a prevalent pattern of alcohol consumption during adolescence (Marshall, 2014). It is defined as the consumption of four drinks for women and five drinks for men in about 2 h, leading to a blood alcohol concentration (BAC) of 0.08 g/dL (National Institute of Alcohol Abuse and Alcoholism [NIAAA], 2004). A growing body of literature has documented anatomical (Squeglia et al., 2012b; Doallo et al., 2014) and functional frontal anomalies linked to BD (Squeglia et al., 2011, 2012a; Campanella et al., 2013). Cognitive deficits in young BDs has been reported, especially regarding executive functions [for a review, see (Montgomery et al., 2012; López-Caneda et al., 2014)] such as inhibitory control (Sanhueza et al., 2011) or working memory (Townshend and Duka, 2005; Scaife and Duka, 2009; Mota et al., 2013). Less attention has been paid to "hot" aspects of executive functions such as affective decision-making [linked to orbital/ventromedial prefrontal cortex (OFC/VMPC), see (Bechara, 2004; Kerr and Zelazo, 2004)]. Alcohol dependent individuals display impairments in decision-making (Verdejo-García et al., 2006; Noël et al., 2007; Brevers et al., 2014), with the severity of alcoholism associated with more pronounced deficits (Noël et al., 2007); however, little consistency has been observed in young BDs (Johnson et al., 2008; Goudriaan et al., 2011; Bø et al., 2016).

Decision-making is a complex process involving choosing between competing actions and assessing the value of short term and long term outcomes (Van den Bos et al., 2013). The Iowa Gambling Task [IGT; (Bechara et al., 1994)] was developed to measure affective decision-making under ambiguity, in which the probabilities of reward and loss are not known. Participants are told that they must gain as much money as possible by choosing cards from four virtual decks. Decks C and D are advantageous and lead to overall gain (they yield lower immediate gains but smaller losses in the long term), whereas decks A and B are disadvantageous (high immediate gains but greater losses in the long term). Decks A and B are equivalent in terms of overall losses, and decks C and D are equivalent in terms of overall gains. The decks also differ in the frequency of punishment or losses: decks A (disadvantageous) and C (advantageous) are associated with more frequent losses, although of smaller magnitude, and decks B (disadvantageous) and D (advantageous) are associated with less frequent losses of greater magnitude. Most studies have used the net gain dimension calculated simply as the total number of cards chosen from advantageous decks, or in the best case, as the preference for advantageous versus disadvantageous decks ([C+D]−[A+B]). However, fewer studies have taken into account the loss dimension represented by the relative preference for decks yielding low punishment frequency versus decks yielding high punishment frequency ([B+D]−[A+C]). This dimension has proved to be important in guiding affective decision-making (Van den Bos et al., 2013; Beitz et al., 2014; Cassotti et al., 2014). Participants must discover the rules for gains and losses by following their hunches and emotion-based signals (Damasio, 1994; Bechara, 2004; Dunn et al., 2006). The process of affective decision-making under ambiguity has been related to the ventromedial (VMPC) and orbitofrontal (OFC) prefrontal cortex, which are closely connected to the limbic system (Clark et al., 2004; Brevers et al., 2013). Healthy participants learn to prefer long term advantageous decks associated with immediate moderate rewards over long-term disadvantageous decks with immediate high rewards. By contrast, patients with ventromedial prefrontal (VM) cortex lesions often make decisions based only on the immediate consequences (Bechara et al., 1994).

Previous studies using the IGT, have shown disadvantageous performance of decision-making tasks by Chinese adolescent BDs relative to occasional (Xiao et al., 2009) and never drinkers (Johnson et al., 2008; Xiao et al., 2012). Similar findings have recently been reported for Korean BDs (Yoo and Kim, 2016), who also selected more cards than non-BDs from the disadvantageous deck B. Goudriaan et al. (2007) reported that poor decision-making was observed in adolescent "chronic high-BDs" compared with "low BDs." Another study by the same group (Goudriaan et al., 2011), observed that poor performance of the IGT was predictive of BD in male but not in female adolescents, which may be explained by the fact that males undertook more BD episodes and consumed more quantity of alcohol than females. In young adults with less extreme patterns of alcohol consumption, BD was associated with differences in performance in the loss dimension but not in the gain dimension (Bø et al., 2016). As far as we are aware, no studies to date have addressed this relationship with a longitudinal design involving repeated measures of decision-making performance during adolescence. The influence of potential confounding factors, such as substance use, psychopathological symptoms, variations in the definition of BD and possible cultural influences, has also been poorly considered. The fact that some studies only took into account the gain dimension and did not control for general executive measures (i.e., working memory or inhibition) are possible limitations, leading to an incomplete comprehension of affective decision-making in adolescent BDs.

The ability to select progressively from the advantageous decks continues to develop during adolescence (Hooper et al., 2004; Cassotti et al., 2011), and even during young adulthood (Cauffman et al., 2010). Children and adolescents also seem to choose cards with infrequent losses. This tendency, also referred to as frequency bias, decreases with age (Huizenga et al., 2007; Cassotti et al., 2011, 2014). Gender differences in developmental trajectories and performance of the IGT are poorly understood. There is no broad agreement about how males and females differ in gain and loss dimensions. Some studies have reported that males outperform females in gains (Overman and Pierce, 2013; Evans and Hampson, 2015), while others propose that both are equally capable of choosing from advantageous decks but that

females are more sensitive to loss frequency (Hooper et al., 2004; Van den Bos et al., 2013).

Thus, the main aim of this study was to determine whether a trajectory of stable BD in healthy university students is associated with disadvantageous decision-making. A further aim was to assess the developmental trajectories during emerging adulthood (18–23 years old) in decision-making, in each gender separately, and taking into account gain and loss dimensions. We considered the following hypotheses: (I) stable BDs will display disadvantageous decision-making relative to age-matched stable non-BDs, (II) males and females will perform equally in net gains, but females will present a stronger frequency bias than males; and (III) both females and males will show improvements in performance during late adolescence.

MATERIALS AND METHODS

Participants

Participants were selected through an anonymous questionnaire administered in class [see (Caamaño-Isorna et al., 2008) for more details]. The questionnaire included the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001) and questions related to alcohol use such as speed of consumption and age of drinking onset. A BD episode was defined as consumption of six drinks at a speed of more than two drinks per hour, bringing the BAC to 0.8 g/l or higher. A standard drink unit of ethanol varies across countries: thus, while in Spain it is defined as 10 g of ethanol, in e.g., USA, it is 14 g. The classification criteria were based on the students' responses to two questions: the third item of the AUDIT (How often do you have six or more drinks on a single occasion? Never/Less than Monthly/Monthly/Weekly/Daily or almost daily) and one question related to the speed of consumption measured as drinks per hour. BDs consumed six drinks on one occasion monthly or weekly, and the speed of alcohol consumption was three drinks or more per hour. The non-BDs were defined as those who never consumed six drinks on one occasion (or less than monthly) and who consumed alcohol at a speed of two drinks or less per hour.

As the objective of this study was to assess the BD trajectory, the sample was classified as stable non-BDs (those who remained as controls during the assessment period), stable BDs (who remained as BDs during the assessment period) and ex-BDs (those who abandoned the BD pattern at the first or second follow-up and remained with non-BD consumption thereafter). Abstainers were not included in the study. The classification criteria did not allow transitions in the trajectories (e.g., a non-BD who changed to a BD at the second evaluation would be excluded from the analysis in the last evaluation but maintained for the previous evaluations). The number of participants decreased throughout the study: 155 participants at baseline (76 non-BDs, 40 females; and 79 BDs, 39 females); 93 at the first follow-up (39 stable non-BDs, 21 females; 33 stable BDs, 14 females, and 21 ex-BDs, 15 females); and 74 at the final follow-up (33 stable non-BD participants, 18 females; 17 stable BDs, 8 females and 24 ex-BDs, 15 females). Each alcohol consumption trajectory included the following number of total data points: 148 stable non-BDs, 129 stable BDs, and 45 ex-BDs. The trajectory of performance in each gender was computed with a total number of 170 data points for females (79 at baseline, 50 at first follow-up, and 41 at second follow-up) and 152 for males (76 at baseline, 43 at first follow-up, and 33 at second follow-up).

Procedure

After being classified according to alcohol consumption, participants were interviewed to obtain clinical and sociodemographic information. To reduce potentially confounding factors, several exclusion criteria were used: personal history of neurological disorders; history of psychopathology (DSM-IV-TR) such as attention-deficit hyperactivity disorder or conduct disorder; current psychopathological symptoms as assessed by the Symptom Checklist-90-R (SCL-90-R) (Degoratis, 1983) (participants were excluded if they had scores above 90th in the Global Severity Index [GSI] or in at least two symptomatic dimensions); consumption of other drugs, except nicotine and cannabis (sporadic cannabis users and smokers were not excluded). None of the participants included in the study consumed cannabis daily. Other exclusion criteria included diagnosis of alcohol use disorders, severe non-corrected motor or sensory deficits, family history of alcoholism in first- and second-degree relatives, and other major psychopathological disorder (depression, anxiety, schizophrenia diagnosis etc.) in first-degree relatives. All three evaluations were made on average every 22 months. In each, a neuropsychological battery was administered together with an interview in which the same exclusionary criteria were considered in order to yield a sample of university students with no other risk factors. Only those participants who attended the previous evaluation (and met the inclusion criteria) were contacted again for each new evaluation. This implies that participants who underwent the final evaluation had also undergone all previous assessments. All participants received some monetary compensation and gave written informed consent in accordance with the Declaration of Helsinki. This research was approved by the bioethics committee of University of Santiago de Compostela.

Material

Iowa Gambling Task (Bechara et al., 1994): The IGT is a computerized version of the gambling task. In this task, individuals are invited to choose a card from four virtual decks of cards presented on a screen and labeled A, B, C, and D. The aim of the task is to earn as much money as possible. The characteristics of the decks are not disclosed and must be inferred gradually on the basis of positive and negative feedback. When the subject selects a card, a message indicating the amount of money won or lost is displayed on the screen. Decks C and D are advantageous and lead to overall gain (lower immediate gains but smaller losses in the long run), whereas A and B are disadvantageous (high immediate gains but greater losses in the long run). Decks A and B are equivalent in terms of overall net losses, and decks C and D are equivalent in terms of overall net gains. The decks also differ in the frequency of loss or punishment, with decks A (disadvantageous) and C

(advantageous) having more frequent punishments but of smaller magnitude and decks B (disadvantageous) and D (advantageous) having less frequent punishments but greater magnitude. The task consists of 5 blocks of 20 cards, i.e., a total of 100 cards. The net gain dimension represents the relative preference for advantageous versus disadvantageous decks ([C+D]−[A+B]). The net loss dimension is the relative preference for low punishment frequency decks versus high punishment frequency decks ([B+D]−[A+C]).

Self-Ordered Pointing Test, abstract design version (SOPT) (Petrides and Milner, 1982): This test consists of a booklet of abstract designs repeated on all pages but with a different position on each new page. The participant is asked to point out a different stimulus on each page without repeating previous choices. The test is divided into four blocks of increasing difficulty (6, 8, 10, and 12 stimuli), and each block consists of three trials. The total number of errors was recorded for each participant. The SOPT assesses planning and self-monitoring aspects of working memory. The scores in the SOPT allow us to control the possible interference of working memory deficits in decision-making.

Statistical Analysis

Generalized linear mixed models (GLMMs), in which maximum log-likelihood was approximated by adaptive Gauss-Hermite quadrature, were used in the statistical analysis (Brown and Prescott, 2014). GLMMs allow analysis of repeated measurements (measurement correlation and intra-individual heterogeneity) with greater statistical power than classical regression models (Gibbons et al., 2010). Unlike other repeated measures analysis, GLMMs can handle a different number of participants in each evaluation. All analyses were performed using the free R (version 3.1.1) statistical software environment (R Core Team, 2015) with the lme4 package (Bates et al., 2014), and all results were expressed as relative risks (RRs) and their 95% confidence intervals (CIs). This type of coefficient requires reference categories in order to establish the comparisons. Values higher than one with significant intervals are indicative of a good performance for gain, whereas values below one reflect less frequency bias for loss.

To construct the models, we used net gain and net loss (over 100 trials and in each block) as dependent variables, with individual observations as level 1 and students as level 2; random effects among students were considered to control initial intra-individual heterogeneity. In order to avoid negative scores, a constant value of 100 was summed to gains and losses. Different models were constructed for females and males in order to assess any developmental changes. The effect of alcohol consumption trajectory and possible interactions with time and gender were modeled. Frequency of cannabis use, age of drinking onset and the GSI score of the SCL-90-R were tested to determine whether they had explanatory roles. The independent variables with a statistical significance lower than 0.2 at a bivariate level were included in the multivariate models. The non-significant independent variables were eliminated from this maximum model when the coefficients of the main exposure variables did not vary by more than 10% and the value of Schwartz's Bayesian Information Criterion (BIC) decreased. The number of errors in the SOPT was used to control the effect of possible working memory deficits. Finally, we used JASP statistical software (JASP Team, 2016) to perform complementary Bayesian independent sample *t*-tests (by time and group), for null-hypothesis significance testing (Masson, 2011).

In order to ensure that the classification of stable trajectories of consumption (e.g., a non-BD who changed to a BD at the second evaluation would be excluded from the analysis in the last evaluation but maintained for the previous evaluations) did not have any relevant influence on the results, we performed the same statistical analysis allowing transitions in consumption trajectory. For example, a non-BD in the first evaluation who changed to a BD in the second assessment was then considered within this new group at that specific time point. In other words, the statistical model considered the specific pattern of consumption at each time point, thus reducing the sample attrition over time. However, the results obtained were almost identical. We therefore used the stable trajectory classification, for the sake of simplicity.

RESULTS

Demographic, Substance Use Variables and Performance

The descriptive characteristics of the sample at baseline are shown in **Table 1**. Groups differed in the following variables: age of onset of alcohol use, $t(137) = 4.83$, $p = 0.001$; total AUDIT scores, $t(124.32) = 15.68$, $p = 0.001$; number of drinks per hour, $t(153) = 14.48$, $p = 0.001$; grams of alcohol consumed during the week, $t(73.61) = 8.44$, $p = 0.001$, and grams of alcohol consumed on the day of highest consumption, $t(71.51) = 5.94$, $p = 0.001$. There were no differences in psychopathological symptoms measured by GSI scores of SCL-90-R test, $t(153) = 0.76$, $p = 0.447$. Groups differed in age, $t(152) = 2.86$, $p = 0.005$, the BDs were slightly older than the non-BDs. Group differences were also found in cannabis use, $X^2(2, N = 153) = 19.50$, $p = 0.001$, and tobacco use, $X^2(2, N = 153) = 8.12$, $p = 0.004$. The groups did not differ in estimated intellectual level as assessed by the Vocabulary subtest (WAIS-III) (Wechsler, 1997). Means and standard deviations for net gain and net loss over time in each trajectory and gender are shown in **Table 2**. **Table 3** depicts how the different trajectories of alcohol consumption performed throughout the task (means by block), with progressively more advantageous cards being chosen.

Gender-Related Differences in Decision-Making

Females and males did not differ in relation to net gain (RR = 0.98, 95% CI [0.90, 1.06], $p = 0.595$) nor in any particular block in this dimension. However, for net loss females showed a 12% RR (1.12, 95% CI [1.03, 1.20], $p = 0.005$) of selecting more cards with a low frequency loss (frequency bias) relative to males. When considering the effect on blocks, males and females performed similarly in loss in the first three blocks of the task. The frequency bias was notable in the last two blocks, i.e., blocks four (RR = 1.03, 95% CI [1.01, 1.06], $p = 0.046$]) and five (RR = 1.05,

TABLE 1 | Group means (standard deviation) for demographic and clinical data at baseline.

	Non-BDs ($n = 76$)	BDs ($n = 79$)
Sex (m/f)	36/40	40/39
Age**	18.58 (0.60)	18.87 (0.63)
Age of onset alcohol use***	15.78 (1.04)	14.8 (1.30)
AUDIT total***	2.95 (2.58)	12.22 (4.55)
Number of drinks per hour***	1.04 (0.84)	3.39 (1.14)
Alcohol (g) consumed during the week[a]***	42.19 (52.79)	302.46 (251.13)
Alcohol (g) consumed on the day of highest consumption[a]***	27.63 (31.93)	166.69 (192.12)
Occasional cannabis users***	0	8
Occasional smokers**	3	24
GSI (SCL-90-R), Pc	46.39 (28.83)	50.09 (31.36)
WAIS-III Vocabulary	12.56 (1.97)	12.11 (1.62)

[a]*The week prior to the evaluation. **$p < 0.01$, ***$p < 0.001$.*

TABLE 3 | Means (and standard deviations) for gain in each block of the IGT.

	Stable non-BDs	Stable BDs	Ex-BDs
Overall performance[a]			
Gain block 1	−1.86 (6.52)	−1.87 (4.12)	−1.36 (7.05)
Gain block 2	2.79 (6.89)	2.99 (7.52)	3.09 (6.70)
Gain block 3	6.45 (8.24)	5.89 (8.19)	6.00 (8.51)
Gain block 4	7.89 (8.12)	8.33 (8.75)	7.45 (7.70)
Gain block 5	9.69 (8.48)	7.71 (9.24)	8.5 (8.64)
Second follow-up[b]			
Gain block 1	−3.00 (6.52)	0.00 (5.14)	−1.48 (8.18)
Gain block 2	6.00 (8.35)	4.29 (8.26)	3.04 (7.18)
Gain block 3	9.94 (8.07)	10.71 (6.16)	6.18 (9.46)
Gain block 4	12.06 (7.39)	12.86 (6.41)	7.48 (7.70)
Gain block 5	11.38 (8.58)	14.00 (7.23)	10.61 (7.30)

Gain = ([C+D]–[A+B]); Loss = ([B+D]–A+C]). [a]*Average performance in the three assessments.* [b]*Average performance after 4 years of follow-up.*

96% CI [1.01, 1.09], $p = 0.006$). This means that females showed a 5% risk of being guided by frequency of loss in the last block in comparison with males. Thus, females chose more decks with low frequency of punishment to a greater extent than males in total, and this effect was particularly evident in the last part of the task.

With respect to deck preferences, deck C was the most frequently chosen by both genders, followed by deck D (both of these are advantageous decks) and then B; deck A was chosen least often. Females chose significantly fewer cards from deck C in 100 trials (RR = 0.83, 95% CI [0.71, 0.98], $p = 0.032$) in comparison with males, more specifically 20% (1/0.83 = RR 1.20) fewer than chosen by males.

Developmental Changes in Decision-Making by Gender

Both females and males showed improvements on the IGT in net gain. However, only females improved in net loss (**Table 4**). Regarding net gain, females showed a significant improvement at the first follow-up (RR = 1.12, 95% CI [1.07, 1.18], $p < 0.001$) and second follow-up (RR = 1.20, 95% CI [1.13, 1.27], $p < 0.001$) relative to baseline. This indicates that at the second follow-up performance of the task was 20% better as females chose more advantageous cards than in baseline. It should be noted that values higher than one with significant intervals are indicative of a good performance in gain. The improvement at the second follow-up was also significantly different from the performance at the first follow-up (RR = 1.07, 95[1.02, 1.11], $p = 0.002$, but smaller (7%). Males also showed a significant improvement at the first follow-up (RR = 1.30, 95% CI [1.22, 1.38], $p < 0.001$) and the second follow-up (RR = 1.33, 95% CI [1.25, 1.43], $p < 0.001$) relative to baseline. However, there were no significant changes between first and second follow-up (RR = 1.00, 95% CI [0.95, 1.05], $p = 0.906$). Thus, the improvement shown by males (30%) was limited to the first follow-up, while females continued to improve until the second follow-up.

In relation to net loss (also in **Table 4**), females showed an improvement at the first follow-up (RR = 0.95, 95% CI, [0.90, 0.99], $p = 0.049$) and the second follow-up (RR = 0.88, 95% CI [0.84, 0.93], $p < 0.001$), and the changes in performance between the first and second follow-up were also significant (RR = 0.92, 95% CI [0.88, 0.96], $p < 0.001$). Values below one reflect less frequency bias. In other words, females showed an improvement of 5% (1/0.95, RR 1.05) in net loss at the first follow-up and improvement of 14% (1/88 = RR 1.14) at the second follow-up relative to baseline. Conversely, males did not show any significant changes in net loss over time.

When considering individual blocks, females presented significant improvements in blocks 3, 4, and 5 in net gain at the second follow-up relative to baseline {e.g., an improvement

TABLE 2 | Means (and standard deviations) for net gain and loss over time.

	Baseline		First follow-up		Second follow-up	
	Gain	Loss	Gain	Loss	Gain	Loss
Females	15.60 (22.83)	30.05 (23.90)	21.69 (25.19)	28.46 (22.51)	33.44 (22.22)	21.05 (25.66)
Males	5.00 (22.31)	10.8 (23.81)	30.12 (28.35)	11.98 (28.46)	37.54 (31.15)	14.44 (31.72)
Stable non-BDs	10.64 (22.03)	18.45 (27.58)	31.95 (23.17)	13.76 (31.17)	36.37 (22.37)	21.97 (33.02)
Stable BDs	11.15 (25.22)	25.70 (22.84)	27.06 (26.05)	18.81 (23.83)	41.86 (21.29)	7.00 (26.51)
Ex-BDs			21.33 (28.33)	29.43 (21.29)	25.83 (27.67)	17.35 (25.24)

Gain = ([C+D]–[A+B]); Loss = ([B+D]–[A+C]).

TABLE 4 | Developmental changes in females and males for gain and loss in each block.

	GLMMs. Relative Risk. 95% CI			
	Females		Males	
	First follow-up[a]	Second follow-up[a]	First follow-up[a]	Second follow-up[a]
Net Gain	1.12 [1.07, 1.18]***	1.20 [1.13, 1.27]***	1.30 [1.25, 1.43]***	1.33 [1.25, 1.43]***
1° Block	0.99 [0.94, 1.04]	0.99 [0.95, 1.06]	1.02 [0.97, 1.09]	1.02 [0.95, 1.08]
2° Block	1.02 [0.97, 1.07]	1.04 [0.99, 1.10]	1.05 [0.99, 1.12]	1.04 [0.98, 1.11]
3° Block	1.05 [0.99, 1.10]	1.07 [1.02, 1.13]**	1.08 [1.02, 1.15]**	1.09 [1.02, 1.16]**
4° Block	1.03 [0.98, 1.08]	1.06 [1.00, 1.11]*	1.09 [1.03, 1.15]**	1.10 [1.03, 1.17]**
5° Block	1.04 [0.99, 1.09]	1.07 [1.01, 1.12]*	1.06 [1.00, 1.12]*	1.07 [1.00, 1.14]*
Net Loss	0.95 [0.90, 0.99]*	0.88 [0.84, 0.93]***	0.98 [0.92, 1.04]	0.98 [0.91, 1.05]
1° Block	1.00 [0.95, 1.05]	1.00 [0.95, 1.05]	1.00 [0.94, 1.06]	0.98 [0.92, 1.05]
2° Block	1.00 [0.95, 1.05]	0.98 [0.93, 1.03]	1.03 [0.98, 1.10]	1.04 [0.98, 1.11]
3° Block	1.01 [0.96, 1.06]	0.98 [0.93, 1.04]	0.99 [0.94, 1.05]	0.99 [0.93, 1.05]
4° Block	0.98 [0.93, 1.03]	0.95 [0.90, 1.01]	0.99 [0.93, 1.05]	0.99 [0.93, 1.06]
5° Block	0.96 [0.91, 1.00]	0.95 [0.90, 0.99]*	0.92 [0.87, 0.98]*	0.94 [0.88, 1.01]

*GLMMs, generalized linear mixed models. CI, confidence intervals. [a]Reference category = baseline. Values higher than one with significant intervals are indicative of a good performance in gain whereas in loss values below one reflect less frequency bias. *p < 0.05, **p < 0.01, ***p < 0.001.*

TABLE 5 | Relationship between binge drinking trajectory and decision-making.

	GLMM. Relative Risk, 95% CIs	
	Stable BDs[a]	Ex-BDs[a]
Net Gain	0.95 [0.83, 1.08]	1.01 [0.86, 1.18]
Net Loss	1.07 [0.93, 1.23]	1.02 [0.87, 1.20]

GLMMs, generalized linear mixed models. CIs, confidence intervals. [a]Reference category = stable non-BDs.

of 7% in block 5 (RR = 1.07, 95% CI [1.01, 1.12], $p = 0.017$)}. Males showed an improvement in the same blocks for net gain at the first follow-up. Although the latter improvement was maintained in the second follow-up (as shown in **Table 4**), there were no additional improvements. This implies that no significant changes between the first and second follow-up were observed in males on gain blocks. In net loss, females showed an improvement of 5% in block 5 (RR = 0.95, 95% CI [0.90, 0.99], $p = 0.042$) at the second follow-up relative to baseline. Males also showed an improvement in the same final block of the task (RR = 0.92, 95% CI [0.87, 0.98], $p = 0.012$), although earlier than females (i.e., at first follow-up).

Binge Drinking during Adolescence

In the IGT, stable BDs performed similarly to stable non-BDs in relation to net gain (RR = 0.95, 95% CI [0.83, 1.08], $p = 0.447$) and net loss (RR = 1.07, 95% CI [0.93, 1.23], $p = 0.322$) and controlling for working memory (number of errors in the SOPT) and age of drinking onset (**Table 5**). Although entering the final model ($p < 0.2$ at the bivariate level), the number of errors in the SOPT and age of onset were not significantly associated with IGT performance. No effects were observed when considering the different blocks of the task individually. Ex-BDs also did not differ significantly from non-BDs participants in the task. No interactions between the pattern of consumption and gender were observed. Frequency of cannabis use and psychopathological symptoms (GSI score of the SCL-90-R) were not significantly associated with performance of the IGT in the bivariate/multivariate models. Complementary Bayesian analysis for null-hypothesis significance showed evidence supporting the null hypothesis (e.g., Bayes factor [BF10] of 0.176 at baseline for the comparison of net gain between stable non-BDs and stable BDs and BF10 of 0.194 at the last follow-up).

DISCUSSION

The main aim of this study was to determine whether a stable BD trajectory was associated with disadvantageous decision-making in healthy university students. Contrary to our hypothesis, a stable pattern of BD throughout late adolescence (18–23 years old) was not associated with poor performance of the IGT. A further aim was to analyze the developmental changes in decision-making during this period and examine differences between females and males in performance of the IGT. Females and males performed equally well in net gain, indicating that both genders were capable of choosing advantageous decks that yield good long term results. However, as we hypothesized, females were more sensitive to loss frequency, i.e., they chose more cards from decks with low loss frequency than males did. This frequency bias was particularly evident in the final blocks of the task and in long-term advantageous decks, as indicated by females choosing significantly fewer cards from deck C (advantageous deck with high frequency loss) than males. Thus, females seem to focus both on long-term advantageous decks and frequency of punishment, which is a rather unsuccessful strategy in this task.

In line with our findings, a developmental study with adolescents observed a stronger frequency bias in females than in males despite both having equivalent performance in gains (Hooper et al., 2004). Similarly, another study found that over 100 trials males and females performed similarly in gains, and both were able to solve the task efficiently choosing more advantageous cards over disadvantageous ones (Van den Bos et al., 2013). Females were more sensitive to losses than males, especially in the long-term advantageous decks, as observed in the present study. According to the authors, females attend to two different aspects of the task – frequency of loss and the long-term pay off – while men only attend to the latter (Van den Bos et al., 2013). Conversely, some studies have found that males outperform females in net gains (Evans and Hampson, 2015). Although the meaning of gender-related differences on IGT performance it is far from clear, the involvement of some neurobiological differences has been suggested (Overman and Pierce, 2013; Van den Bos et al., 2013). In a study using positron emission tomography (PET), men performed better on the task (measured as cards from advantageous decks minus cards from disadvantageous decks) and showed greater lateralized brain activity in the right hemisphere than women (Bolla et al., 2004). This finding may be associated with gender-related differences in processing information, i.e., men tend to be more right-oriented (global information) and woman more left-oriented (detailed information), as explained in Van den Bos et al. (2013). The present results might be consistent with the above as females seem to focus on detailed aspects of the task (long term advantageous decks and frequency of loss) rather than the global outcome (gains in long term advantageous decks).

Secondly, as we expected, both genders showed improvements in performance during emerging adulthood in gain. The improvement in net gain was evident in the final blocks of the tasks but not at the beginning, which might suggest neuromaturational developmental rather than simple practice effects. The final blocks of the task seem to involve different cognitive requirements than the first part, probably involving "cold" executive process to a greater extent (Noël et al., 2007; Brevers et al., 2014). Females showed improvements in net gain over a longer time (until a later age) than males, although this probably reflects more opportunity for improvement due to the relatively poor initial performance (stronger frequency bias at baseline) in this task. Regarding net loss, the frequency bias decreased in females over time. However, males did not show any changes in loss over time, probably because this dimension is not as relevant in their performance as in females. These findings parallel previous studies showing that the ability to select progressively from the "good" decks on the IGT continues to improve not only during adolescence (Hooper et al., 2004; Cassotti et al., 2011) but also during early adulthood (Cauffman et al., 2010) and that the frequency bias decreased with age (Huizenga et al., 2007; Cassotti et al., 2011, 2014).

Finally, stable BD throughout the university years was not associated with poor performance of the IGT. Stable BDs and ex-BDs performed similarly to stable non-BDs regarding gain and loss, considering both net scores and individual blocks. Likewise, Bø et al. (2016) found that the BD score of young adults was not predictive of difficulties in choosing from advantageous decks on the IGT. However, heavy drinking was associated with selecting more cards from decks with frequent losses (only in the first 40 trials). The authors of the study calculated the frequency of loss as decks ([A+D]−[B−C]), which to our view, does not clearly account for high versus low frequency of punishment. In a recent study (Yoo and Kim, 2016), Korean student BDs selected more cards from deck B and showed disadvantageous decision making (they chose more cards from decks A and B) relative to non-BDs, particularly in the third and fourth block. The loss dimension was not analyzed, and working memory- or a general executive function score- was not accounted for. In addition, BD participants had to score between 12 and 26 in the AUDIT for inclusion in the study. Thus, the level of alcohol consumption may have been higher in this sample than in our sample, i.e., a cut-off of >20 warrants diagnostic evaluation for alcohol dependence, as indicated in the AUDIT guidelines (Babor et al., 2001). Johnson et al. (2008) found that Chinese adolescent BDs showed disadvantageous decision-making relative to "never-drinkers" in the last 50 trials. Interestingly, comparison of BDs with adolescent "ever drinkers" (a group with similar characteristics to the non-BDs in the present study) did not reveal any differences in performance, similarly to our findings. The same was observed in the comparison between BDs and "past 30 days drinkers" (a group with more drinking problems than "ever drinkers"). Two studies by the same research group showed that performance of the IGT by Chinese adolescent BDs (only three females were consistent BDs) was poorer than in occasional drinkers (Xiao et al., 2009) and found higher activity in the left amygdala and insula bilaterally -regions that form part of the neural circuitry involved in affective decision-making- in BDs relative to never drinkers (Xiao et al., 2012). No differences in performance between males and females were reported in these three previous studies with Chinese adolescents or in the Korean sample (Yoo and Kim, 2016). In this respect, the extent to which cultural differences in the IGT may influence task performance requires further study (Singh and Khan, 2012).

Another study based in the US reported disadvantageous IGT performance in chronic high-BDs relative to low-BDs, although working memory was not controlled for Goudriaan et al. (2007). Age of drinking onset or the age of the first time being drunk was not predictive of IGT performance. The authors reported that females showed a frequency bias. In this study some of the participants, particularly high-BDs, were diagnosed with both alcohol and cannabis abuse/dependency as well as other DSM-IV diagnoses [e.g., antisocial personality disorder which has been associated with poor IGT performance (Miranda et al., 2009)]. Goudriaan et al. (2011) showed that disadvantageous decision-making may be a predictor of heavy alcohol use. Poor performance of the IGT (percentage of cards form advantageous decks) was predictive of high levels of heavy drinking in male but not in female adolescents. The fact that men reported heavier alcohol use than women may explain this gender interaction – women had lower scores both on the quantity/frequency of

alcohol use and fewer BD episodes. Inhibitory control -measured by a stop signal task- was not predictive of heavy drinking, when baseline alcohol use was controlled for. The last two studies only analyzed the first 80 trials of the task because of an artifact in the data, which is a possible constraint.

Together, the above-mention studies have shown little consistency, possible due to the previous considerations (e.g., psychiatric disorders, methodological issues). Overall, it seems that poor decision-making is associated with high levels of heavy drinking, as occurs in more severe forms of alcohol consumption such as alcohol dependence (Brevers et al., 2014). To our knowledge, this is the first longitudinal study assessing the relationship between BD and decision-making- involving repeated measures of the IGT – in young adults with no other risk factors. Our findings indicate that a less severe pattern of BD is not related to impairments in decision-making in university students. Further studies using other executive tasks and considering BD trajectories with different levels of consumption and taking into account both gain and loss dimensions are needed to confirm these results. In addition, increasing the number of IGT trials [as suggested in Brevers et al. (2014)] may be useful to determine specific decision-making deficits. The IGT is a complex task that may involve different cognitive and affective processes at the beginning of the task (exploration guided by emotion or intuition) than in the last part (some knowledge about probabilities; executive functions). For instance, Noël et al. (2007) found that alcoholic participants who had recently undergone detoxification displayed poorer performance of the last 20 trials of the IGT and other executive tasks (inhibition of prepotent responses, manipulation of information stored in working memory etc.). Response inhibition was the best predictor of impaired performance in the last part of the IGT. Thus, this modification may be helpful for identifying subtle executive difficulties, especially in a population such as university student BDs with no other risk factors. Furthermore, normal participants seemed to keep improving their performance when another set of 100 cards was added at the end of the first 100 trials (Overman and Pierce, 2013), which according the authors may indicate that the process of decision making is not fully complete at the end of the original version. In our case, this may serve to identify possible "slow learners" in relation to excessive alcohol consumption.

One possible limitation of this study is the sample attrition. This mainly affects the analysis of progression over time (each follow-up relative to baseline) and especially the last assessment. GLMMs offer the advantage of being able to handle different number of participants in each evaluation. Thus, a participant who has just two assessments is included in the analysis until that point. Therefore, the findings related to overall performance in males versus females or the trajectories of consumption are less affected by this limitation, as a greater number of data points are included. Besides, these models also consider the response correlation in repeated measures – i.e., correlated measurement errors and heterogeneity of participants - resulting in greater statistical power (Gibbons et al., 2010). Another potential limitation is the fact that practice effects may represent a confounding factor in the interpretation of developmental improvements, as the same version of the IGT was used for all the assessments. However, the assessments were made on average every 2 years and the characteristics of the decks were not disclosed. Indeed, participants did not show any improvements over time in the first part of the task (40 first trials). To our view, these findings suggest that knowledge accumulated from previous evaluations does not substantially help participants to perform the task. In other words, the first trials seem to be as difficult as at baseline, with "an exploratory phase" remaining, despite some familiarity with the general procedure.

CONCLUSION

Decision-making -as assessed by IGT performance- seems to continue to improve in late adolescence. Both genders are equally capable of learning throughout the task, preferring advantageous over disadvantageous decks. However, females are more sensitive to loss frequency than males. Finally, healthy university students with a stable BD trajectory performed similarly in gain and loss dimensions on the IGT relative to age-matched non-BDs. In view of the above, disadvantageous performance in decision-making under ambiguity may be associated with more severe or extreme forms of heavy drinking.

AUTHOR CONTRIBUTIONS

CC, MC, FC-I, FC, and SR, participate revising it critically for important intellectual content. CC, FC-I, FC, SR, and MC, made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data. All gave final approval of the manuscript.

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Alcohol Binge Drinking and Executive Functioning during Adolescent Brain Development

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Alcohol consumption in adolescents causes negative effects on familiar, social, academic life, as well as neurocognitive alterations. The binge drinking (BD) pattern of alcohol is characterized by the alternation of episodes of heavy drinking in a short interval of time, and periods of abstinence, a practice that can result in important brain alterations; even more than regular alcohol consumption. The prefrontal cortex, which acts as neural support for the executive processes, is particularly affected by alcohol; however, not all studies are in agreement about how BD alcohol consumption affects executive functioning. Some research has found that alcohol consumption in adolescence does not significantly affect executive functioning while others found it does. It is possible that these discrepancies could be due to the history of alcohol consumption, that is, at what age the subjects started drinking. The aim of our study is to assess the performance on executive functioning tasks of 13–19-year-old adolescents according to their pattern of alcohol consumption. We hypothesize that BD adolescents will perform worse than non-BD subjects in tasks that evaluate executive functions, and these differences will increase depending on how long they have been consuming alcohol. Three hundred and twenty-two students (48.14% females; age range 13–22 years; mean aged 16.7 ± 2.59) participated in the study; all of them had begun drinking at the age of 13 years. Participant were divided into three groups, according to their age range (13–15, 16–18, and 19–22 years) and divided according to their pattern of alcohol consumption (BD and control groups). Then, the subjects were evaluated with neuropsychological tasks that assess executive functions like working memory, inhibition, cognitive flexibility, or self-control among others. The entire sample showed a normal improvement in their executive performance, but this improvement was more stable and robust in the control group. Regarding the executive performance among age groups, control subjects only obtained better results than BDs in the 19–22-year-old range, whereas the performance was quite similar at younger ages. Considering that all the BD subjects started drinking at the same age (13 years old), it is possible that a kind of compensation mechanism exists in the adolescent brain which allows them to reach a

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normal performance in executive tasks. This theoretical mechanism would depend upon neuronal labor, which could lose efficacy over time with further alcohol ingestion. This process would account for the differences in neuropsychological performance, which were only observed in older students with a longer history of alcohol consumption.

Keywords: adolescence, alcohol, binge drinking, executive functioning, history of consumption, prefrontal cortex

INTRODUCTION

Alcohol consumption in adolescents causes negative effects on familiar, social, and academic life, as well as neurocognitive alterations (Jennison, 2004; Jacobus and Tapert, 2013; White and Hingson, 2014). The binge drinking (BD) pattern of alcohol consumption, widespread among adolescents, is characterized by the alternation of episodes of heavy drinking in a short interval of time, and periods of abstinence (Courtney and Polich, 2009). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has defined "BD" as a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to about 0.08% or above in about 2 h. This pattern corresponds to consuming five or more drinks (male) or four or more drinks (female) in a session at least once in the previous 15–30 days (Courtney and Polich, 2009). BD is responsible for many of the social- and health-related problems affecting adolescents today (Miller et al., 2007; Nelson et al., 2009; Popovici and French, 2013; Kivimaki et al., 2014; Moure-Rodríguez et al., 2014). It is not clear yet if the BD pattern of alcohol consumption can cause brain damage or, by contrast, certain brain abnormalities lead to alcohol abuse (see Petit et al., 2014).

Adolescence is a critical developmental period where some neuromaturational changes lead to significant improvements in complex cognitive functions such as planning, problem solving, working memory, or inhibitory control, namely the executive functions (Luna et al., 2010; Diamond, 2013; Rubia, 2013); however, this maturation process makes these circuits highly vulnerable to the neurotoxic effects of alcohol (Oscar-Berman and Marinkovic, 2007; Bava and Tapert, 2010). The BD pattern of alcohol intake is characterized by repeated episodes of heavy drinking which lead to a great elevation of blood alcohol levels, followed by periods of moderate or null consumption, a practice that can lead to even more important brain alterations than regular alcohol intake (Duka et al., 2003, 2004; Lacaille et al., 2015). The brain transformations seen during adolescence are region-specific and the prefrontal cortex is one of those which mature later (Crews et al., 2007; Casey et al., 2008); this region, that acts as neural support for the executive processes (Fuster, 2001), seems to be particularly affected by alcohol (Weissenborn and Duka, 2003; Hartley et al., 2004; Goudriaan et al., 2007; Scaife and Duka, 2009; Pleil et al., 2015; Trantham-Davidson and Chandler, 2015). This problem could be exacerbated since adolescents are less sensitive than adults to the aversive effects of ethanol, such as the motor impairing, anxiolytic effects, and to hangover discomfort (Spear, 2014); then, they can consume more alcohol before they feel the aversive effects.

There is much scientific literature about the negative effects in neurocognitive performance produced by alcohol consumption, a practice that in adolescence causes a wide variety of neurocognitive deficits with implications for learning and intellectual development (Zeigler et al., 2005). Several studies have revealed the BD's effects in different cognitive processes, especially in visuospatial abilities, attention, memory, or executive functions (Hartley et al., 2004; Goudriaan et al., 2007; García-Moreno et al., 2008; Johnson et al., 2008; Heffernan et al., 2010; Hanson et al., 2011; Parada et al., 2011a, 2012; Mota et al., 2013; Gil-Hernandez and Garcia-Moreno, 2016; Jones et al., 2016). However, the results of these studies are not fully congruent, especially when executive functions are evaluated.

Executive functions are responsible for control and organize the intentional behavior and are necessary to achieving an adequate adaptation in the society, the school, and the workplace (Jurado and Rosselli, 2007); furthermore, executive functioning develops specifically during adolescence (Crone, 2009) according to the maturation of the parietal and prefrontal cortices (Blakemore and Choudhury, 2006). As we have mentioned before, this prolonged maturational trajectory could explain a particular vulnerability of executive functioning to the effects of alcohol. However, not all studies are in agreement about how BD alcohol consumption affects these processes. For example, some of them have found deficits especially in attention and working memory (Weissenborn and Duka, 2003; Hartley et al., 2004; Townshend and Duka, 2005; García-Moreno et al., 2008; Scaife and Duka, 2009; Sanhueza et al., 2011; Parada et al., 2012), others in decision making (Goudriaan et al., 2007; Johnson et al., 2008), or in tasks of behavioral inhibition (McCarthy et al., 2012; Stautz and Cooper, 2013), planning ability (Weissenborn and Duka, 2003; Hartley et al., 2004; Sanhueza et al., 2011), and cognitive flexibility (Townshend and Duka, 2005; Scaife and Duka, 2009; Sanhueza et al., 2011). However, Gil-Hernandez and Garcia-Moreno (2016) found that adolescents BD scored higher in dysexecutive symptomathology but obtain similar results as the control group in tasks of executive performance. Some authors even argue that heavy drinking does not result in measurable impairments in basic executive functions like sustained attention, inhibition, shift attention, and working memory (Tapert and Brown, 1999; Randall et al., 2004; Landa et al., 2006; Martínez and Manoiloff, 2010; Boelema et al., 2015).

One likely explanation for this variability could be the differences observed in selected samples (age, gender, ethnicity, etc.), the tests used for assessment, or the criteria for calculating alcohol intake (Parada et al., 2011b). Randall et al. (2004) found differences in personality traits both in drinking and non-drinking adolescents and they suggest that differences in personality could be one factor to explain the differences in cognitive performance. They stated that non-drinkers responded to the stress of cognitive testing with a more adverse mood

than BD subjects; then, the effects of BD alcohol consumption on neuropsychological performance could be comparable to the effects of stress on the performance of non-drinkers. This is in line with research that supports the idea that moderate alcohol consumption can have health benefits for cognitive functioning (Peele and Brodsky, 2000). The history of alcohol intake, the time since an individual started to drink according to BD pattern, could also help to explain the differences found in this topic; we believe that it is reasonable assumption to think that subjects who have been drinking for longer periods of time exhibit greater neuropsychological alterations than new or recent drinkers. A few years of BD pattern of alcohol consumption may not be enough to damage prefrontal circuits in a sufficient level to exhibit cognitive deterioration. However, acute alcohol intake causes early brain alterations (Spagnolli et al., 2013; Zheng, 2017), ergo some kind of compensatory mechanism must have been implemented, by which BD subjects obtained similar scores to non-drinkers. This compensatory mechanism would depend upon neuronal effort, which could lose efficiency over time if alcohol ingestion doesn't stop.

The aim of our study is to assess the effect of history of alcohol consumption on the performance in executive functioning tasks in a sample of 13–20 years old adolescents who had begun to drink at 13 years old. We hypothesize that BD adolescents will obtain worse results than non-BD subjects in test of executive functions, such as working memory, cognitive flexibility, or self-control, among others. Moreover, it has been hypothesized that the older adolescents will exhibit higher differences since they will have been drinking for a longer period of time.

MATERIALS AND METHODS

This study is part of a broader project, which we have been conducting for the last several years. The material and procedures have been previously described (Gil-Hernandez and Garcia-Moreno, 2016); here, we will outline some of them.

Participants

Three hundred and twenty-two students (age range 13–22 years; mean aged 16.7 ± 2.59) participated in the study; 48.14% women ($n = 155$, mean aged 16.97 ± 2.67) and 51.86% men ($n = 167$, mean aged 16.44 ± 2.5). First, all participants, who were students from secondary schools and universities in Madrid (Spain), fulfilled a self-referred questionnaire (ESAJ-S) collectively in their classrooms. This questionnaire was developed specifically for these studies and includes questions about demographic, medical, social, and personal features of the subject, the full version of the Alcohol Use Disorders Identification Test (AUDIT, Saunders et al., 1993), and questions related to the use of alcohol (number of BD episodes, age of onset on alcohol consumption, etc.). In order to evaluate the items related to alcohol consumption we took the recommendations of the World Health Organization (2000) and the specifications of the European School Survey Project: Alcohol and other Drugs (The European School Survey Project on Alcohol and Other Drugs [ESPAD], 2011) into account. The sample utilized in the study was obtained from the group of participants in the wider research; the inclusion criterion was having started drinking following a BD pattern before they turned 14 years old. Regular consumption of cannabis or other drugs, personal history of neurological or relevant systemic disease, personal or familiar alcohol use disorder (DSM-IV criteria), major mental disorder, and history of alcoholism in first-degree relatives were considered as exclusion criteria. Smokers and sporadic cannabis users (two joints or less in a month) were not excluded from the study.

The students selected were assigned to one of three groups according to their age (13–15 years old, $n = 112$; 16–18 years old, $n = 109$; and 19–22 years old, $n = 101$). Then, within each of those groups, the subjects were assigned to one of two groups according to their pattern of alcohol consumption (**Table 1**). The country in which the study is being carried out must be taken into account, because there are differences in the grams of alcohol of the Standard Drinking Units (SDUs) among countries. For instance, a SDU in the United States contains 14 g of ethanol, 8 g in the United Kingdom, and 10 g in Spain. To avoid these variations we used the criterion of the World Health Organization (2000) and the groups were as follows:

- Binge drinking (intensive alcohol consumption): Subjects who drink more than 6 (men) or 4 (women) SDU (10 g each) during one episode of intake (3–4 continuous hours) at least once a month in the last 6 months. All subjects from this group had begun to drink at the age of 13 years, that is, they had experienced a BD episode before the age of 14 years and then continued to drink.
- CTR (control group): Subjects who do not consume any alcohol or only do it on special occasions (birthdays, new year, etc.).

According to the original procedure (Gil-Hernandez and Garcia-Moreno, 2016), neuropsychological assessments were conducted between Tuesday and Thursday to avoid the proximity of the weekend, and participants were asked to abstain from consuming drugs and alcohol within 24 h prior to tests. The testing took place individually in the University and participating centers' premises. Students voluntarily participated in the study after being fully informed of the objectives and process of the study. In all cases, including those who were over 18 years, the parents were informed and they signed a consent form. The study was exempt from ethical approval procedures; however, all procedures are in accordance with the Spanish legislation, Law 14/2007 of July 3, the Code of Ethical Principles for Medical Research Involving Humans Subjects outlined in the Declaration of Helsinki, and the Ethical Principles of Psychologists and Code of Conduct according to the American Psychological Association.

Materials and Measures

The subjects were evaluated with the following neuropsychological tools:

Subtests of the Wechsler Memory Scale (WMS-III; Wechsler, 1997)

- Digits and spatial span (forward and backward condition). These tests are commonly used to evaluate short-term

TABLE 1 | Configuration of the experimental groups and consumption features.

	13–15 ($n = 112$)	16–18 ($n = 109$)	19–22 ($n = 101$)
BD	Age: 13.82 ± 0.93	Age: 17.13 ± 0.83	Age: 19.75 ± 0.88
	♀: $n = 16$ (13.75 ± 1)	♀: $n = 28$ (17.04 ± 0.82)	♀: $n = 36$ (19.48 ± 0.51)
	♂: $n = 22$ (13.86 ± 0.89)	♂: $n = 33$ (17.21 ± 0.82)	♂: $n = 23$ (19.9 ± 0.85)
	Audit total*,+: 11.72 ± 2.3	Audit total*: 13.16 ± 2.1	Audit total*: 12.27 ± 1.79
	BDE-3m*,+: 2.66 ± 0.94	BDE-3m*: 4.51 ± 1.23	BDE-3m*: 3.42 ± 0.72
	Tobacco**: 31.6%	Tobacco**: 44.3%	Tobacco*: 54.2%
	Cannabis: 7.9%	Cannabis: 14.8%	Cannabis: 16.9%
CTR	Age: 13.66 ± 0.8	Age: 16.75 ± 0.81	Age: 19.67 ± 0.93
	♀: $n = 33$ (13.70 ± 0.81)	♀: $n = 19$ (16.68 ± 0.82)	♀: $n = 23$ (19.92 ± 1.02)
	♂: $n = 41$ (13.63 ± 0.8)	♂: $n = 29$ (16.79 ± 0.84)	♂: $n = 19$ (19.43 ± 0.95)
	Audit total*: 1.28 ± 1.09	Audit total*: 2.27 ± 1.14	Audit total*: 2.81 ± 0.94
	BDE-3m*: 0	BDE-3m*: 0	BDE-3m*: 0
	Tobacco**: 10.8%	Tobacco**: 16.7%	Tobacco*: 33.3%
	Cannabis: 1.4%	Cannabis: 6.2%	Cannabis: 7.1%

*BDE-3m: binge drinking (BD) episodes experienced by subjects in the last 3 months. *$p < 0.01$; **$p < 0.05$ between BD and CTR groups. $^{+}p < 0.01$ BD group scores in the three age groups. The post hoc analysis shows significant differences in AUDIT and BDE between 13–15 years and the others age groups, but there is no difference between 16–18 and 19–22 years.*

verbal and spatial memory (Richardson, 2007) as well the executive component of these cognitive processes (Baddeley, 2003). In the digits test, the subjects have to repeat sequences of numbers of increasing difficulty in direct or reverse order (working memory); and the number of successful sequences was recorded (DIG-F and DIG-B). The spatial span has a similar procedure, but the subjects have to repeat the sequence in which the examiner taps cubes placed on a board, in direct or reverse order; the number of successful sequences was recorded too (SS-F and SS-B).

– Letter–Number sequencing subtest. The subject is presented with a mixed list of numbers and letters and their task is to repeat the list by saying the numbers first in ascending order and then the letters in alphabetical order. This subtest appears to require more than just immediate memory and there is no minimum academic skill prerequisite other than knowing the numbers 1–9 and having a functional knowledge of the alphabet. Moreover, the Letter–Number Sequencing subtest has high face validity as a working memory task (Hill et al., 2010). The number of successful sequences was recorded (LN).

Verbal Fluency

Verbal fluency is a cognitive function that facilitates information retrieval from memory. Tests of verbal fluency evaluate an individual's ability to retrieve specific information within restricted search parameters (Lezak et al., 2004). Successful retrieval depends upon executive control over cognitive processes such as selective attention, selective inhibition, mental set shifting, internal response generation, and self-monitoring. Verbal fluency tasks have shown to produce brain activation in the prefrontal dorsolateral region of the left hemisphere (Gourovitch et al., 2000). Prefrontal activation during phonemic and semantic verbal fluency tasks is higher than the one observed in other verbal task, where generating and self-monitoring items is not necessary (specific words, in this case) (Kono et al., 2007; Tupak et al., 2012). The task included two conditions:

– Phonemic fluency: The participants had to say loudly as many words as possible that begin with the letter F in 1 min, then with A, and finally, with S. The number of total correct words was recorded (PhF).
– Semantic fluency: The participants had to say loudly as many names as possible of animals (1 min) and fruits (1 min). The number of total correct words was recorded (SF).

Trail Making Test (TMT; Reitan, 1992)

The trail making test (TMT) is a neuropsychological tool commonly used to assess executive processes such as attention, cognitive flexibility, working memory, and other executive functions (Lezak et al., 2004; Mitrushina et al., 2005; Strauss et al., 2006). In TMT-A, the participant must draw a line connecting a series of numbers in sequential order. In TMT-B, the subjects have to carry out the same processes, but including letters in alphabetical order. The time spent on completing both parts (TMT-A and TMT-B), and the difference between time B and time A (TMT-BA) is recorded.

Stroop Color–Word Task (Stroop, 1935)

This well-know test is an appropriate procedure for examining selective attention and cognitive flexibility. This task can be applied following several different formats; we chose Golden's (1978) method, which consist of three pages with (i) color words printed in black ink, (ii) color hues printed as XXXX, and (iii) color hues printed as competing color words (e.g., "green" printed in red ink), respectively. The participants had 45 s to read correctly each page. The variables recorded in this task were the number of words read (STP-W), the number of colors named (STP-C), and the items with word–color interference (STP-WC). Interference is caused by a color word printed in an incongruent

color, leading to slower reactions and more errors as compared to color words printed in the congruent color and neutral words not printed in a color; an interference index was calculated too (STP-I). Recent neuroimaging studies have shown that especially the rostral cingulate zone and the dorsolateral prefrontal cortex become active during interference (Ridderinkhof et al., 2004; Carter and van Veen, 2007).

Statistical Analysis

First, we determined the normality of variables' distribution by the Kolmogorov–Smirnov test, and used the Levene's test to prove the homoscedasticity between BD and control groups. We have used Student's *t*-test to analyze the group mean differences in Audit and BDE-3m variables, and the Chi-square test for the frequency differences in tobacco and cannabis consumption. Then, we use an ANOVA to compare Audit scores and BDE-3m from BD subjects in the three age groups. To prove the natural age-related improvement in executive functioning, we carried out Pearson's correlation analyses between the age of the subjects and their performance in executive tasks for the whole sample and for both groups separately; then, we calculate a Fisher *r*-to-*z* transformation to test differences between correlation coefficients. After this, we used Student's *t*-test to check the possible average differences between control and BD groups, studying each age group separately. Finally, we calculate Cohens' *d* effect size (Cohen, 1988) to test the magnitude of the difference. Differences were considered statistically significant at $p < 0.05$. The data were analyzed by use of the IBM SPSS statistics package for Windows, version 23.0.

RESULTS

We analyzed the descriptive features of the sample (**Table 1**). The BD and CTR groups exhibited differences in the total score of the Audit test in the three age groups {13–15: [$t(45.75) = -26.45$; $p = 0.000$]; 16–18: [$t(96.31) = -34.56$; $p = 0.000$]; and 19–22: [$t(92.24) = -34.45$; $p = 0.000$]}, where the BD subject scored higher than CTR ones. We also found significant differences in the DBE-3m values {13–15: [$t(37) = -17.47$; $p = 0.000$]; 16–18: [$t(60) = -28.55$; $p = 0.000$]; and 19–22: [$t(58) = -36.32$; $p = 0.000$]}, where again the BD subject scored higher than CTR ones. In relation with tobacco consumption, the percentage of smokers in the BD group was significantly higher than in CTR in the three age groups (13–15: $\chi^2 = 7.38$, $p = 0.007$; 16–18: $\chi^2 = 9.38$, $p = 0.007$; and 19–22: $\chi^2 = 7.38$, $p = 0.038$). However, no differences were found in cannabis use (13–15: $\chi^2 = 3.12$, $p = 0.08$; 16–18: $\chi^2 = 1.98$, $p = 0.16$; and 19–22: $\chi^2 = 2.15$, $p = 0.15$). When we compared BD subjects from the three age groups, we found significant differences in Audit total scores ($F = 16.24$, $p = 0.000$) and in BDE-3m episodes ($F = 20.72$, $p = 0.000$). The *post hoc* analysis revealed that the 13–15 group scored significantly lower than the 16–18 and 19–22 groups in both variables, and that no differences were found between these two groups.

Table 2 shows the Pearson correlation indexes found between executive variables and age of the subjects. As expected, when we study the whole sample, all neuropsychological variables correlate significantly with the age of the subjects, indicating that executive functioning improves with age in all subjects, irrespective of experimental group to which they belong. Negative values of the *r* in TMT variables indicate a negative correlation because these scores reflect the time spent solving the task and a higher time indicates a worse performance. Nevertheless, there were differences in the correlation coefficients between BD and CTR groups; specifically, these significant differences were observed in SS-F, LN, TMT, and STP-C and STP-WC. In all cases, the direction of correlation was equal but changes the value except in the STP-WC variable, where both values are close to zero.

With Student's *t*-test we didn't find statistical differences between BD and CTR groups at 13–15 age range (**Table 3**). Something similar occurs with subjects 16–18 years old; in this case, we only found differences in the *digits forward* test (*t*- and *p*-values are provided in the corresponding table), where the BD group obtained better results than the CTR group (**Table 4**) with a moderate effect size ($d = 0.518$); it means that BD group performs roughly 0.5 standard deviations above CTR group. Subjects between 19 and 22 years of age exhibited more performance differences according to their alcohol consumption pattern (**Table 5**). The CTR group performed better in *SS-F* with a low to moderate effect size ($d = 0.468$), in *LN* with a moderate to high difference ($d = 0.705$), in the three variables of the *TMT* (*TMT-A, TMT-B*, and *TMT-BA*) with a high effect size in the first and second case ($d = 1.473$ and $d = 0.955$, respectively) and low to moderate in the third one ($d = 0.449$), and in *STP-C* task with a moderate to high difference ($d = 0.755$). As we stated before, negative values of the *t* in TMT variables indicate higher scores of BD subjects, that is, a worse performance of this group.

DISCUSSION

The main objective of the present study was to determine the effects of the history of BD alcohol consumption on executive functioning during adolescent brain development in students who started to drink at the age of 13 years. Firstly, our results show that both BD drinkers and non-drinkers progressively improve their executive functioning with age; however, CTR subjects showed a clear age-related improvement whereas BD subjects do not. Executive functions emerge early in child development and change significantly during the preschool years, but they continue to develop during adolescence in parallel with the development of the prefrontal cortex (Zelazo et al., 2008). With increasing age, prefrontal activity becomes more focal and specialized while irrelevant and diffuse activity in this region is reduced (Brown et al., 2005; Durston et al., 2006). During adolescent development an improvement in intellectual functioning occurs in certain number of functions like speed of processing, sustained attention, abstract thought, working memory, set shifting, decision making and planning, and response inhibition (Rubia et al., 2000, Bedard et al., 2002; Rueda et al., 2004; Blakemore and Choudhury, 2006; Crone et al., 2006a,b; Casey et al., 2008; Yurgelun-Todd, 2007; Geier et al.,

TABLE 2 | Correlations between age of the subjects and the scores in the executive tasks, first in the whole sample and after, separated by groups.

		All		CTR		BD		CTR vs. BD	
Test	**Variable**	***r***	**Sig.**	***r***	**Sig.**	***r***	**Sig.**	**Fisher *Z***	***p***
Digits (WMS-III)	DIG-F	0.125	**0.012**	0.164	**0.036**	0.04	0.615	0.95	0.342
	DIG-B	0.097	**0.042**	0.087	0.266	0.156	**0.050**	−0.62	0.535
Spatial span (WMS-III)	SS-F	0.297	**0.000**	0.386	**0.000**	0.182	**0.022**	1.98	**0.047**
	SS-B	0.471	**0.000**	0.502	**0.000**	0.402	**0.000**	1.12	0.263
Letter–number (WMS-III)	LN	0.270	**0.000**	0.375	**0.000**	0.167	**0.036**	2.01	**0.044**
Verbal fluency	PHF	0.273	**0.000**	0.270	**0.000**	0.123	0.125	1.36	0.174
	SF	0.185	**0.000**	0.183	**0.019**	0.088	0.272	0.86	0.390
Trail making test	TMT-A	−0.223	**0.000**	−0.406	**0.000**	−0.018	0.826	−3.67	**0.000**
	TMT-B	−0.326	**0.000**	−0.507	**0.000**	−0.147	0.065	−3.65	**0.000**
	TMT-BA	−0.265	**0.000**	−0.397	**0.000**	−0.153	0.055	−2.36	**0.020**
Stroop test	STP-W	0.383	**0.000**	0.447	**0.000**	0.286	**0.000**	1.66	0.100
	STP-C	0.370	**0.000**	0.500	**0.000**	0.252	**0.001**	2.59	**0.010**
	STP-WC	0.144	**0.005**	0.181	**0.020**	−0.011	0.891	1.72	**0.090**
	STP-I	−0.143	**0.005**	−0.217	**0.005**	−0.234	**0.003**	0.16	0.873

Significant values are in bold.

TABLE 3 | Mean differences between BD and control groups of 13–15-year-old subjects.

		13–15 years group						
Test	**Variable**	**Group**	**Mean**	***SD***	***t***	***DF***	**Sig.**	**Cohen's *d***
Digits (WMS-III)	DIG-F	CTR	7.32	1.84	−0.048	110	0.962	
		BD	7.34	1.88				
	DIG-B	CTR	6.73	1.54	1.215	110	0.227	
		BD	6.34	1.72				
Spatial span (WMS-III)	SS-F	CTR	7.14	1.62	0.696	110	0.488	
		BD	6.92	1.36				
	SS-B	CTR	6.26	1.73	0.452	110	0.652	
		BD	6.11	1.57				
Letter–number (WMS-III)	LN	CTR	10.14	2.17	0.073	110	0.942	
		BD	10.11	1.78				
Verbal fluency	PHF	CTR	37.77	8.26	0.321	110	0.749	
		BD	37.26	7.21				
	SF	CTR	31.28	6.78	0.532	110	0.596	
		BD	30.58	6.36				
Trail making test	TMT-A	CTR	31.04	8.89	−0.452	110	0.652	
		BD	31.87	9.70				
	TMT-B	CTR	72.50	18.16	−0.325	110	0.746	
		BD	73.66	17.27				
	TMT-BA	CTR	41.46	15.49	−0.110	110	0.913	
		BD	41.79	14.15				
Stroop test	STP-W	CTR	98.49	12.92	−0.016	110	0.988	
		BD	98.53	12.62				
	STP-C	CTR	68.92	10.44	0.089	110	0.930	
		BD	68.74	10.01				
	STP-WC	CTR	45.57	10.79	−0.692	110	0.491	
		BD	46.97	8.88				
	STP-I	CTR	5.13	7.18	−1.111	110	0.269	
		BD	6.64	6.02				

TABLE 4 | Mean differences between BD and control groups of 16–18-year-old subjects.

		16–18 years group						
Test	**Variable**	**Group**	**Mean**	***SD***	***t***	***DF***	**Sig.**	**Cohen's *d***
Digits (WMS-III)	DIG-F	CTR	7.04	1.41	−2.681	107	**0.009**	**0.518**
		BD	7.79	1.46				
	DIG-B	CTR	6.33	1.73	−1.612	107	0.110	
		BD	6.82	1.42				
Spatial span (WMS-III)	SS-F	CTR	7.85	1.52	−1.061	107	0.291	
		BD	8.19	1.79				
	SS-B	CTR	6.65	1.66	−1.6	107	0.112	
		BD	7.21	1.97				
Letter–number (WMS-III)	LN	CTR	11.25	1.91	0.29	107	0.772	
		BD	11.15	1.77				
Verbal fluency	PHF	CTR	41.17	8.39	−0.555	107	0.580	
		BD	42.11	9.19				
	SF	CTR	32.96	6.46	−1.189	107	0.237	
		BD	34.51	6.98				
Trail making test	TMT-A	CTR	28.06	7.08	−0.714	107	0.477	
		BD	29.07	7.44				
	TMT-B	CTR	62.33	14.90	−0.116	106.93	0.908	
		BD	62.71	18.49				
	TMT-BA	CTR	34.27	14.02	0.205	107	0.838	
		BD	33.64	17.33				
Stroop test	STP-W	CTR	113.04	12.75	0.888	107	0.377	
		BD	110.89	12.45				
	STP-C	CTR	79.77	12.16	1.52	107	0.132	
		BD	76.31	11.51				
	STP-WC	CTR	52.02	8.67	0.068	107	0.946	
		BD	51.90	9.47				
	STP-I	CTR	5.43	6.68	−1.156	107	0.250	
		BD	6.91	6.59				

Significant values are in bold.

2009, 2010). BD alcohol consumption affects prefrontal cortex development and could interfere with the normal improvement of neurocognitive abilities like executive functions (Parada et al., 2012). In general, our results are consistent with these findings; however, something different occurs when we compare the level of improvement in BD and control subjects.

We found no differences in executive performance between CTR and BD subjects from 13 to 18 years of age; however, the 19–22 years BD subjects obtained worse scores in several executive tasks. Correlation between alcohol consumption and other drugs in adolescence and structural and functional alterations in different brain regions has already been documented (see Feldstein et al., 2014) as well as a decline in performance on neuropsychological tests of attention, memory, or executive functions (see Dager et al., 2013). However, in our study, BD adolescents until the age of 18 years have shown similar performance to that of the controls, and even better in some tests; with these results we cannot state that the BD pattern has affected executive functioning at this age. It seems BD has no impact on the neuropsychological performance of adolescents with no more than 5 years of alcohol consumption, that is to say, a short history of alcohol consumption. A possible cause could be the characteristics of the tests used in this study. Many of the tests used to assess executive functioning come from clinical settings and were originally designed to measure other psychological processes (Lezak et al., 2004). For this reason, these tests are very useful when are used in people with a high degree of brain deterioration, but they can be less accurate when are used in healthy subjects. In our study, we assessed healthy adolescent students, with a short history of alcohol consumption and without problems in their familiar, social, and academic life. In order to determine the early effects of the BD, Barkley (2011) proposed an alternative procedure, the use of scales of executive functioning or the observation of subjects' performance in daily activities. In a sample of 12–18-year-old students, Gil-Hernandez and Garcia-Moreno (2016) found no differences between BD and control subjects on executive performance tasks, but the BD group exhibited a more pronounced dysexecutive symptomatology with problems related to inhibition, intentionality, or executive memory. Then, a possible explanation for the absence of differences on executive functioning could be a limited capacity of the

TABLE 5 | Mean differences between BD and control groups of 19–22-year-old subjects.

		19–22 years group						
Test	**Variable**	**Group**	**Mean**	***SD***	***t***	***DF***	**Sig.**	**Cohen's *d***
Digits (WMS-III)	DIG-F	CTR	8.02	1.47	1.359	97.448	0.177	
		BD	7.58	1.83				
	DIG-B	CTR	7.19	1.71	0.575	99	0.567	
		BD	7.00	1.59				
Spatial span (WMS-III)	SS-F	CTR	8.88	1.99	2.309	99	**0.023**	**0.468**
		BD	7.93	2.07				
	SS-B	CTR	8.93	1.83	1.299	99	0.197	
		BD	8.37	2.30				
Letter–number (WMS-III)	LN	CTR	12.02	1.57	3.509	99	**0.001**	**0.705**
		BD	10.95	1.48				
Verbal fluency	PHF	CTR	42.93	6.06	1.925	99	0.057	
		BD	40.39	6.85				
	SF	CTR	34.14	5.76	1.329	99	0.187	
		BD	32.58	5.89				
Trail making test	TMT-A	CTR	22.64	5.24	−7.193	99	**0.000**	**1.473**
		BD	31.10	6.21				
	TMT-B	CTR	49.86	11.41	−4.801	**94.346**	**0.000**	**0.995**
		BD	65.17	20.43				
	TMT-BA	CTR	27.21	8.75	−2.386	**85.806**	**0.019**	**0.449**
		BD	34.07	19.47				
Stroop test	STP-W	CTR	113.98	14.97	1.473	99	0.144	
		BD	109.81	13.27				
	STP-C	CTR	83.00	7.71	3.678	99	**0.000**	**0.755**
		BD	76.46	9.51				
	STP-WC	CTR	49.09	7.70	0.915	99	0.362	
		BD	47.51	9.16				
	STP-I	CTR	0.57	8.98	−1.109	99	0.270	
		BD	2.52	8.48				

Significant values are in bold.

test used to discriminate the effects of prefrontal deterioration in these subjects. However, these same tests are capable of finding differences in executive performance between BD and control subjects when the 19–22-year-old groups are assessed. Then, it looks like regular alcohol consumption would progressively damage neuronal circuits until a point when cognitive failure would be evident. Differences in results between executive performance tests and dysexecutive questionnaires can reveal a latent dysfunction in prefrontal circuits whose effects are not evident in neuropsychological tasks but affect daily activities. Concerning this, we want to point out to several studies that have already established that a moderate dose of alcohol is sufficient to affect inhibitory control (see a review in Field et al., 2010), yet not enough to produce evident alterations in other neuropsychological tests.

An alternative explanation may be the existence of a different pattern of brain activation to solve the same task. Crego et al. (2010) found no significant differences between the control and BD groups in a working memory task; however, with event-related potentials, they found a hypoactivation in the anterior prefrontal cortex of BD subjects compared to control ones during the cognitive task. They argued that this apparent inconsistence between the cognitive and the neurophysiological results could be due to the low sensitivity of the task used or to the short history of alcohol consumption of the subjects from the BD group. Other brain imaging studies have found both decreased and increased brain activity in several brain regions during memory and executive tasks (Schweinsburg et al., 2011; Squeglia et al., 2011; Xiao et al., 2013). Then, the fact that BD adolescents didn't show worse results than non-drinkers in neuropsychological tests but they exhibited different patterns of brain activation could mean that some kind of compensatory mechanism exists in brain activity of BD subjects which allows them to obtain an adequate performance (Campanella et al., 2013). This means that an additional recruitment of neural resources would be required in BD subjects to perform the tasks with the same level of performance as the control group, something that has been observed with other cognitive processes (Zölliga et al., 2010). A study with verbal memory and fMRI has shown that BD adolescents require the activation of more cerebral areas than CTR subjects to solve these neuropsychological tasks with

a similar level of performance (Schweinsburg et al., 2010). Two related studies with even-related potentials founded that BD subjects showed a higher neural activation than control subjects in their EEG records in several neuropsychological tasks where both groups demonstrated similar performance (López-Caneda et al., 2012, 2013). According to the authors, the results may reflect the use of additional neural resources in order to successfully attend the demands of the task and that, when BD alcohol intake stops, this neural recruitment is diminished. Nonetheless, the neuronal effort required could lose efficiency over time if alcohol ingestion doesn't stop. This loss of efficiency can be the explanation for the worst neuropsychological performance in older subjects with a longer history of BD alcohol consumption (Hartley et al., 2004; Goudriaan et al., 2007; García-Moreno et al., 2008, 2009; Parada et al., 2011a, 2012; Sanhueza et al., 2011).

In a nutshell, both BD and control subjects develop cognitive and intellectual abilities normally throughout adolescence. However, subjects who drink alcohol heavily show an incipient deterioration of their performance over time; before this, brain circuits exhibit some signs of alteration especially in prefrontal areas. Heavy alcohol drinking in adolescents leads to a certain dysfunction of prefrontal circuits, which only manifest after several years of BD pattern maintenance. Prefrontal dysfunction is not so clearly demonstrated in the neuropsychological tests because BD subjects score negatively only after time has passed with alcohol consumption. It is not absolutely clear whether the prefrontal signs might have been caused by alcohol intake or they were present before the start of alcohol consumption. We are going to abide by the first option since some of these signs can experience some changes if the alcohol intake stops (López-Caneda et al., 2014; Carbia et al., 2017). Nevertheless, more interdisciplinary research is necessary, especially with earlier age groups in order to determine the brain nets configuration before the start of alcohol intake and their changes once the consumption has been began. All in all, we believe there is a need to more thoroughly study the deleterious effects of alcohol consumption in young people to detect early signs of effects on the brain, and to design more effective interventions.

AUTHOR CONTRIBUTIONS

LG-M and SG-H have designed the study; SG-H, PM, CP, and RG-G carried out the neuropsychological assessment; LG-M and EN performed data analysis; and all authors have participated in the drafting and revision of the manuscript, and they have approved the final version for publication.

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Blood Alcohol Concentration-Related Lower Performance in Immediate Visual Memory and Working Memory in Adolescent Binge Drinkers

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The binge drinking (BD) pattern of alcohol consumption is prevalent during adolescence, a period characterized by critical changes to the structural and functional development of brain areas related with memory and cognition. There is considerable evidence of the cognitive dysfunctions caused by the neurotoxic effects of BD in the not-yet-adult brain. Thus, the aim of the present study was to evaluate the effects of different blood alcohol concentrations (BAC) on memory during late adolescence (18–19 years old) in males and females with a history of BD. The sample consisted of 154 adolescents (67 males and 87 females) that were classified as refrainers if they had never previously drunk alcoholic drinks and as binge drinkers if they had drunk six or more standard drink units in a row for men or five or more for women at a minimum frequency of three occasions in a month, throughout the previous 12 months. After intake of a high acute dose of alcohol by binge drinkers or a control refreshment by refrainers and binge drinkers, subjects were distributed into four groups for each gender according to their BAC: BAC0-R (0 g/L, in refrainers), BAC0-BD (0 g/L, in binge drinkers), BAC1 (0.3 – 0.5 g/L, in binge drinkers) or BAC2 (0.54 – 1.1 g/L, in binge drinkers). The subjects' immediate visual memory and working memory were then measured according to the Wechsler Memory Scale (WMS-III). The BAC1 group showed lower scores of immediate visual memory but not of working memory, while lower performance in both memories were found in the BAC2 group. Therefore, the brain of binge drinkers with moderate BAC could be employing compensatory mechanisms from additional brain areas to perform a working memory task adequately, but these resources would be undermined when BAC is higher (>0.5 g/L). No gender differences were found in BAC-related lower performance in immediate visual memory and working memory. In conclusion, immediate visual memory is more sensitive than working memory to the neurotoxic effects of alcohol in adolescent binge drinkers of both genders, being a BAC-related lower performance, and without obvious differences between males and females.

Keywords: blood alcohol concentration, binge drinking, immediate visual memory, working memory, adolescents

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INTRODUCTION

The binge drinking (BD) pattern of alcohol consumption is highly prevalent during adolescence. The quantity of alcohol, frequency of consumption and intermittency between binges have been shown to be important defining factors of BD and thus need to be delimitated in more detail. A blood alcohol concentration (BAC) of 0.8 g/L is required by BD criteria (National Institute of Alcohol Abuse and Alcoholism [NIAAA], 2004; Wechsler and Nelson, 2008), with men and women reaching this value after consuming 5 or more drinks and 4 or more drinks, respectively, in a short time period (2 h). This amount of alcohol is equivalent to the intake of approximately 60 g of alcohol in men and 50 g in women (6/5 or more drinks, respectively) (Parada et al., 2011a) when adapted to the Spanish population, although the Observatorio Español sobre Drogas [OED] (2016) accepts the criterion of 5/4 drinks (men/women respectively) in a 2-h period. A BD pattern is confirmed when frequency is at least once in the last 2 weeks (Courtney and Polich, 2009) or in the last month (Parada et al., 2011a), but using a longer time frame (last year) allows greater specificity in the classification of binge drinkers, as a necessary component of alcohol research and intervention (Cranford et al., 2006; Presley and Pimentel, 2006). Finally, the intermittence between BD episodes (according to the previously mentioned frequency) seems to be the most important factor involved, as the repeated alternation between intoxication and withdrawal is particularly deleterious for the brain, due to the excitotoxic cell death it provokes (Maurage et al., 2012; Petit et al., 2014).

Binge drinking is typically initiated during adolescence, a period (10–19 years old according to World Health Organization) characterized by critical changes to the structural and functional development of brain areas related with memory and cognition, particularly superior associative cortex (e.g., prefrontal cortex) which undergoes myelination, pruning and synaptic reorganization (Petit et al., 2013b; López-Caneda et al., 2014a), among other processes. Significant changes in the volume and shape of the hippocampal complex, another area which plays an important role in memory functions (e.g., immediate visual memory -IVM- and declarative memory), have also been observed in this developmental period (Gogtay et al., 2006; DeMaster et al., 2014; Krogsrud et al., 2014), being these changes remarkably heterogeneous among the different hippocampal subregions (Gogtay et al., 2006). In fact, alcohol-related performance deficits on tasks assessing cognitive processes such as attention, memory and executive functions, in the not-yet-adult brain are greater during adolescence (Crean et al., 2010; Risher et al., 2013) and become more pronounced with BD pattern consumption (López-Caneda et al., 2014a; Peeters et al., 2014). Thus, the BD adolescent population constitutes a risk cohort of brain damage, particularly if we bear in mind that it has been demonstrated that BD episodes can be more harmful for the brain than an equivalent amount of alcohol without withdrawal episodes (Duka et al., 2004; Petit et al., 2014).

Epidemiological studies have suggested that BD in youths is associated with an increased risk of alcohol abuse/dependence in adulthood (e.g., Chassin et al., 2002) or, in other words, that BD pattern may be considered as a precursor of alcohol use disorders (AUDs). In adolescents with AUDs, a reduction of hippocampal volume and prefrontal cortex has been observed (De Bellis et al., 2000, 2005), and has been related to cognitive deficits in IVM -more dependent of the hippocampus- and working memory (WM) -more dependent of the prefrontal cortex-.

In healthy late adolescents (up to 19 years old), the acute effects of alcohol on memory are poorly understood (Pihl et al., 2003). Despite the large amount of information provided by the literature, the majority of studies include broader age ranges and they encompass several developmental stages, such as youth (Grattan-Miscio and Vogel-Sprott, 2005; Schweizer et al., 2006; Day et al., 2013), adulthood (Dougherty et al., 2000; Weissenborn and Duka, 2003; Moulton et al., 2005; Söderlund et al., 2005; Paulus et al., 2006; Brumback et al., 2007; Rose and Duka, 2007; Saults et al., 2007; Cash et al., 2015), as well as older adults (Boha et al., 2009; Leitz et al., 2009; Bisby et al., 2010a,b; Montgomery et al., 2011; Poltavski et al., 2011; Wetherill and Fromme, 2011; McKinney et al., 2012; Hoffman and Nixon, 2015; Weafer et al., 2016). Besides the mnesic impact of acute BD, there are also studies showing effects of BD history in Spanish binge drinkers (Parada et al., 2011b; Sanhueza et al., 2011; Mota et al., 2013; Carbia et al., 2017) and international population (Squeglia et al., 2011; Campanella et al., 2013). On the other hand, research studying the effects of a BD episode's BAC or other BACs on memory is inconsistent because of the influence of different factors, such as: a) the BD pattern has differential effects on the mnesic and executive functions dependent on the temporal-medial and prefrontal regions (López-Caneda et al., 2014a,b) the different types of memory are not similarly affected or are BAC-dependent (Sneider et al., 2013), and so there are studies showing a deterioration of visual memory (Schweizer et al., 2006) or the WM (Pihl et al., 2003; Grattan-Miscio and Vogel-Sprott, 2005; Schweizer et al., 2006; Saults et al., 2007; Day et al., 2013), while others do not observe any deleterious effect on the kind of memory in question (e.g., Moulton et al., 2005; Söderlund et al., 2005; Paulus et al., 2006; Rose and Duka, 2007); and c) the use of different memory tests (e.g., SOPT, Self-ordered Pointing Task; CANTAB, Cambridge Neuropsychological Test Automated Battery; BVRT, Benton's Visual Retention Test. . .) for evaluating such mnesic effects.

Detrimental effects of alcohol use on cognitive functioning in adolescents are not limited to severe, long-term drinking behaviors and can be seen in dose-dependent episodic short-term drinking (Nguyen-Louie et al., 2015). Acute BD intoxication negatively affects spatial WM, planning abilities, response time and inhibition (e.g., Weissenborn and Duka, 2003; Squeglia et al., 2011; López-Caneda et al., 2014b). Evidence suggests that excessive drinking and resulting withdrawal symptoms dysregulate glutamine receptor activity, leading to degeneration and death of neurons. These sequelae of neurotoxic events may be detected through behavioral cognitive impairments in neuropsychological assessments (for reviews, see Jacobus and Tapert, 2013; López-Caneda et al., 2014a).

Gender differences in WM of young healthy subjects have been reported, indicating a male advantage in this memory, with females exhibiting disadvantages with a small effect size in

both verbal and visuospatial WM (Zilles et al., 2016). This male advantage could be explained by activating effects of testosterone (Janowsky et al., 2000). Nevertheless, age and specific task modulate the magnitude and direction of the effects (e.g., Zilles et al., 2016; Voyer et al., 2017). This kind of differences is not so clear in IVM. Gender differences in the effects of alcohol have been also informed, supporting the view that the brains of male and female adolescents may be differentially affected by alcohol use (Alfonso-Loeches et al., 2013). There is evidence suggesting that female adolescents are more vulnerable to the neurotoxic effects of alcohol on cognition (Caldwell et al., 2005; Squeglia et al., 2011; Alfonso-Loeches et al., 2013), since the cognitive tolerance effect of alcohol on IVM develops in BD women but not in BD men (Vinader-Caerols et al., 2017). Other authors have found that men generally report lower sensitivity to alcohol (individuals need more alcohol to experience the same sensations or impairments) than women, and reactivity to alcohol-related cues is more pronounced in male than in female binge drinkers (e.g., Petit et al., 2013a). These results might at least partially explain why men typically show a higher prevalence of alcohol consumption than women. However, in Spain, the incidence of alcohol consumption in 14–18 year-old adolescents is higher in females than males (Observatorio Español sobre Drogas [OED], 2016). With respect to the BD pattern during adolescence, it is similar in 14–16 year-old adolescents and is more common among men than women in the age range of 17–18 years (Observatorio Español sobre Drogas [OED], 2016). A recent study in Spanish university alumni has revealed the existence of different typologies of alcohol users, with differences among males and females (Gómez et al., 2017). In the light of these data, it would seem crucial to consider gender differences when exploring the relationship between BD and memory in late adolescents.

Thus, considering (a) the different criteria that accompany the BD pattern initiated during the critical period of adolescence, (b) the unclear effects of alcohol, either acute consumption or BD history, on memory (IVM and WM), and (c) the potential greater vulnerability of women to the neurotoxic effects of alcohol; the aim of the present study was to evaluate the effects of different BACs on IVM and WM during late adolescence (18–19 years old) in healthy male and female individuals with a BD history (maintained during last year). We hypothesized a BAC-related lower performance on IVM and WM in adolescent binge drinkers, being women more sensitive than men. Also, having a BD history will be associated to lower performance compared to refrainers.

MATERIALS AND METHODS

Participants

Experimental subjects were undergraduate students from the University of Valencia, Spain, who filled in a self-report questionnaire containing items enquiring about consumption of drugs, frequency and level of alcohol consumption, hours and quality of sleep, physical health, and psychological health. One hundred and fifty-four participants (67 males and 87 females, 18–19 years old) were recruited on the basis of the inclusion and exclusion criteria. The following inclusion criteria were used: 18–19 years old, a healthy body mass index (mean in men: 22.11 $\pm$ 0.34; and mean in women: 22.02 $\pm$ 0.31) and good health (without major medical problems). The exclusion criteria were as follows: taking medication; a history of mental disorders (diagnosed by a health professional according to DSM criteria); an irregular sleep pattern (non-restorative sleep and/or irregular schedule); having consumed, even sporadically, any drug (apart from alcohol) or having a history of substance abuse, including caffeine (our criterion: $\leq$2 stimulant drinks/day), tobacco (our criterion: $\leq$10 cigarettes/day), and alcohol; and having first-degree relatives with history of alcoholism. A telephone interview of approximately 15 min was conducted with each selected subject in order to confirm the information provided in the self-report and to arrange the date and time of the test.

Selected students were invited to participate in the study if they had reported refraining from alcohol consumption or a history of alcohol use classified as following a BD pattern according to the NIAAA criteria for Spain (see López-Caneda et al., 2014a) during the previous year. The mean age at onset of alcohol use was 14.7 $\pm$ 0.11 for binge drinkers. Participants were classified as refrainers if they had never previously drunk alcoholic drinks and as binge drinkers if they had drunk six or more standard drink units (SDU = 10 g of alcohol) in distilled spirits (alcohol content $\geq$40% vol., according to the BD habits referred by the subjects) in a row for men or five or more SDU in a row for women at a minimum frequency of three occasions in a month, throughout the previous 12 months.

Informed consent was obtained from all participants and the study was conducted in accordance with the guidelines for human experimentation of the Ethics Committee of the University of Valencia (ethical authorization number: H1380224121187) and with those of the Helsinki Declaration. Participants were told to abstain from drinking alcohol and performing heavy physical exercise during the evening/night prior to the experiment, and all subjects were instructed to follow their normal sleep patterns. Subjects were told to follow their usual meal routine at least 2 h before the experimental session.

The male subgroups consisted of 12–23 participants each, while the female subgroups consisted of 12–27 participants each. In the latter, data about the menstrual cycle were registered in the self-report and the telephone interview, and cycle phase was taken into account in the test in order to counterbalance this variable in each group.

Tests and Apparatus

An alcoholmeter (Alcoquant®6020, Envitec, Germany) was employed to measure the BAC before and after intake of a drink.

The Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) was employed to measure alcohol abuse among the subjects. The AUDIT consists of 10 questions that evaluate the quantity and frequency of alcohol intake and alcohol-related behaviors and consequences. It uses a range of 0–40, in which a score of 8 or more in men and 6 or more

in women indicates alcohol abuse. A higher score is related to greater severity of alcohol abuse.

The State-Trait Anxiety Inventory (STAI) (Spielberger, 1984) was used to measure anxiety. This is a questionnaire consisting of 20 items referring to self-reported state anxiety and 20 items referring to trait anxiety. All subjects completed the standardized Spanish version of the STAI.

IVM and WM were both assessed using the Wechsler Memory Scale 3rd Edition (WMS–III; adapted version for Spanish population) (Wechsler, 2004), a broadly used tool for assessing these kind of memories. The IVM subscale requires the respondent to recognize faces and remember scenes. The WM subscales require the respondent to put in order letter-number sets and reproduce visual-spatial sequences. Subjects' scores on the IVM and WM scales were transformed into centiles according to the subject's age.

Procedure

All participants signed an informed consent and a confidentiality agreement of data on arrival at the laboratory. BAC was measured using the alcoholmeter in all subjects to ensure that they had not drunk alcohol previously on the day in question, and the alcohol use of the BD adolescent subjects was assessed using the AUDIT test (none of these subjects were assessed as alcohol-dependent). Then refrainers' and binge drinkers' drank 330 ml of lime- or orange-flavored refreshment (control groups) and binge drinkers' drank a high acute dose of alcohol. Alcohol was administered in a fixed dose of 120 ml (38.4 g) consisting of vodka mixed with the refreshment for both genders or in function of their body weight (0.9 g alcohol / kg body weight in men and 0.8 g alcohol/kg body weight in women). The subjects were instructed to consume their drink within a period of 20 min. After finishing the drink, all subjects rinsed their mouths with water and BAC was repeatedly measured every 5 min throughout the waiting period, and until the BAC reached its peak (approximately 20 min after consuming the drink). This peak of BAC was considered the value to classify the participants into the experimental groups. The subjects performed then the STAI, IVM and WM tests. BAC was measured once again at the beginning of the tests, between the tests and at the end of the experiment. According to the BAC registered for the subjects (including the control groups, which consumed only the refreshment), four groups were constituted for each gender: BAC0-R (0 g/L, in refrainers), BAC0-BD (0 g/L, in binge drinkers), BAC1 (0.3 – 0.5 g/L, in binge drinkers) and BAC2 (0.54 – 1.1 g/L, in binge drinkers). Three subjects were excluded from the rest of the study because either they obtained a BAC under 0.3 g/L or they did not finish the drink.

All the tests were performed between 4:00 pm and 8:00 pm, and subjects that received alcohol remained on the premises until their alcohol concentration dropped to legal limits for driving (less than 0.3 g/L).

TABLE 1 | Characteristics of the study population.

(A) Demographic characteristics.

	Refrainers ($n = 42$)			Binge drinkers ($n = 112$)		
	Men ($n = 18$)	**Women ($n = 24$)**	**Men + Women ($n = 42$)**	**Men ($n = 49$)**	**Women ($n = 63$)**	**Men + Women ($n = 112$)**
Mean number of stimulant drinks: Coke, tea or coffee/day	0.5 ± 0.19	0.5 ± 0.13	0.5 ± 0.11	0.8 ± 0.14	0.7 ± 0.11	0.8 ± 0.09
Smoker: no/yes	18/0	24/0	42/0	44 / 5	54/9	98/14
BMI	22.7 ± 0.80	21.7 ± 0.43	22.1 ± 0.42	22.7 ± 0.33	21.5 ± 0.28**	22.0 ± 0.22
STAI Trait	29.4 ± 5.27	26.7 ± 4.41	27.9 ± 3.35	31.4 ± 3.82	33.2 ± 3.45	32.4 ± 2.55
STAI State	23.1 ± 3.87	26.8 ± 4.98	25.2 ± 3.27	26.1 ± 2.46	31.5 ± 2.7	29.1 ± 1.87

(B) Alcohol history among binge drinkers.

	Binge drinkers ($n = 112$)	
	Men ($n = 49$)	**Women ($n = 63$)**
Age at first alcohol consumption	14.5 ± 0.19	14.6 ± 0.13
Mean number of occasions per month	2.8 ± 0.12	2.7 ± 0.10
Mean number of drinks per occasion	6.8 ± 0.20	6 ± 0.24*
Mean number of BD episodes per month	2.7 ± 0.15	2.4 ± 0.15
Mean duration of BD pattern (in months) until the beginning of experiment	14.2 ± 0.98	12.5 ± 0.91

*The results are expressed as number or mean ± SEM for refrainers, occasional consumers, and binge drinkers. BMI, Body Mass Index. STAI, State and Trait Anxiety Inventory. *$p < 0.05$ Statistically significant difference between men and women in the same group according to Student's t-tests. **$p < 0.01$ Statistically significant difference between men and women in the same group according to Student's t-tests.*

Statistical Analyses

The data were subjected to parametric analysis after checking that they met the criteria for normality and homogeneity of variances. The BAC data for both genders were analyzed to ensure there were not statistically significant differences between the genders in the BAC1 and BAC2 groups. Next, an ANOVA was performed for each measure (IVM and WM); each analysis contained the between-subject factors "BAC" (BAC0-R, BAC0-BD, BAC1 and BAC2) and "Gender" (men and women) as independent variables. When their interaction was statistically significant, pairwise comparisons were carried out. The alpha values for comparisons were set at 0.049 and 0.0099, after applying the Bonferroni correction. All analyses were performed using the "SPSS" Statistics software package, version 22.0 for Windows (IBM Corp, 2013). Additionally, the statistical power of acute and chronic (BD history) effects of alcohol for IVM and WM was calculated by the G*Power software, version 3.1.9.2 for Windows (the effect-size value was previously calculated using Cohen's *d* formula).

RESULTS

The characteristics of the study population for refrainers and binge drinkers are summarized in **Table 1**.

A scatterplot depicting the distribution of BACs in men and women is shown in **Figure 1**. ANOVA analyses did not show statistically significant differences between the genders in either BAC1 [$F(1,22) = 3.472$, *ns*] or BAC2 [$F(1,36) = 0.304$, *ns*].

A summary of descriptive statistics for IVM and WM is shown in **Table 2**.

Immediate Visual Memory

The BAC factor was statistically significant [$F(3,146) = 9.354$, $p < 0.001$], with a poorer performance of the IVM task registered in adolescents with BAC1 and BAC2 *versus* BAC0-R ($p < 0.05$ and $p < 0.001$, respectively), and in adolescents with BAC2 *versus* BAC0-BD ($p < 0.005$) (see **Figure 2**). In addition, no significant differences in performance were observed between BAC0-R and BAC0-BD groups ($p > 0.05$). Neither the Gender factor [$F(1,146) = 3.847$, *ns*] nor the BAC and Gender interaction [$F(3,146) = 1.476$, *ns*] was statistically significant.

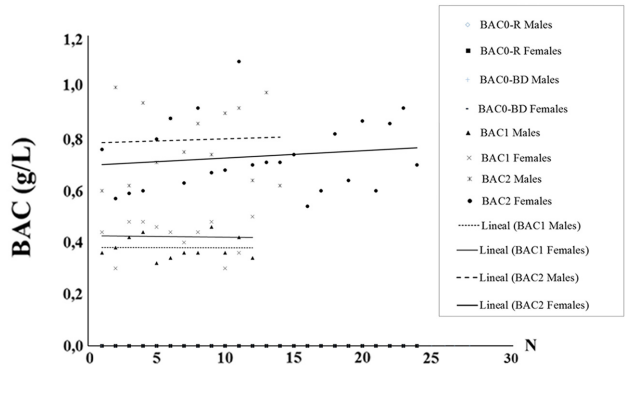

FIGURE 1 | Scatterplot depicting the distribution of BACs obtained in the sample of male and female adolescents.

Working Memory

The BAC factor was statistically significant [$F(3,146) = 10.353$, $p < 0.001$]. The *post hoc* comparisons revealed that the adolescents in the BAC2 group (but not those in the BAC1 group) performed the WM task worse than those in the BAC0-R and BAC0-BD groups (*ps* < 0.001); BAC2 adolescents performed worse than their BAC1 counterparts ($p < 0.05$); and no significant differences were observed between the BAC0-R and BAC0-BD groups ($p > 0.05$); (see **Figure 3**). The factor Gender was also statistically significant [$F(1,146) = 7.970$, $p < 0.01$], with men performing better than women (see **Figure 4**). Finally, the interaction of BAC and Gender was not statistically significant [$F(3,146) = 1.254$, *ns*].

DISCUSSION

The main aim of the present study was to evaluate the neurotoxic effects of different BACs on IMV and WM in adolescent binge drinkers. To provide greater specificity in the classification of alcohol users among the university students that composed our study population, a moderate BAC (BAC1, around 0.4 g/L) and a BD BAC (BAC2, around 0.8 g/L) were evaluated in 18-19-year-old male and female binge drinkers that had met the criteria for a BD pattern over a longer time frame (during the previous year), with a minimum of three BD episodes per month. This pattern, characterized by repeated alternations between acute intoxication and withdrawal periods, is particularly neurotoxic, independently of the global alcohol intake (Maurage et al., 2012), as it leads to several cognitive impairments in the not-yet-adult brain (Jacobus and Tapert, 2013; López-Caneda et al., 2014a). One distinctive contribution of this work was to evaluate, together in the same study, the acute and chronic (BD history) impact of this pattern of alcohol consumption, as well as the possible gender differences.

In relation to IVM, our results show that the scores in this memory were lower in binge drinkers with a moderate BAC (BAC1, around 0,4 g/L) and a BD BAC (BAC2, around 0,8 g/L), whose performance was lower than that of refrainers. Nevertheless, binge drinkers with a moderate BAC, but not the BD BAC group, did not show any impairment of IVM with respect to binge drinkers that received the refreshment. A tolerance phenomenon could explain this lack of differences between these groups (BAC1 versus BAC0-BD), but the absence of a group of refrainers receiving alcohol in our design (for ethical reasons) does not allow us to directly evaluate this phenomenon. In a previous study (Vinader-Caerols et al., 2017), we observed an effect of tolerance on IVM impairment by alcohol in women but not in men. We are not aware of any study that has evaluated the effects of different BACs on IVM in adolescents, although damage to this memory has been reported with a BAC of 0.86 – 0.79 g/L (Schweizer et al., 2006), while other studies have not observed any deleterious effect with a similar BAC (Söderlund et al., 2005).

TABLE 2 | Descriptive statistics for IVM and WM.

	Immediate visual memory					Working memory				
	Men	*n*	Women	*n*	Statistical power[1]	Men	*n*	Women	*n*	Statistical power[1]
BAC0-R (0 g/L in refrainers)	39.24 ± 6.57	18	55.62 ± 5.49	24		56.34 ± 5.74	18	40.41 ± 4.05	24	
BAC0-BD (0 g/L in BD)	44.73 ± 5.65	23	40.51 ± 5.43	27	0.177	51.37 ± 4.99	23	36.05 ± 3.26	27	0.050
BAC1 (0.3–0.5 g/L)	23.89 ± 7.26	12	31.14 ± 10.17	12	0.987	43 ± 6.59	12	35.46 ± 6.58	12	0.386
BAC2 (0.54–1.1 g/L)	10.89 ± 4.49	14	26.68 ± 4.6	24	0.999	23.8 ± 4.4	14	23.55 ± 3.47	24	0.999

The results are expressed as mean ± SEM. [1] *The Statistical Power is referred to comparisons with BAC0-R.*

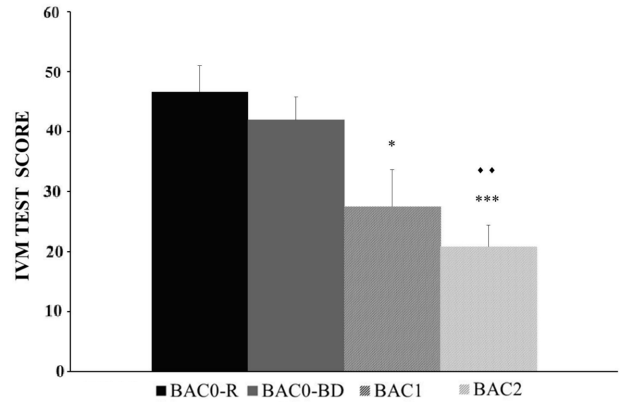

FIGURE 2 | Performance of the Immediate Visual Memory task (Mean ± SEM) by male and female adolescents with different BACs (BAC0-R: 0 g/L, in refrainers; BAC0-BD: 0 g/L, in binge drinkers; BAC1: 0.3 – 0.5 g/L, in binge drinkers; and BAC2: 0.54 – 1.1 g/L, in binge drinkers). *$p < 0.05$, ***$p < 0.001$ versus BAC0-R; ♦ ♦ $p < 0.005$ *versus* BAC0-BD.

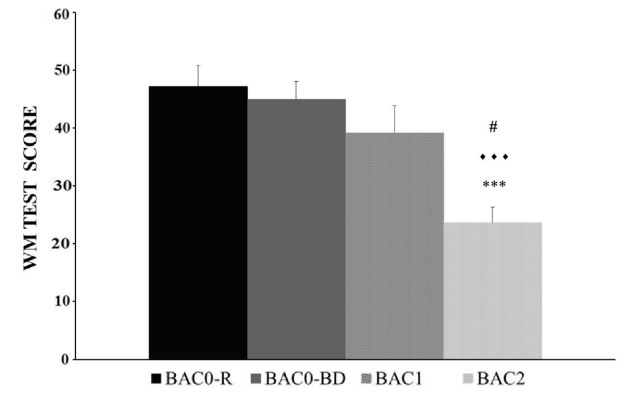

FIGURE 3 | Performance of the Working Memory task (Mean ± SEM) by male and female adolescents with different BACs (BAC0-R: 0 g/L, in refrainers; BAC0-BD: 0 g/L, in binge drinkers; BAC1: 0.3 – 0.5 g/L, in binge drinkers; and BAC2: 0.54 – 1.1 g/L, in binge drinkers). ***$p < 0.001$ versus BAC0-R; ♦ ♦ ♦ $p < 0.001$ versus BAC0-BD; # $p < 0.05$ *versus* BAC1.

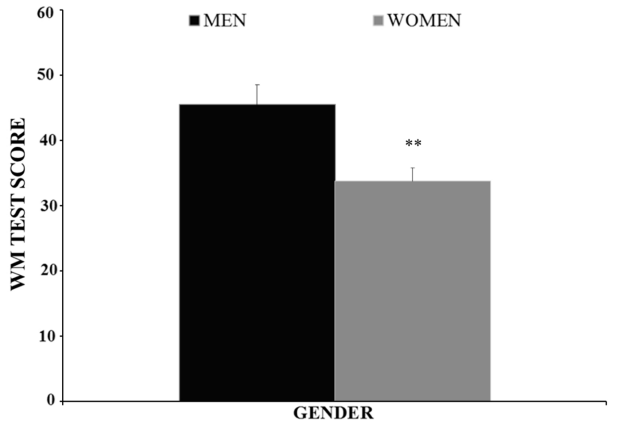

FIGURE 4 | Performance of the Working Memory task (Mean ± SEM) by male and female adolescents. **$p < 0.01$ *versus* Men.

With respect to WM, the lower performance on this memory in the binge drinkers was dependent on BAC. Some authors have suggested that the lack of effect in tasks like WM could be due to that brain employs alternative networks, compensating the damage produced by alcohol (Tapert et al., 2001, 2004; Caldwell et al., 2005). Our results are in agreement with this interpretation suggesting that the brain of binge drinkers with a moderate BAC (around 0.4 g/L) could be employing compensatory mechanisms in additional brain areas to perform a WM task adequately (Tapert et al., 2004; Caldwell et al., 2005), but that these resources would be undermined when BAC is higher (>0.5 g/L). Such compensatory mechanisms have been reported in memories related to executive functions, as WM, in alcoholics (Desmond et al., 2003). These authors suggest that brain activation in left frontal and right cerebellar regions that control verbal WM may require a compensatory increase in order to maintain the same level of performance as controls. In the same way, previous studies have reported that young binge drinkers exhibit anomalies in neural activity involved in attentional/WM processes, and suggest that this anomalous neural activity reflects underlying dysfunctions in neurophysiological mechanisms, as well as the recruitment of additional attentional/WM resources to enable said binge drinkers to perform the task adequately (López-Caneda et al., 2013). Thus, our findings are in accordance with similar studies which found that acute alcohol (measured by breath alcohol content) was associated with an impairment of WM performance and mental flexibility, without affecting motor performance, measured by the Trail Making Test in 18–20 old

adolescents with BD history (Day et al., 2013), and with reports of an impairment of WM with a BAC greater than 0.6 g/L (Pihl et al., 2003; Saults et al., 2007).

We cannot draw firm conclusions about the chronic effect of BD pattern on IVM and WM from our study. This is due to the lack of -for ethical reasons- a comparison group for the individuals that consumed a drink (i.e., a control group consisted of refrainers receiving a high dose of alcohol); as well as the low statistical power in the comparisons between binge drinkers that received refreshment and refrainers (see **Table 2**). Nevertheless, our results point out that maintaining a BD history over the previous year did not negatively affect the performance of the BAC0-BD group when compared with refrainers, either in IVM or WM. All the reviewed studies are in line with our results with respect to a BD history and IVM (e.g., García-Moreno et al., 2009; Parada et al., 2011b; Sanhueza et al., 2011; Mota et al., 2013). There are also several studies in agreement with our results in WM (e.g., Johnson et al., 2008; Winward et al., 2014; Boelema et al., 2015), where no differences in WM performance were observed between adolescents with BD history and controls. Similarly, Carbia et al. (2017) have reported that a stable BD during late adolescence and emerging adulthood is not associated with deficits in decision-making. Nevertheless, there are discrepancies amongst the literature, with studies showing better performance of refrainers in comparison to subjects with BD history (e.g., García-Moreno et al., 2008, 2009).

A greater cognitive vulnerability of women to the acute effects of alcohol has been highlighted by previous research (Vinader-Caerols et al., 2014, 2017); however, we have observed no gender differences in BAC-related lower performance in IVM and WM in the present study. We believe that an increased BAC cancels out these cognitive differences between men and women, though these interpretations obviously require further investigation. Independently of the BAC obtained, no genders differences were observed in IVM, but they were in WM, with men performing better than women. This is in accordance with other studies showing that visuospatial functioning of the WM is superior in males than in females (Rizk-Jackson et al., 2006; Vinader-Caerols et al., 2017). However, it should be mentioned that few studies have examined gender differences in WM and those that have done so report mixed results (Lejbak et al., 2011).

Our study suffers from some limitations which must be noted, such as the lack of an alcohol sensitivity measure (we will include an alcohol sensitivity questionnaire in our future research). Other variables apart from anxiety, such as depression or impulsivity, could have interfered with the interpretation of the results. Likewise, the use of different tests/batteries for evaluating IVM and WM (e.g., SOPT, Self-ordered Pointing Task; CANTAB, Cambridge Neuropsychological Test Automated Battery; BVRT, Benton's Visual Retention Test...) contributes to the disparity of results from the studies in this field. Among these tasks, the Wechsler Memory Scale -employed in our study- is a broadly used tool for assessing this kind of memories. On the other hand, longitudinal studies that contemplate the moment of onset of adolescent BD would be useful in establishing the causes and effects of this pattern of alcohol use. Similarly, longitudinal studies could determine whether abnormalities in brain function persist or emerge if alcohol consumption is maintained (e.g., Correas et al., 2016), or whether they recover or brake their evolution when the binging ceases (e.g., López-Caneda et al., 2014b). Discovering the causes and effects of individual differences in alcohol consumption patterns is instrumental to designing programs and policy to reduce the impact of drinking in a highly vulnerable population such as adolescent and young people. Despite the mentioned limitations, the methodology of this work can provide unique empirical data on this field of research, taking into account the absence of research that focuses on the acute effects of alcohol in individuals younger than 20 years old.

CONCLUSION

Our study shows that: (i) IVM is more sensitive than WM to the neurotoxic effects of acute alcohol in adolescents with a BD history, with BAC-related lower performance being noticeable (IVM score was lower with BAC1 and BAC2, while WM score was lower only when BAC reached levels of BD; i.e., around 0.8 g/L); and (ii) No gender differences are observed in BAC-related performance in IVM and WM (we believe that an increased BAC overrides these cognitive differences between men and women). Nevertheless, further research is needed in order to consolidate these conclusions.

AUTHOR CONTRIBUTIONS

CV-C and SM designed the study. AD and AM collected the data. CV-C, AD, and AM analyzed the data. CV-C and SM interpreted the data and wrote the first version of the manuscript. All authors collaborated on writing the final version of the manuscript.

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MINI REVIEW
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Binge Drinking and the Young Brain: A Mini Review of the Neurobiological Underpinnings of Alcohol-Induced Blackout

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Binge drinking has significant effects on memory, particularly with regards to the transfer of information to long-term storage. Partial or complete blocking of memory formation is known as blackout. Youth represents a critical period in brain development that is particularly vulnerable to alcohol misuse. Animal models show that the adolescent brain is more vulnerable to the acute and chronic effects of alcohol compared with the adult brain. This mini-review addresses the neurobiological underpinnings of binge drinking and associated memory loss (blackout) in the adolescent and young adult period. Although the extent to which there are pre-existing versus alcohol-induced neurobiological changes remains unclear, it is likely that repetitive binge drinking in youth has detrimental effects on cognitive and social functioning. Given its role in learning and memory, the hippocampus is a critical region with neuroimaging research showing notable changes in this structure associated with alcohol misuse in young people. There is a great need for earlier identification of biological markers associated with alcohol-related brain damage. As a means to assess *in vivo* neurochemistry, magnetic resonance spectroscopy (MRS) has emerged as a particularly promising technique since changes in neurometabolites often precede gross structural changes. Thus, the current paper addresses how MRS biomarkers of neurotransmission (glutamate, GABA) and oxidative stress (indexed by depleted glutathione) in the hippocampal region of young binge drinkers may underlie propensity for blackouts and other memory impairments. MRS biomarkers may have particular utility in determining the acute versus longer-term effects of binge drinking in young people.

Keywords: binge drinking, alcohol-induced blackout, adolescent, young adult, hippocampus, memory, magnetic resonance spectroscopy

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INTRODUCTION

Binge drinking (BD) is the dominant type of alcohol misuse in young people (SAMHSA, 2009; Archie et al., 2012; Hermens et al., 2013). Alcohol use typically begins in adolescence with the prevalence of BD increasing sharply between 12 and 25 years old (to ∼40–50%), which is a pattern observed across Western countries (SAMHSA, 2011; Archie et al., 2012; AIHW, 2014; Schuckit et al., 2015). Although young people drink less frequently than older adults, they tend to drink

more on each occasion (SAMHSA, 2009) and drinking to intoxication is especially common in teenagers (White and Hayman, 2006). Hence, single incident-excessive alcohol consumption or BD is often accompanied with adverse effects. These include increased risk of injury or accidental death, drink driving, unsafe sexual practices, periods of unconsciousness, as well as an increased likelihood of being a perpetrator or victim of assault (Bonomo et al., 2004; Mundt et al., 2012). A universal definition of BD remains lacking, however, it is generally accepted that it refers to "a single drinking session leading to intoxication" (Berridge et al., 2009). The USA's National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2017) has a more specific definition of: "a pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08 g/dL." Furthermore, this would be within a period of about 2 h, which "typically occurs after four drinks for women and five drinks for men." Despite this, numerous studies and surveys have opted for a simpler definition of BD as five or more drinks per single drinking occasion, for both sexes (SAMHSA, 2011; Degenhardt et al., 2013).

Prevalence and Patterns of Binge Drinking in Young People

National surveys in the United States and Australia show that around 40% of young adults (aged ∼20–25 years[1]) report at least monthly BD. Similarly, in both countries around 5–6% of adolescents (aged 12–17 years) report this pattern of drinking (with a sharp increase to ∼15% by 16–17 years) (AIHW, 2017; SAMHSA, 2017). Across 35 European countries, around one third of 16 year olds report monthly BD (EMCDDA/ESPAD, 2016). The Australian survey (AIHW, 2017) also asked about any 'loss of memory after drinking.' Of those reporting monthly BD, 16–17 year olds had the highest rates of such memory loss (32%) with the next highest being the 20–24 year olds (24%). In terms of those with yearly but not monthly BD, 100% of 12–15 year olds reported alcohol-related memory loss, compared to the next highest group the 18–19 year olds (49%)[2].

Longitudinal studies have provided important insights into the longer-term effects that adolescent BD may have on memory loss. Degenhardt et al. (2013) conducted a 15-year prospective study of N = 1943 Australians (from 14 to 15 years old) and found that 52% of males and 34% of females reported past-week adolescent BD. Furthermore, the vast majority continued to be BD into their adulthood and this was more likely in males, those who had antisocial behaviors and adverse consequences of drinking in adolescence. Notably, the adverse consequences included 'intense drinking' (i.e., when the subject could not remember the night before) as well as social problems, and alcohol-related sexual risk taking and injury/violence. Similarly, a longitudinal study of N = 1402 English adolescents who reported drinking alcohol prior to 15 years showed that 29% experienced alcohol-induced blackout (AIB)[3]. At follow-up, 57 and 74% had AIBs by 16 and 19 years, respectively (Schuckit et al., 2015). Although this study did not evaluate BD *per se*, the authors found that there was a general association between increased alcohol quantities and AIBs. One of the trajectories identified (30% of the sample) was thought to be prone to AIBs at age 16 due to links between their extroversion, peer substance use and BD (high BAC). However, the authors would not rule out other potential factors including family history of alcohol problems. Taken together, these findings suggest that young people who undertake BD are particularly prone to experiencing AIBs (Schuckit et al., 2015; Wetherill and Fromme, 2016). As a further complication, it remains a challenge to distinguish between the acute versus longer-term effects of BD in young people. These differential impacts of BD are addressed in the following sections.

Early Binge Drinking: A Window of Vulnerability

The prevalence of BD in young people is particularly concerning given the damaging effects of alcohol on the developing adolescent-to-young adult brain (Hermens et al., 2013; Cservenka and Brumback, 2017). Despite this, there remains a relative paucity of neurobiological studies investigating the acute and longer-term effects of BD in young people (Hermens et al., 2013), particularly with respect to AIBs. Clark et al. (2008) suggest that the asynchronous development of the prefrontal cortex with respect to the limbic system in adolescence/young adulthood drives the heightened vulnerability to the effects of alcohol. Brain maturation continues well into the third decade of life, particularly in regards to prefrontal executive functions (EFs) (De Luca et al., 2003), which can result in an increased propensity for risky, impulsive behaviors and experimentation. In this period there are substantial changes in brain structure, with gray matter (GM) decreasing non-linearly in the cerebral cortex and linearly in the cerebellum and subcortical structures (caudate, putamen, pallidum), whereas in other subcortical structures (amygdala, hippocampus) slight, non-linear increases in GM volume are observed (Ostby et al., 2009). Additionally, white matter (WM) increases non-linearly in the cerebrum and cerebellum (Ostby et al., 2009). Hence, the period of adolescence-to-young adulthood is often viewed as a 'window of vulnerability,' particularly in the context of substance misuse (Bava and Tapert, 2010; Hermens et al., 2013). Young alcohol misusers first show impairments in memory and EF, which correspond with structural changes in hippocampal and prefrontal brain regions (Bava and Tapert, 2010; Hermens et al., 2013; Squeglia et al., 2015; Gropper et al., 2016; Wilson et al., 2017). Given its progressive development throughout adolescence the hippocampus is thought to be particularly susceptible to alcohol, including acute dysfunction causing blackout (Zeigler et al., 2005). Such dysfunction may be due to the increased sensitivity of the adolescent brain to the acute effects of alcohol and/or the maturational changes and associated heightened vulnerability

[1]The age range in the Australian Institute of Health Welfare (AIHW) survey was 20–24 years; whereas in the Substance Abuse and Mental Health Services Administration (SAMHSA) survey it was 20–25 years.

[2]For the 16–17 year old group with yearly but not monthly BD, the rate of 'loss of memory after drinking' could not be confirmed because of high sampling error.

[3]Schuckit et al. (2015) used the term 'alcohol-related blackout' however, alcohol-induced blackout is more commonly used and therefore "AIB" is term used throughout this paper.

driving longer-term effects of exposure. Due to ethics and legal issues, research on the acute effects of alcohol on younger people is not possible, and as such animal studies (see below) have been crucial in our understandings of how the adolescent brain is particularly vulnerable to BD (Zeigler et al., 2005). Despite this, several human studies have provided important insights into the cognitive effects of acute alcohol ingestion. Acheson et al. (1998) conducted a randomized, repeated-measures placebo-controlled trial of alcohol (0.6 g/kg) in $N = 12$ healthy adults. They found that compared to placebo alcohol significantly impaired the acquisition of both semantic and non-verbal memory. Importantly, younger subjects (21–24 years) performed worse in the alcohol condition compared to their older peers (25–29 years) in immediate and delayed recall (visuo-spatial) and delayed recognition (verbal memory). Similarly, Vinader-Caerols et al. (2017) examined the acute effects of alcohol (i.e., doses of 0, 0.3–0.5, or 0.54–1.1 g/L) in past 12-month refrainers or BD aged 18–19 years. Compared to their BD and non-drinking peers those who consumed the highest acute dose showed the most impaired immediate visual and working memory, while the lower dose BD group showed impaired immediate visual memory only.

Other studies have examined the potential longer-term, dose-dependent effects of BD on cognitive performance. Nguyen-Louie et al. (2016) examined verbal learning and memory in adolescents (12–16 years) who were determined (6 years after baseline) to be moderate, binge or extreme-binge drinkers (≤4, 5+, or 10+ drinks/occasion). At follow-up, the extreme-BD group performed significantly worse than the moderate drinkers in verbal learning, as well as cued and free short delayed recall (BD performed at an intermediate level). Furthermore, for every additional drink consumed in adolescence, there was a linearly increasing deleterious effect on a range of learning, recall and recognition measures. In contrast, a more recent longitudinal study (Boelema et al., 2015) of $N = 2230$ Dutch adolescents found no differences among non-, light-, and heavy-drinkers in terms of the maturation of four measures of EF (i.e., inhibition, working memory, and shift- and sustained attention).

Animal Models

Earlier studies by Swartzwelder and colleagues utilized rat hippocampal slices to demonstrate the effects of acute alcohol exposure on the pre-pubertal/adolescent brain. Swartzwelder et al. (1995b) showed that alcohol has greater suppression of *N*-methyl-D-aspartate (NMDA) receptor-mediated synaptic potentials in pre-pubertal as compared with adult rats. Thus, the authors suggested that young drinkers may be at greatest risk of compromised cognitive function (i.e., anterograde memory formation) related to hippocampal NMDA activity. In other similar studies, this group provided further evidence of perturbed hippocampal function in adolescent but not adult rats; with attenuated long-term potentiation (LTP; important in the acquisition of spatial memory as well as learning and memory formation or 'synaptic plasticity') being observed across three different doses, including those more representative of human intoxication (Swartzwelder et al., 1995a; Pyapali et al., 1999). More recently, Risher et al. (2015) utilized 'adolescent intermittent ethanol' exposure via intragastric gavage for 16 days (until adulthood) before examining the acute effects of alcohol on hippocampal slices, and found enduring structural and functional abnormalities, reflecting synaptic immaturity.

Two subsequent studies probed and evaluated the longer-term effects of alcohol in adolescent and adult rats performing memory tasks. Markwiese et al. (1998) injected rats with alcohol (1.0 or 2.0 g/kg) or saline 30 min before trials on a spatial memory task, over a 5-day period. Notably, alcohol significantly impaired adolescent but not adult rats in spatial memory acquisition. As a follow-up to this, White et al. (2000) exposed rats to binge-style alcohol (i.e., 5.0 g/kg, 48-h intervals) or saline over a 20 day period. Animals were then tested (20 days post final dose) on an elevated plus maze and trained to perform spatial working memory task. Interestingly, prior exposure to alcohol and group status did not affect plus maze behavior nor spatial working memory performance, however, the animals exposed to binge-style alcohol as adolescents showed significant impairments in working memory when undertaken during an alcohol challenge (1.5 g/kg) compared to the other three groups (including binge-exposed adults). Importantly, the overall findings of studies utilizing intraperitoneal injections have been observed in similar studies utilizing self-administration protocols. Vargas et al. (2014) showed that voluntary binge drinking during adolescence produced enduring WM deficits in prefrontal circuitry and poorer performance in working memory, which was over and above the effects of vapor exposure (modeling dependence; over a longer period) during adulthood, suggesting that the adolescent brain has a heightened sensitivity to alcohol.

Acute Alcohol Use, Memory Loss: Blackout

'Blackout' or the loss of memory during an episode of drinking was first documented as an important indicator of alcoholism (Jellinek, 1946). However, it is now understood as phenomenon that can be experienced by any drinker, as it is typically induced by BD with a rapid increase in BAC; although there are a range of factors that are thought to increase the likelihood of blackout (Rose and Grant, 2010). Most definitions of blackout refer to there being a breakdown in the transfer of information from short-term to long-term storage (Acheson et al., 1998; White, 2003; Siqueira and Smith, 2015). Importantly, this occurs while immediate (very brief short-term) and remote (long-term; formed prior to intoxication) memory abilities remains intact (White, 2003). More specifically, an AIB leads to a failure in forming new explicit memories (i.e., facts and events) (Lister et al., 1991). Such anterograde amnesia occurs despite the subject continuing to participate in events (e.g., holding a conversation) that they will not remember later (White, 2003; Lee et al., 2009).

There is no objective test to determine that one is experiencing a blackout (Goodwin, 1995; Pressman and Caudill, 2013; Wetherill and Fromme, 2016). Thus, observers rely on the subject's self-report which is itself constrained by the concept of being asked to 'remember not remembering' (Wetherill and

Fromme, 2016). Detailed research has led to the identification of two qualitatively different types of blackouts: 'en bloc' (complete) and fragmentary (partial), first described almost 50 years (Goodwin et al., 1969a,b) these terms remain valid today (White, 2003; Rose and Grant, 2010). AIBs should not be confused with losing consciousness (i.e., "passing out"), rather an AIB is the memory lost from the conscious state whereby en bloc blackouts represent the complete interruption of memory transfer (an absence of encoding) and fragmentary blackouts (FBs) reflect partial obstruction of memory formation (a deficiency of encoding), which may be ameliorated via cueing (Lee et al., 2009; Rose and Grant, 2010).

For Acheson et al. (1998), AIBs stems from two processes: first, alcohol reduces one's ability to process new information (Maylor and Rabbitt, 1993), then it facilitates faster forgetting (Maylor and Rabbitt, 1987). Importantly, rapid forgetting is a hallmark of hippocampal dysfunction (Squire et al., 2004), however, not all BD experience blackout, implying that genetic factors also play a role (Lee et al., 2009). Genetic epidemiological research supports this assumption. An Australian study of 2324 twin pairs reported a 52.5% heritability rate of lifetime AIBs (Nelson et al., 2004). Interestingly, it was speculated that genes whose products mediate alcohol's effects on hippocampal neurotransmission probably underlie such risk. On the other hand, early alcohol exposure may have specific impacts on longer-term hippocampal functioning as suggested by a longitudinal study of $N = 1145$ young adults (Marino and Fromme, 2016). Whereby, earlier drinking age was associated with more frequent blackouts (over 3-year period) which persisted despite a reduction in BD episodes.

A paucity of neuroimaging studies has directly examined AIB. However, functional magnetic resonance imaging (fMRI) studies undertaken to date provide evidence for neurobiological vulnerabilities that may exist prior to alcohol use onset and become more evident after BD patterns emerge (Wetherill and Fromme, 2016). Wetherill et al. (2012) utilized two fMRI sessions (nil vs. alcohol ingestion) to compare $N = 12$ university students (21–23 years) with a past 12-month history of FB to $N = 12$ peers without FB in a contextual memory task. The groups did not differ in performance or neural activity during the nil alcohol session. However, in the alcohol session (0.08% breath alcohol concentration) the FB group showed decreased blood-oxygen-level dependency (BOLD) response during encoding and recollection of contextual details in dorsolateral prefrontal and parietal regions.

Subsequently, this same group conducted an fMRI study in substance-naïve 13 year olds (Wetherill et al., 2013). At 5-year follow-up, the investigators compared inhibitory processing in those who remained substance naïve ($n = 20$) versus those who had transitioned into heavy drinkers with ($n = 20$) or without ($n = 20$) a history of AIB. Interestingly, at baseline the AIB group showed greater activation (increased BOLD) in frontal and cerebellar brain regions during inhibitory processing compared to both other groups. The authors suggested this provided evidence of inherent vulnerabilities to inhibitory processing difficulties that likely contribute to alcohol-induced memory impairments (Wetherill and Fromme, 2016).

Magnetic Resonance Spectroscopy: Probing the Neurochemistry of Blackout

Magnetic resonance spectroscopy (MRS) has provided evidence of *in vivo* neurochemical perturbations associated with alcohol misuse in human (Lee et al., 2007; Hermann et al., 2012; Ende et al., 2013; Yeo et al., 2013) and animal (Hermann et al., 2012) studies. However, only two MRS studies have specifically examined AIBs. Silveri et al. (2014) examined neurochemical profiles in the frontal and parietal-occipital lobes of BD aged 18–24 years. Compared to their light-drinking (LD) peers ($N = 31$), BD ($N = 21$) showed reduced gamma-aminobutyric acid (GABA) and *N*-acetylaspartate (NAA; a marker of neuronal integrity) in the anterior cingulate cortex (ACC). Furthermore, BD with a history of AIBs also showed significantly reduced glutamate compared LD. Follow-up analyses suggested that the reductions in GABA and NAA were more pronounced in BD with AIBs. There was also a trend for a reduction in glutamate in this subgroup. Importantly, all subjects had experience as college students, had high-average to superior IQ and none had an alcohol use disorder (AUD). Thus, the authors suggested that these findings might serve as early markers of risk in young individuals who continue hazardous drinking. Notably, only GABA was found to be significantly associated with cognitive performance, with lower levels of ACC-GABA being associated with worse performance in attentional switching and response inhibition.

To our knowledge, only one other study has specifically investigated AIB utilizing MRS. Our group (Chitty et al., 2014) examined the relationship between *in vivo* glutathione (GSH; the brain's primary anti-oxidant) levels in young people with bipolar disorder (aged 18–30 years), given the high levels of alcohol use common to this psychiatric group and alcohol's propensity to trigger oxidative stress (via the production of reactive oxygen species) in the brain (Nordmann et al., 1990). Despite no significant difference in overall risky drinking levels compared to healthy controls, the bipolar disorder group showed an association between increased alcohol use and decreased frontal (ACC) and hippocampal GSH. We supposed that this association might be evidence of memory impairment related to alcohol-induced oxidation, since increases in oxidative stress have also been linked to impairments in synaptic plasticity and memory, and decreased capacity to exhibit LTP (Pellmar et al., 1991; Auerbach and Segal, 1997).

Hippocampus: The Target of Further Investigation

Although mechanisms around AIBs are becoming increasingly understood, a detailed understanding of the neurobiological vulnerability (and why some individuals experience blackouts) remains unknown (Wetherill and Fromme, 2016). We would argue that more research targeting the neurochemistry and functioning of the hippocampus is needed to address this. More broadly, the hippocampus has been implicated in the pathogenesis of AUD (White and Swartzwelder, 2004). Furthermore, a substantive amount of work has led to the hippocampus being a focal point in studies of both the

acute and chronic effects of alcohol use (Abrahao et al., 2017), particularly given its inhibition of glutamate binding [suppression of NMDA receptors (NMDAr)] (Strelnikov, 2007). It is also well-established that with chronic alcohol use, NMDAr binding sites increase in number and level of functioning (up-regulation), as demonstrated in rodents who show increased glutamate transmission in the hippocampus after repeated ethanol administration (Chefer et al., 2011). Furthermore, upon alcohol withdrawal, excessive glutamate activity resulting from increased numbers of NMDAr leads to a state of excitoxicity that can contribute to neurodegeneration (Hunt, 1993). Thus, periods of BD followed by abstinence may trigger cycles of neural responses that facilitate such neurotoxicity and associated cognitive impairments (Zeigler et al., 2005). Future studies should explore this by specifically examining factors associated with (and without) AIB, in particular, the underlying neurochemistry. This is crucial given the two key mechanisms underlying AIBs (Rose and Grant, 2010); that is: (i) a breakdown or blocking of short-term memory transfer, followed by; (ii) compromised subsequent retrieval caused by disruptions in hippocampal pyramidal cell activity. Crucially, the neurochemical processes underpinning these steps are: (i) potentiation of GABA-mediated inhibition; and (ii) interference of hippocampal NMDAr activation, leading to decreased LTP (Rose and Grant, 2010). The role of GSH may be important too given its status as a marker of oxidative stress. Furthermore, glutamate is a precursor of both GABA and GSH therefore the relationship between these metabolites (all measured via MRS) may be crucial to understanding individual differences in AIBs.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Verbal Learning and Memory in Cannabis and Alcohol Users: An Event-Related Potential Investigation

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Aims: Long-term heavy use of cannabis and alcohol are known to be associated with memory impairments. In this study, we used event-related potentials to examine verbal learning and memory processing in a commonly used behavioral task.

Method: We conducted two studies: first, a small pilot study of adolescent males, comprising 13 Drug-Naive Controls (DNC), 12 heavy drinkers (HD) and 8 cannabis users (CU). Second, a larger study of young adults, comprising 45 DNC (20 female), 39 HD (16 female), and 20 CU (9 female). In both studies, participants completed a modified verbal learning task (the Rey Auditory Verbal Learning Test, RAVLT) while brain electrical activity was recorded. ERPs were calculated for words which were subsequently remembered vs. those which were not remembered, and for presentations of learnt words, previously seen words, and new words in a subsequent recognition test. Pre-planned principal components analyses (PCA) were used to quantify the ERP components in these recall and recognition phases separately for each study.

Results: Memory performance overall was slightly lower than published norms using the standardized RAVLT delivery, but was generally similar and showed the expected changes over trials. Few differences in performance were observed between groups; a notable exception was markedly poorer delayed recall in HD relative to DNC (Study 2). PCA identified components expected from prior research using other memory tasks. At encoding, there were no between-group differences in the usual P2 recall effect (larger for recalled than not-recalled words). However, alcohol-related differences were observed in a larger P540 (indexing recollection) in HD than DNC, and cannabis-related differences were observed in a smaller N340 (indexing familiarity) and a lack of previously seen > new words effect for P540 in Study 2.

Conclusions: This study is the first examination of ERPs in the RAVLT in healthy control participants, as well as substance-using individuals, and represents an important advance in methodology. The results indicate alterations in recognition memory processing, which even if not manifesting in overt behavioral impairment, underline the potential for brain dysfunction with early exposure to alcohol and cannabis.

Keywords: RAVLT, principal components analysis, recollection, familiarity, alcohol, cannabis

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INTRODUCTION

Acute as well as chronic use of both alcohol and cannabis can result in memory dysfunction (see, for example, Solowij and Battisti, 2008; Konrad et al., 2012; Crane et al., 2013; Schoeler and Bhattacharyya, 2013; Bernardin et al., 2014; Broyd et al., 2016). Recent research has focused on the possible effects of younger age of onset of use (e.g., Pope et al., 2003; Wagner et al., 2010; Crane et al., 2015), dose-dependent effects in recreational vs. heavy users (e.g., Chye et al., 2017), and the possibility of recovery with abstinence (e.g., Yücel et al., 2016).

In this study we focus on a well-known test of verbal learning and memory, the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941; Lezak et al., 2004). The RAVLT tests memory for 15-item lists of unrelated words and allows for measurement of learning across five trials (Trials I-V), followed by recall of a second list (Trial B), and then immediate (Trial VI) and delayed recall (Trial VII), and recognition of the initial list. The RAVLT is widely used, easy to administer, and has published norms available (e.g., Vakil et al., 1998, 2010; Carstairs et al., 2012).

Regular cannabis users have been shown to perform more poorly than non-using controls on the RAVLT and related memory tasks when not acutely intoxicated (for review see Broyd et al., 2016). Impairments have been reported by our team for both adult (Solowij et al., 2002) and adolescent cannabis users (Solowij et al., 2011). Cannabis-related deficits in memory and learning appear not to be permanent (e.g., Pope et al., 2001; Broyd et al., 2016), with meta-analytic reviews suggesting that only small magnitude effects are apparent in the first few weeks of abstinence (of the order of $d = 0.25$ to 0.35), and these become smaller and non-significant with extended abstinence (to around $d = 0.15$; Schreiner and Dunn, 2012).

There are disparities in the reported results for alcohol dependent groups or heavy drinkers in comparison to controls. For alcohol dependence, Phelan (2013) reported fewer words recalled over Trials I-V for alcohol dependent participants (approaching significance), and alcohol dependence was also associated with poorer recognition performance. On the other hand, Waugh et al. (1989) report intact performance over Trials I-V, but significantly poorer performance for heavy drinkers consuming 81–130 g of alcohol per day on Trial V and VI. A meta-analytic study of alcohol dependence reports deficits with medium effect sizes that do not fully recover with extended abstinence (>365 days; Stavro et al., 2012). Amongst young heavy drinkers, Parada et al. (2011) report greater proactive interference, while Winward et al. (2014) reported impairments in delayed recall despite similar initial memory performance. However, our team has found no differences between adolescent drinkers and non-drinkers in RAVLT performance (Solowij et al., 2011), while Kokavec and Crowe (1999) reported trends toward *better* performance among binge drinkers.

In the current study, we examine in detail the memory performance of groups of young heavy drinkers, cannabis users (most, but not all, of whom were also heavy drinkers), and controls who neither used cannabis nor drank heavily. In addition to studying behavioral measures, we also examine electrophysiological functioning using event-related potentials or ERPs. These represent the brain's average electrical response to an event, resulting in peaks and troughs of electrical negativity and positivity corresponding to various stages of processing, reviewed below. In several studies, electrophysiological and neuroimaging measures have proven to be more sensitive to drug effects than behavioral measures (e.g., Solowij et al., 1995; Maurage et al., 2009; Norman et al., 2011; Mahmood et al., 2013) and may indicate subtle deficits in processing which are not yet strong enough to influence gross measures such as error rates and reaction time. Our group has previously reported differences in ERPs associated with word list learning between light and heavy drinkers in the absence of behavioral performance differences (Fox et al., 1995), and also ERP alterations and verbal memory deficits in chronic cannabis users (Battisti et al., 2010).

Despite the importance of studying brain function to identify subtle or underlying processes, only two papers have examined ERPs in the RAVLT (Babiloni et al., 2009, 2010). Babiloni et al. (2009) recorded intracerebral electrical activity in patients with temporal lobe epilepsy during the recall phase of the RAVLT, and examined event-related synchronization in the theta band for words which were recalled vs. words which were not recalled. In 2010, they presented traditional ERP analyses of the same participants, with a late positive peak apparent around 350 ms post-stimulus being larger for recalled than unrecalled words. While these results are in line with expectations for memory tasks as reviewed below, they are not easily generalizable to a wider population. Firstly, as epilepsy patients have abnormal patterns of brain activity, it is difficult to predict the pattern of brain activity in healthy control participants, much less potential differences in substance abusing individuals. Secondly, intracerebral recording techniques are less sensitive to noise than scalp-recorded ERPs. Lastly, presumably because of time and posture constraints associated with neurosurgery, the recognition portion of the RAVLT was not performed.

It is likely that the RAVLT has not been used in other ERP studies due to signal:noise ratio (SNR) difficulties. SNR is a function of both the size of the signal and the number of trials available for averaging, and as a rule of thumb, the largest ERP components may require 30–60 trials per condition to achieve adequate SNR, while the smallest (e.g., brainstem auditory evoked potentials) may require several thousand (Luck, 2004). Thus, the RAVLT has too few trials to produce reliable ERPs with acceptable SNRs for analysis via traditional methods.

The current study, however, uses established statistical procedures which can identify latent sources of variability in ERP waveforms. In general, principal components analysis (PCA) is a technique used to extract latent variables explaining variance in a dataset. When applied to ERPs in the temporal domain, PCA extracts factors which explain a large proportion of variance across time between subjects, conditions, and scalp sites, while noise, explaining a smaller proportion of variance, is reduced (Donchin and Heffley, 1978; Coles et al., 1986). Factor loadings can be analyzed to determine the time over which a particular component is active, while the peak component amplitudes for each identified factor of interest (analogous to the more traditional peak-picked component amplitudes) can be assessed statistically (via ANOVA or MANOVA) to examine potential

differences in scalp distribution, and between conditions and groups.

One major difference in ERP waveforms associated with recall is the amplitude of the P2 component, being larger to words which are later recalled, compared to those which are not recalled (e.g., Chapman et al., 1978; Smith, 1993; Babiloni et al., 2010). Peak or mean amplitude measures have often been employed, despite Chapman et al. (1978) noting that the P2 related to memory overlaps in time with an earlier positive peak of the evoked potential, and that PCA-derived rather than peak measures of the grand average ERP may capture the P2 recall effect more precisely. We expect to observe similar differences in PCA-derived ERP measures in the recall phase of the RAVLT, for words which are vs. are not recalled.

Secondly, we expect to observe in the recognition phase of the RAVLT two major effects known as the parietal old/new effect and the frontal familiarity effect. Early studies on recognition memory reported more positive-going waveforms for previously studied (old) words compared to new words (e.g., Sanquist et al., 1980; Warren, 1980). However, later studies reported dissociation between effects at frontal vs. parietal sites, supporting a dual-process model of recognition memory, which asserts that recognition judgements may be made based on two types of information: familiarity (remembering) and recollection (knowing). Familiarity-based recognition involves a global matching process between study items and test items, while recollection requires a distinct memory signal involving the retrieval of the context of learning (for a review see Wilding and Rugg, 1996; Curran, 2000; Rugg and Curran, 2007). The ERP index of recollection is the parietal old/new effect, a parietally maximal positivity occurring 400–800 ms post-stimulus (here termed P600), often larger in the left hemisphere, and larger for previously studied words compared to new words. The index of familiarity is held to be the N400, a negativity occurring around 300–500 ms post-stimulus, typically at mid-frontal sites, which is more negative (larger) for new words. These effects have been functionally separated by experimental paradigms more complex than the RAVLT (e.g., Rugg et al., 1998; Curran, 2000), but based on those results we can predict different familiarity and recollection effects in the recognition phase of the RAVLT for List A, List B and New words (see Method for details).

The current studies build upon previous work examining memory in young heavy drinkers and cannabis users by including the first analysis of ERPs in addition to behavioral performance during the RAVLT. In a small pilot study of male adolescents, recorded with a reduced scalp montage, we first show proof of concept, that even with low numbers of trials, we can extract meaningful components from the ERPs which behave in predictable ways. In a subsequent larger study of young adults of both sexes, with a larger scalp montage, and more detailed information about use of alcohol, cannabis, and other drugs, we again demonstrate the viability of examining ERPs in the RAVLT (and that ERPs may be more sensitive to effects of alcohol and cannabis use, and of sex, than behavioral measures alone). To foreshadow the results, consideration of ERPs adds sensitivity to the analyses, since some substance-related differences were observed in ERP comparisons which were not apparent in behavioral data.

STUDY 1

Methods

Participants

Participants were 33 males (aged between 16 years and 18 years 11 months) recruited from a larger, separate cohort of adolescents (Mattick et al., 2017) who since age 12 have reported yearly on their use of alcohol and other substances. Participants were eligible to participate if they were not regular users of any other drug apart from alcohol, cannabis or tobacco, had normal or corrected vision, were not using psychoactive medications, and had never suffered a seizure or serious head injury. We recruited participants with a range of alcohol and cannabis consumption patterns, although because the sample sizes are small, and use of alcohol and/or cannabis was relatively low, we report exploratory analyses of drug-related effects in Supplementary Material only. All participants gave written informed consent, and the protocol was approved by the University of New South Wales Human Research Ethics Committee before data collection began in an EEG laboratory at the University of Tasmania.

Procedures

The experimenter showed the participant the lab and recording equipment and described the experimental protocol before written informed consent was obtained. Participants then completed a short demographics questionnaire as well as questions about their alcohol and other drug use, and the Wechsler Test of Adult Reading (Holdnack, 2001).

A modified version of the RAVLT (Rey, 1941) was administered with standard instructions and word lists (i.e., drum, curtain, bell etc. for List A, and desk, ranger, bird, etc. for List B; Lezak et al., 2004). Because we wanted to use the words traditionally included in the RAVLT, but also to standardize the duration of their presentation, in line with many other ERP memory studies, we used a visual rather than auditory presentation modality. Participants were presented with the 15 List A words, displayed for 200 ms, with a 1000 ms stimulus onset asynchrony, in white capital letters on a black screen. Two seconds after the end of each sequence of 15 words, the word RECALL appeared in green text, prompting participants to recall, out loud, as many words as possible in any order. This was repeated five times (Trials I-V). Next, the 15 List B words were presented, with the same timing and instructions (Trial B). Following this, participants were unexpectedly asked to recall as many List A words as possible, without another presentation of that list (Trial VI). Participants then completed a 20 min non-verbal distractor task, followed by again being unexpectedly asked to recall List A words (Trial VII).

For the recognition part of the experiment, some further modifications were necessary for compatibility with ERP techniques. The usual method for the recognition phase is to present the 15 List A words, 15 List B words, and 20 new words in random order on a sheet of paper, and ask the participant to circle the List A words. Here, we presented the words one at a time,

in white capitals on a black background, and asked participants to press one button (e.g., with the left hand) for List A words, and a different button (e.g., with the right hand) for "Other" words (i.e., List B and New words). The response assignment was counterbalanced between participants. Words were displayed on the screen until the participant made a response, and were then replaced by a black screen for 500 ms, when the next word appeared. For recall performance, we counted the number of words correctly recalled on Trials I-VII; we gave credit for words that were pluralized. For the recognition phase, we counted the number of words correctly categorized as List A/Other, and the time taken to make the response, for List A, List B and New words.

EEG Recording and Analysis

Continuous monopolar EEG was recorded from 30 scalp sites using an elasticised cap with sintered Ag/AgCl electrodes. Additional electrodes recorded vertical and horizontal EOG. All electrodes were referenced to linked mastoids and grounded midway between FPz and Fz. Electrode impedances were below 5 kΩ. Signals were recorded between 0.05 and 30 Hz, and sampled at 1,000 Hz using NeuroScan recording software and hardware.

The EEG was filtered with a bandpass from 0.1 Hz (down 12 dB/octave) to 24 Hz (down 24 dB/octave, zero phase shift), and then corrected for eye movements using NeuroScan's inbuilt procedure (Semlitsch et al., 1986). Noisy electrodes were interpolated offline using Curry 7; 6 participants had one interpolated channel, 4 participants had two, and 1 participant had three. All epochs began 100 ms prior to and ended 900 ms after stimulus presentation, and were baselined during the prestimulus interval. Epochs were rejected if amplitude exceeded ±100 μV in any scalp channel. For ERPs in the recall phase, we created average ERPs for the presentation of words in Trials I-B which were "Remembered" or "Not Remembered" in the immediately subsequent recall period (Babiloni et al., 2010). An average of 47 trials (minimum 30) were included for Remembered words, while an average of 39 trials (minimum 21) were included for Not Remembered words. For the recognition phase, we created average ERPs to correctly categorized "List A," "List B," and "New" words. One participant performed poorly on the recognition task such that only 3 trials were available for averaging for List A words; this participant was excluded from analyses of ERPs from the recognition phase. For the remaining participants, an average of 13 List A trials (minimum 10), 14 List B trials (minimum 9), and 18 New trials (minimum 13) were included in the ERPs, representing more than 97% of the available trials for all three trial types.

Data Reduction

ERP data were downsampled to 200 Hz to increase the ratio of cases (subjects, conditions, sites) to variables (timepoints) and were then subjected to separate temporal principal components analyses (PCA) for the recall and recognition phases of the experiment, using Matlab 9.2 (R2017a) and the ERP PCA Toolkit (v2.53; Dien, 2010). Each PCA used the covariance matrix, Kaiser normalization, and varimax rotation (Kayser and Tenke, 2003, 2006; Dien et al., 2005), and Horn's Parallel Test (Horn, 1965) was used to identify the number of factors to be extracted and rotated. The Recall PCA (Remembered and Not Remembered trials) had 1980 cases (33 participants × 2 conditions × 30 sites), and was restricted to 14 factors which together accounted for 92.51% of variance. Factors were labeled based on their polarity and peak latency. Three positive factors were identified in the P2 time range, however only Factor 6, labeled P175 (peaking at 175 ms, maximal at FCz, and explaining 4.4% of unique variance) showed the expected Remembered > Not Remembered effect and thus is the only P2 component discussed here. For completeness, the additional factors peaking in the P2 range, as well as factors peaking at 440 ms (N400 time range) and 630 ms (P600 time range) are presented in Supplementary Material.

The Recognition PCA (on List A, List B and New words) had 2880 cases (32 subjects × 3 conditions × 30 sites), and was restricted to 13 factors which together explained 93.72% of variance. Factor 1, labeled P640 (peaking at 640 ms, maximal at CPz, explaining 24.76% of variance) was identified as reflecting the classical parietal Old/New (P600) effect, while Factor 2, labeled N415 (peaking at 415 ms, maximal at C4, explaining 18.41% of variance) was identified as reflecting the frontocentral N400 effect.

Statistical Analysis

For recall performance, several separate within-subject MANOVAs were performed. To assess differences in learning rate over Trials I-V, we ran a MANOVA with Trial as a factor (I, II, III, IV, V); polynomial contrasts on the trial factor assessed the change over trials, although only linear and quadratic trends were examined. To assess proactive interference (i.e., poor recall of new material due to interference from learning of old materials), we compared Trial I with Trial B. For assessment of retroactive interference (i.e., poor recall of old material due to interference from learning of new material), we compared Trial V with Trial VI. We assessed forgetting over time by comparing Trial V with Trial VII. Descriptive statistics only (means and standard errors) were calculated for the accuracy and reaction time for correctly categorized words in the Recognition phase.

Peak component amplitudes from the sites F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 were each assessed with three-way MANOVAs with factors Lateral (left/midline/right), Sagittal (frontal/central/parietal) and Type (for the recall phase: Remembered, Not Remembered; for the recognition phase: List A, List B, New). Contrasts on the Sagittal factor compared activity at frontal sites with that at parietal sites, and their average with activity at central sites. Contrasts on the Lateral factor compared activity at left hemisphere sites with that at right hemisphere sites, and their average with activity at midline sites. Such contrasts are optimal for efficiently deriving maximal information about component topography. For the recognition phase, planned contrasts on the Type factor for N415 (indexing familiarity) compared activity for List A vs. List B words (highly familiar words vs. less so), and their mean (words which had been presented before) vs. New (not seen before). For the P640 (indexing recognition), we compared List A words with the mean of List B and New words (indicating correct source recollection of the word as being List A vs. Other), and compared List B

with New words (although this is necessarily confounded with familiarity). These analyses are important for characterizing the topographic distribution of the component, and differences in amplitude and topography between different trial types.

As the contrasts were planned and there were no more of them than the degrees of freedom for effect, no Bonferroni-type adjustment to alpha was necessary (Tabachnick and Fidell, 2001). Because this is a first step in examining ERPs in the RAVLT, with a small sample size and low power, but with an aim to report potential discoveries to spur future research, we report any effect with $p < 0.100$.

RESULTS AND DISCUSSION

Demographics

Participants' mean age was 17.2 years (SD = 0.7 years), and standardized scores on the WTAR were in the normal range (mean 102.7, SD = 16.5). Five participants were left-handed.

Behavioral Performance

Figure 1 shows the mean number of words recalled by participants for each trial. There were highly significant increases in the number of words remembered over Trials I-V (linear trend $F = 312.74$, $p < 0.001$; quadratic trend $F = 17.64$, $p < 0.001$; for all effects reported in this section $df = 1.32$), indicating learning of words over trials. On average, participants remembered fewer words for Trial B than for Trial I ($F = 4.77$, $p = 0.036$), indicating proactive interference. Participants remembered significantly fewer words for Trial VI compared to Trial V ($F = 9.91$, $p = 0.004$), indicating retroactive interference. Participants remembered significantly fewer words for Trial VII than for Trial V ($F = 20.64$, $p < 0.001$), indicating forgetting after a delay of 20 min. Categorisation of List A, List B and New words was generally accurate (List A: mean = 13.5, SD = 2.3; List B: mean = 14.0, SD = 1.3; New: mean = 18.3, SD = 1.9). RT for correct categorisations was similar across trial types (List A: mean = 885.6 ms, SD = 309.4 ms; List B: mean = 879.9 ms, SD = 205.0 ms; New: mean = 932.4 ms, SD = 231.5 ms).

Despite our modifications to the RAVLT required for recording and analyzing ERPs, we observed the within-subject effects typically seen in the standard version—that is, learning over trials, proactive and retroactive interference, and forgetting after a delay. The slightly poorer performance of our group relative to published norms (e.g., Carstairs et al., 2012) may be a consequence of our decision to use the visual rather than auditory modality for stimulus presentation, since free recall is typically better for words presented verbally than in print (e.g., Murdock and Walker, 1969), at least for Trial I (van der Elst et al., 2005), as well as the lack of opportunity to revisit words in the recognition phase.

Recall ERPs

Figure 2 (left) shows the grand mean waveforms for ERPs in the Recall phase for Remembered and Not Remembered words. The PCA-identified P175 was larger at frontal than parietal sites ($F = 18.17$, $p < 0.001$; all $df = 1.32$), and had a tendency to larger amplitudes at central than frontal/parietal sites ($F = 3.95$, $p = 0.056$; see **Figure 3** for topographic plots of activity across sites). It was also larger in the midline than hemispheres ($F = 37.50$, $p < 0.001$). At frontal sites, the midline > hemispheres effect was reduced compared to the effect at parietal sites ($F = 13.95$, $p = 0.001$), while at central sites a left > right effect was observed, which was reversed and reduced at frontal/parietal sites ($F = 9.03$, $p = 0.005$).

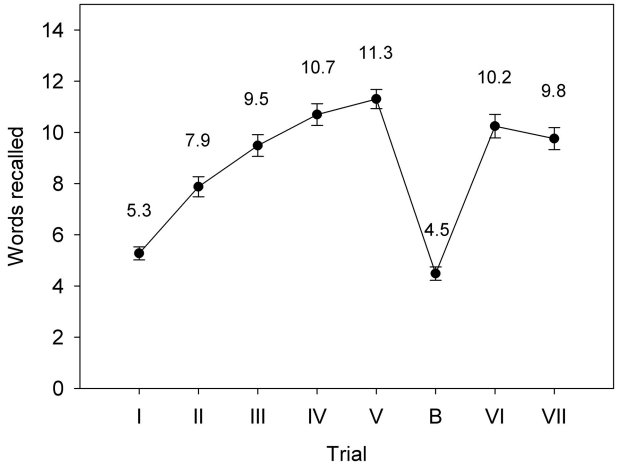

FIGURE 1 | Mean RAVLT performance in the Recall phase for the adolescent males (Study 1). Error bars represent the standard error of the mean.

There was a Type main effect ($F = 12.37$, $p = 0.001$), with larger amplitudes for Remembered than Not Remembered words, particularly at central compared to frontal/parietal sites ($F = 2.99$, $p = 0.093$). Remembered words showed a small left > right effect at frontal sites, and a larger right > left effect at parietal sites, while Not Remembered words showed a small right > left effect frontally, and a larger left > right effect at parietal sites ($F = 4.68$, $p = 0.038$). Further, the midline > hemispheres effect was equal in magnitude for Remembered and Not Remembered words at frontal sites, but was larger for Remembered than Not Remembered words at parietal sites ($F = 5.60$, $p = 0.024$).

For completeness, the analyses of the P210 and P260 components (neither of which showed significant Remembered > Not Remembered effects) are included in Supplementary Material, as well as analyses of the later N440 and P630 components identified by the PCA of the Recall ERPs.

Recognition ERPs

Figure 2 (right) shows the grand mean waveforms for ERPs in the Recognition phase for List A, List B and New words. Despite relatively few trials being included in each participant's average, the grand mean ERPs nonetheless present component morphology in line with expectations. Again, a clear N1-P2 complex can be seen, followed by a frontal negativity peaking around 400 ms and appearing similar in amplitude for List B and New words, followed by a larger parietal late positivity peaking around 550 ms, largest for List A words.

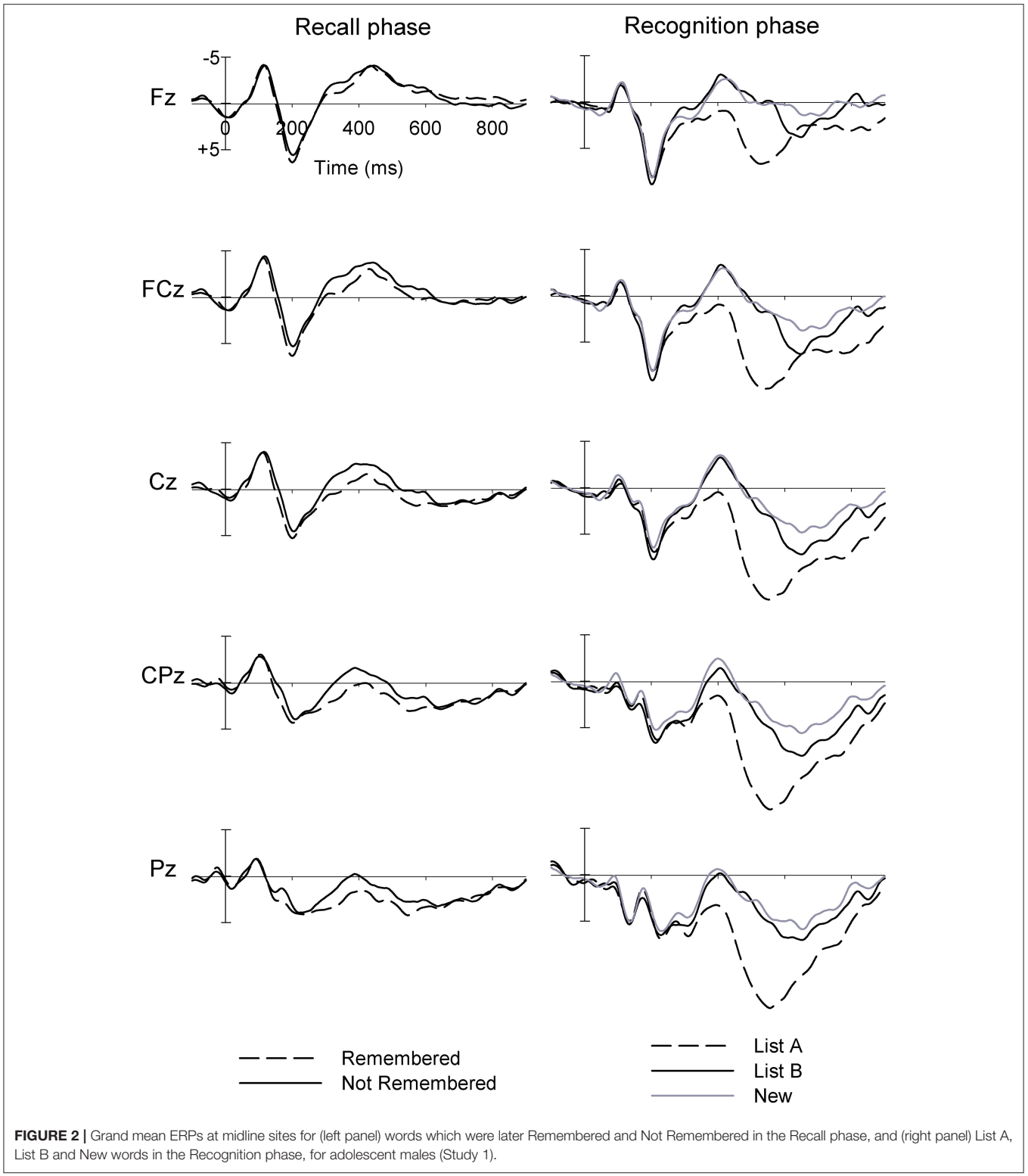

FIGURE 2 | Grand mean ERPs at midline sites for (left panel) words which were later Remembered and Not Remembered in the Recall phase, and (right panel) List A, List B and New words in the Recognition phase, for adolescent males (Study 1).

N415

Topographic plots of N415 activity are presented in **Figure 3**. The N415 was more negative at central than frontal/parietal sites ($F = 57.77$, $p < 0.001$; $df = 1, 31$ for this and P640 topographic analyses), and more negative in the right than left hemisphere ($F = 5.59$, $p = 0.025$). For New words vs. previously seen words, the N415 tended to be more negative for New than List A/B words ($F = 3.34$, $p = 0.077$). New words were associated with a

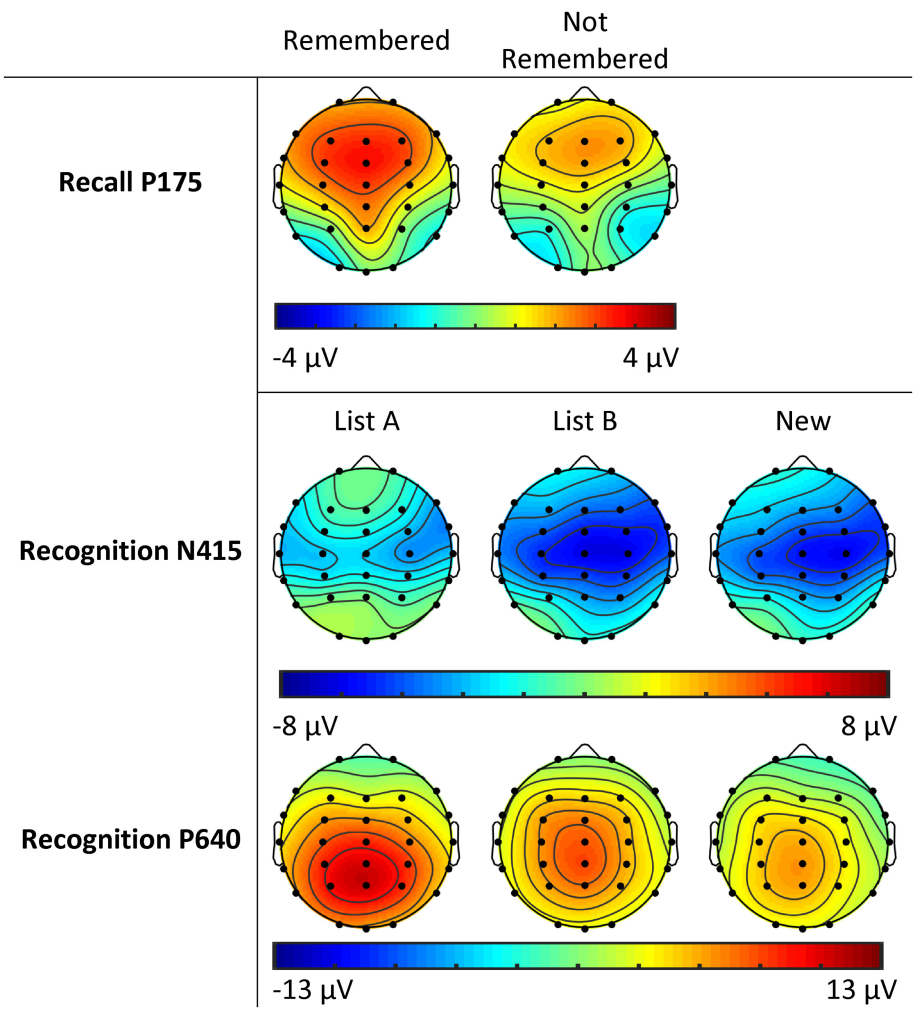

FIGURE 3 | Topographic plots of activity across sites and conditions for P175 in the Recall phase, and N415 and P640 in the Recognition phase for adolescent males (Study 1).

midline > hemispheres effect, while the opposite was observed for previously seen words ($F = 5.98$, $p = 0.020$). Comparing between previously seen words, List B words showed greater negativity than List A words ($F = 14.58$, $p = 0.001$). List A words showed reduced midline amplitude relative to the hemispheres, while List B words showed greater midline than hemispheric amplitude ($F = 29.05$, $p < 0.001$). List A words showed a slightly larger right > left effect at central compared to frontal/parietal sites, while List B words showed a reduced effect at central relative to frontal/parietal sites ($F = 4.35$, $p = 0.045$).

P640

The P640 was more positive at parietal than frontal sites ($F = 33.00$, $p < 0.001$) and at central than frontal/parietal sites ($F = 20.23$, $p < 0.001$; see **Figure 3**). Positivity was greater on the left than right ($F = 5.51$, $p = 0.025$), and greater still at midline sites ($F = 16.54$, $p < 0.001$). The midline > hemispheres effect was greater at parietal than frontal sites ($F = 29.25$, $p < 0.001$), and greater still at central sites ($F = 24.74$, $p < 0.001$).

In comparisons of List A with Other (List B and New) words, a type main effect was apparent ($F = 6.82$, $p = 0.014$), with greater positivity for List A words. This was particularly the case at parietal compared to frontal sites ($F = 48.08$, $p < 0.001$). Additionally, List A words displayed a midline > hemispheres effect parietally, and a much smaller, and reversed effect frontally, while Other words were associated with midline > hemispheres effect at both frontal and parietal sites ($F = 15.80$, $p < 0.001$).

In comparisons of List B with New words, greater positivity was observed for List B words ($F = 11.90$, $p = 0.002$). The topography of this differed: List B words were associated with a somewhat smaller parietal > frontal gradient than New words ($F = 3.65$, $p = 0.066$). The left > right effect was somewhat stronger for New than List B words ($F = 3.16$, $p = 0.085$).

On the whole, we observed the ERP components that we expected based on research using other memory tasks, with typical topographies and differences in amplitude according to trial type (words which were Remembered vs. Not Remembered, in the Recall phase, and for List A, List B and New words in

the Recognition phase). This suggests that PCA can be used to identify ERP components during the RAVLT; our study is the first to attempt this with healthy control participants, let alone substance-using groups (see Supplementary Materials). The P175 showed a Remembered > Not Remembered main effect, with a frontal maximum as expected (e.g., Mangels et al., 2001). Similarly, N415 and P640 in the recognition phase showed the expected frontocentral and centroparietal maxima, respectively. N415 was larger for New than familiar (List A and List B) words, and larger for List B than List A words, consistent with a component reflecting (un)familiarity (e.g., Rugg et al., 1998; Curran, 2000), while P640 was largest for List A words, consistent with correct recollection of the source of the word (Rugg et al., 1998; Curran, 2000), and larger for List B than New words (although the latter effect is of course confounded with familiarity). In summary, this pilot study provides proof of concept that meaningful ERP components associated with recall and recognition can be extracted using PCA techniques in a modified version of the RAVLT, and that these behave in a manner predictable from other research.

However, in this pilot study with appropriately small sample sizes, we were underpowered to detect group differences associated with alcohol and/or cannabis use (reported in Supplementary Materials), particularly since we recruited relatively light drinkers and cannabis users, compared to our previous studies of heavier users where greater deficits might be expected (e.g., Solowij et al., 2011). In the second study, we report the results of a separately conducted examination of a larger sample of young adults. For this study, we collected more detailed information about use of alcohol, cannabis, and other drugs, with eligibility criteria requiring slightly heavier use, larger samples including both male and female participants, and recorded EEG from a denser scalp montage to increase the information available for PCA.

STUDY 2

METHODS

Participants

Participants were 104 young adults (aged between 18 years and 21 years 11 months), who were recruited into three groups based on their reported use of alcohol and cannabis. The "Cannabis Users" (CU) group (9 females, 11 males) used cannabis regularly (at least twice a month in the past year). The "Heavy Drinkers" (HD) group (16 females, 23 males) engaged in heavy drinking (four or more Australian standard drinks, equal to 40 g alcohol, on one occasion) regularly (at least monthly in the past year), but used cannabis less than twice a month over the past year (including irregular/occasional use, and never having used cannabis). Lastly, the "Drug-Naive Controls" (DNC) group (20 females, 25 males) neither used cannabis regularly (less than twice a month over the past year, including never) nor engaged in heavy drinking regularly (less often than once a month over the past year, including irregular heavy drinkers, those who never engaged in heavy drinking, and those who did not drink any alcohol).

Participants were recruited via posters displayed on the university campus and via participant referral, and were excluded if they had ever had an epileptic seizure, a serious head injury or period of unconsciousness, uncorrected hearing or vision problems, or regular (at least twice a month) use of other drugs. Additionally, participants reported no use of medication other than contraception or antibiotics. Participants were screened for a history of psychiatric illness: 3 participants in each group (2 female DNC, 2 female HD and 3 female CU) reported depression and/or anxiety; all other participants reported no personal history of psychiatric illness. We did not assess or screen for a family history of psychiatric illness, including substance abuse. All participants gave written informed consent, and the protocol was approved by the University of New South Wales Human Research Ethics Committee before data collection began in an EEG laboratory at the University of New South Wales. Our sample represented the Australian population, in which over half of those aged 18-21 years regularly drink heavily (that is, consume more than four standard drinks, equivalent to 40 g alcohol, at least once a month; AIHW, 2011), while approximately 10% of 18–29 year olds use cannabis at least once a month (AIHW, 2011).

Procedures

The experimenter showed the participant the lab and recording equipment and described the experimental protocol before written informed consent was obtained. Participants then completed a short demographics questionnaire and modified versions of the Alcohol Use Disorders Identification Test (AUDIT, Saunders et al., 1993) and the Drug Use Disorders Identification Test-Extended (DUDIT-E, Berman et al., 2007). Question 3 of the AUDIT was modified from "How often do you have six or more standard drinks on one occasion?" to "four or more standard drinks" to reflect Australian alcohol consumption guidelines (NHMRC, 2009). Participants were requested to reference a standard drinks guide provided while they completed this section. Only the first section of the DUDIT-E was administered, and was used to screen participants for eligibility to the study. That section assesses the frequency of use of a range of drug classes other than alcohol, with the options: Never (score = 0), Tried it once or more (1), Once a month or less often (2), 2–4 times a month (3), 2–3 times a week (4), 4 times a week or more (5). Twenty-nine DNC and 12 HD participants had a total score of zero (CU by definition scored at least 3), and no participant in this study scored more than 2 for any drug class (except tobacco and cannabis; this was an exclusion criterion of the study). Use of tobacco does not contribute to the total score. **Table 1** shows the demographic characteristics of the participants included in the study.

All participants also underwent structured interviews assessing lifetime alcohol use and lifetime cannabis use using a modified version of the Lifetime Drinking History interview (Skinner, 1977). This assesses the frequency and quantity of alcohol consumption in relatively homogenous phases from the age of onset of regular drinking (one standard drink per month), and can be used to assess the number of standard drinks consumed in the participant's lifetime [because these scores are

TABLE 1 | Demographic information for males and females in each group in the sample of young adults (Study 2).

	Drug-Naive Controls (DNC)				Heavy drinkers (HD)				Cannabis users (CU)			
	Females ($n = 20$)		Males ($n = 25$)		Females ($n = 16$)		Males ($n = 23$)		Females ($n = 9$)		Males ($n = 11$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	19.9	1.2	20.0	1.1	20.0	1.2	19.7	1.2	20.1	1.2	20.5	1.2
% Daily smokers	0.0		0.0		0.0		13.0		11.1		27.3	
% Right handed	90.0		100.0		81.3		78.3		77.8		90.9	
AUDIT score#	3.1	2.9	2.9	3.0	9.5	3.3	9.1	2.6	9.3	4.6	11.4	4.6
Lifetime standard drinks (log units)†	1.4	1.2	1.5	0.9	2.7	0.5	2.6	0.4	2.8	0.5	3.0	0.4
Lifetime standard drinks (mean and CI)†	25.2	(7.8–81.4)	31.6	(14.2–70.0)	470.4	(254.4–869.8)	391.0	(267.6–571.3)	624.6	(314.4–1240.8)	1, 029.2	(581.9–1,820.1)
Age of onset of regular drinking	18.5	1.6	18.0	1.7	17.5	1.6	17.3	1.3	16.3	1.2	16.6	1.0
Duration of regular drinking	1.4	1.5	2.0	1.7	2.5	1.6	2.4	1.4	3.8	1.7	3.9	1.1
DUDIT-E score	0.7	1.3	0.6	0.8	1.4	1.5	2.2	2.1	6.7	2.0	7.5	3.8
DUDIT-E range	0–4		0–2		0–4		0–9		3–9		3–15	
Age first regular cannabis use*									17.0	1.2	17.4	1.2
Duration regular cannabis use, years*									2.1	1.5	2.6	1.1
Frequency of cannabis use (days/month), last 6 months, median and range*									4.2	(1.8–18.2)	12.9	(2.0–30.0)

#*AUDIT scores are useful only for internal comparison between groups, due to the alteration to Question 3 as described in the text.*

†*Due to non-normal distributions, lifetime standard drinks were converted to log scores prior to statistical analysis; the mean and SD reported are in log units, while the numbers in brackets below give the inverse log of the mean, and the confidence interval calculated for that mean, in units of standard drinks.*

**n = 7 females, 10 males; data were not recorded for the first three cannabis user participants.*

non-normally distributed, statistical analysis is performed on the log (base 10) of total consumption+1, to avoid taking the log of zero]. Participants referred to the standard drinks guide during the alcohol section of the interview. For participants who had never consumed one standard drink per month, the age of onset was entered as the participant's age on the day of testing, and the duration (years) of regular drinking was entered as zero. The cannabis section was used to calculate the age of first regular use, the duration of regular use, and frequency of use in the 6 months prior to testing for the cannabis user group.

EEG Recording and Analysis

The RAVLT task was completed and scored as described for Study 1. Continuous monopolar EEG was recorded from 60 scalp sites using an elasticised cap with tin electrodes. Additional tin cup electrodes recorded activity from the left and right mastoid as well as vertical and horizontal EOG. All electrodes were referenced to an electrode on the tip of the nose, grounded midway between FPz and Fz. Electrode impedances were below 5 kΩ. Signals were recorded DC to 200 Hz, amplified 10 times, and sampled at 1,000 Hz using NeuroScan recording software and hardware (Synamps 2). EEG data was re-referenced offline to linked mastoids before filtering, eye movement correction, interpolating, epoching, baselining, artifact rejection and averaging proceeded as described for Study 1. One female HD participant had exceptionally noisy mastoid channels in both the recall and recognition EEG files, and her data were excluded from all ERP analyses (but included in behavioral measures). The EEG file for the recognition phase was lost for one male HD; however, his behavioral performance for that phase could be retrieved from the Presentation log file. The grand mean waveforms for the Recall and Recognition phases of the experiment are displayed in **Figure 4**.

Data Reduction

PCA for the ERP data proceeded as described in Study 1. The PCA on Remembered and Not Remembered trials had 12,360 cases (103 participants × 2 conditions × 60 sites), and factor extraction and rotation was restricted to 16 factors on the basis of Horn's Parallel Test (Horn, 1965), together accounting for 93.73% of variance. Two positive factors were identified in the P2 time range. Only one of these, labeled P185 (Factor 5 peaking at 185 ms, maximal at FC1, explaining 6.29% of unique variance) displayed a Remembered > Not Remembered effect. Analyses of the other P2-like factor (Factor 4), as well as factors peaking at 380 ms (Factor 2) and 535 ms (Factor 1) are described in Supplementary Material.

The PCA on List A, List B and New words had 18,360 cases (102 participants × 3 conditions × 60 sites); factor extraction and rotation was restricted to 14 factors, together explaining 93.46% of variance. Factor 1 was labeled P540 (peaking at 540 ms, maximal at P1, explaining 25.08% of variance), and was identified as reflecting the classical parietal Old/New effect, while Factor 3, labeled N340 (peaking at 340 ms, maximal at Cz, explaining 19.53% of variance) was identified as reflecting the frontocentral N400 effect.

Statistical Analysis

Statistical analysis for demographic and behavioral measures proceeded as described for Study 1 except with the additional factors Sex and Group being included in MANOVAs for behavioral measures. We included sex as a factor in our analyses because women tend to outperform men on verbal memory tasks (e.g., Andreano and Cahill, 2009; Carstairs et al., 2012), because there is growing evidence that males and females may be differently susceptible to the long-term cognitive effects of chronic alcohol and cannabis misuse (e.g., Pope and Yurgelun-Todd, 1996; Townshend and Duka, 2005; Crane et al., 2013), and because the inclusion of women in the young adult but not adolescent sample may contribute to differences between the study results. Contrasts on the Group factor (for this and all other analyses) separately compared the performance of DNC with HD, and HD with CU. These group comparisons were selected because alcohol consumption by the CU group was similar to that in the HD group (see results). Thus the DNC vs. HD comparison assesses the effect of heavy drinking, while the CU vs. HD comparison assesses the effect of cannabis use while controlling for heavy drinking; although we allow that there could be interactive effects of alcohol and cannabis, examination of these is beyond the scope of this study.

A two-step approach was taken with analyses of ERP data, to accurately describe the topography of the PCA-identified components, and to assess the important Group and Sex main effects and interactions. First, as in Study 1, peak component amplitudes from the sites F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 were each assessed with three-way MANOVAs with factors Lateral (left/midline/right), Sagittal (frontal/central/parietal) and Type (for the recall phase: Remembered, Not Remembered; for the recognition phase: List A, List B, New), with contrasts as described above.

In the second step, the average activity was calculated from a number of sites identified via the above step as the regions of maximum amplitude, and these single variables (one for each component) were entered into separate Type × Group × Sex MANOVAs. Contrasts on the Group and Type factors were as mentioned above. An alpha level of 0.05 was adopted throughout Study 2, although we report limited effects approaching significance where they indicate the possibility of group differences, and also report effect sizes (Cohen's *d*) where appropriate. In all cases, a negative effect size represents poorer performance in the HD than DNC group, or in the CU than HD group.

RESULTS AND DISCUSSION

Demographics

The groups were well matched for age, with no significant effects of group or sex (all $p > 0.175$; for this section $df = 1.98$ unless otherwise reported). Within each group, the proportion of right-handed participants was not significantly different between males and females (all $p > 0.106$). Within each group, the proportion of daily tobacco use was equal between males and females (all $p > 0.133$). Greater AUDIT scores were observed for HD relative to DNC ($F = 74.36$, $p < 0.001$), but were equal for HD relative to CU

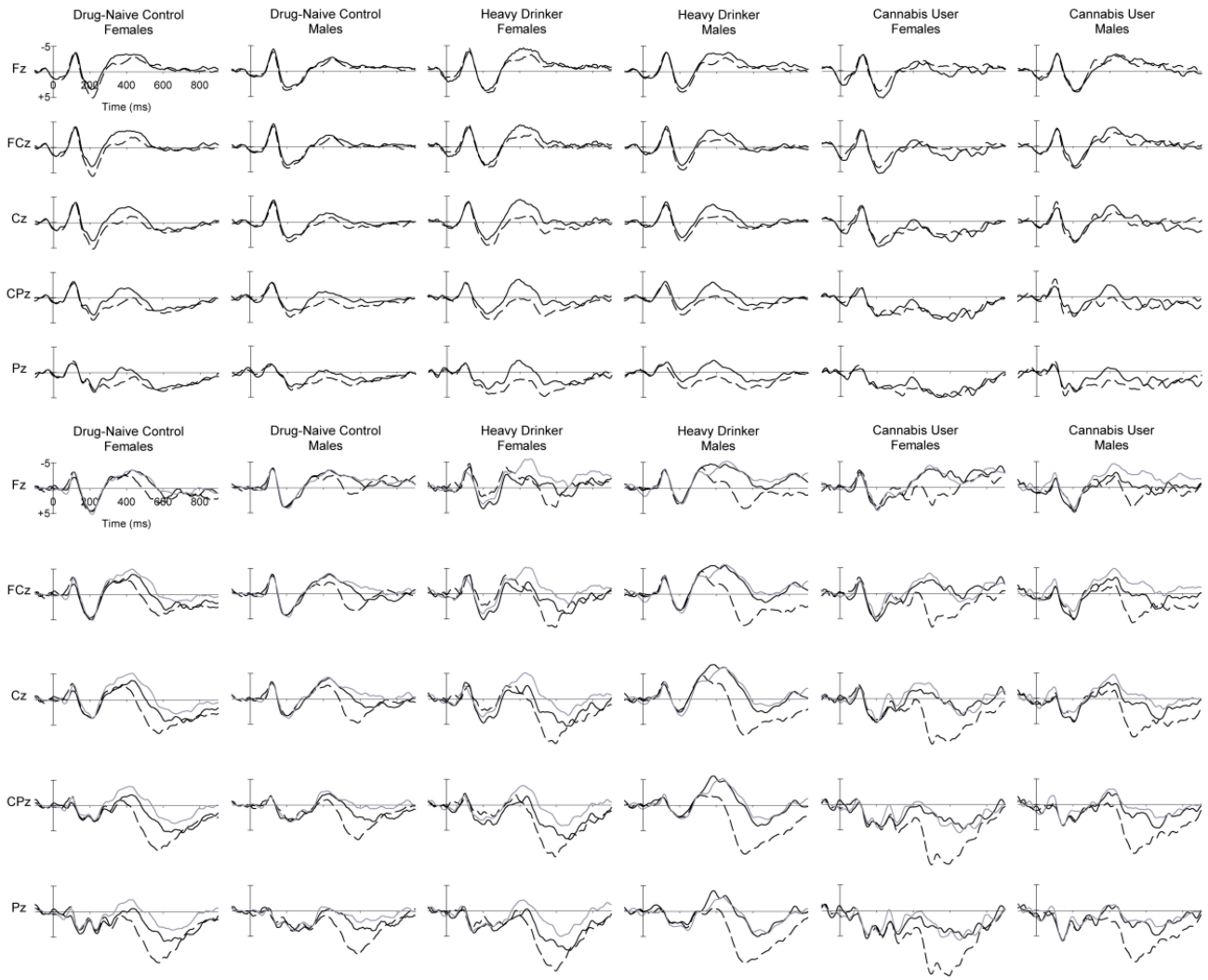

FIGURE 4 | Grand mean ERPs at midline sites for (top panel) words which were later Remembered (dashed) and Not Remembered (solid) words in the Recall phase, and (bottom panel) List A (dashed), List B (black solid) and New (gray solid) words in the Recognition phase, for female and male young adults (Study 2) in the DNC, HD and CU groups.

($F = 1.33$, $p = 0.251$), with no main effects or interactions with sex (all $p > 0.184$). (Log) lifetime drinks were significantly greater for HD relative to DNC ($F = 50.08$, $p < 0.001$), but were equal for CU relative to HD ($F = 1.68$, $p = 0.197$), with no main effects or interactions with sex (all $p > 0.480$). Age of onset of regular drinking was significantly younger for HD relative to DNC ($F = 7.17$, $p = 0.009$), and younger still for CU relative to HD ($F = 5.41$, $p = 0.022$), with no main effects or interactions with sex (all $p > 0.599$). Consistent with this, the duration of regular drinking was longer for HD relative to DNC ($F = 4.77$, $p = 0.031$), and for CU relative to HD ($F = 10.94$, $p = 0.001$), with no sex main effects or interactions (all $p > 0.287$). DUDIT scores were significantly greater for the HD compared to DNC group ($F = 7.89$, $p = 0.006$) and for the CU compared to HD group ($F = 102.06$, $p < 0.001$), with no sex main effects or interactions (all $p > 0.219$). The increase for the HD relative to DNC group was mainly due to a greater incidence of experimentation with cannabis; when cannabis use frequency was excluded from the total score, HD scores were not significantly different to DNC ($F = 2.81$, $p = 0.097$). The increase for the CU relative to HD group was due mostly to the increased cannabis use score but also partly due to a greater incidence of experimentation with other drugs; when cannabis use frequency was excluded from the total score, CU still scored significantly higher than HD ($F = 29.91$, $p < 0.001$). For the CU group, there were no sex differences for age of first regular use [$F_{(1, 15)} = 0.28$, $p = 0.606$], duration of regular use [$F_{(1, 15)} = 0.60$, $p = 0.451$], or frequency of use in the past 6 months ($p = 0.193$). Seven of the female CU and 10 of the male CU engaged in heavy drinking at least monthly ($\chi^2 = 3.65$, $p = 0.301$).

In summary, we recruited samples of young adults which were generally comparable, but differed as expected on the substance use measures. However, while it was our intention to match the

CU and HD groups for alcohol use, in order to examine the effect of cannabis use after controlling for alcohol use, we note that the CU group showed an earlier onset and longer duration of regular alcohol use, despite similar consumption overall. Therefore, it is possible that this early alcohol exposure, rather than cannabis use *per se*, may be responsible for any group differences observed between CU and HD groups. Furthermore, since we used an Australian definition of binge drinking (consumption of 40 g of alcohol on one occasion; NHMRC, 2009), the ability to compare our sample with others using different definitions of binge/heavy drinking (e.g., NIAAA, 2004) is somewhat limited. However, we point out that there was considerable variation above the minimum quantity/frequency criterion for entry to the study, and that it seems likely that similar outcomes would be observed however the groups were constructed, as in the literature concerning inhibitory control among heavy drinkers reviewed in Smith et al. (2014). Lastly, we did not assess or control for the presence of a family history of psychiatric illness, including substance abuse; this is an important predictor of cognitive dysfunction (e.g., Acheson et al., 2009, 2014), and should be screened for in future research.

Behavioral Performance

Table 2 shows performance measures for each group and sex; for the analyses reported here $df = 1.98$. Across groups, there were highly significant increases in the number of words remembered over Trials I-V (linear trend $F = 1096.83$, $p < 0.001$; quadratic trend $F = 158.70$, $p < 0.001$), indicating learning across trials.

TABLE 2 | Behavioural performance for males and females in the Drug-Naïve Controls (DNC), Heavy Drinker (HD) and Cannabis User (CU) groups in the sample of young adults (Study 2).

	DNC				HD				CU			
	Females ($n = 20$)		Males ($n = 25$)		Females ($n = 16$)		Males ($n = 23$)		Females ($n = 9$)		Males ($n = 11$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
RECALL PHASE PERFORMANCE												
Trial I	7.1	1.5	6.4	1.7	6.4	1.5	6.6	1.6	7.2	1.7	7.4	2.5
Trial II	10.7	1.8	10.1	1.5	10.0	2.0	9.6	1.9	9.9	2.1	10.2	3.0
Trial III	12.0	1.9	11.6	1.4	12.1	1.7	11.0	2.0	12.1	1.5	12.0	2.6
Trial IV	13.0	1.4	12.5	1.2	13.3	1.7	11.7	1.9	12.1	1.2	12.2	2.0
Trial V	13.2	1.3	12.8	1.5	13.6	1.2	12.8	1.9	12.9	1.1	13.5	1.0
Trial B	6.0	1.5	6.2	1.6	6.5	1.9	5.6	1.8	6.7	2.0	5.7	2.1
Trial VI	12.4	1.7	11.7	2.1	12.3	2.3	11.2	2.1	11.8	2.0	12.2	2.6
Trial VII	12.5	2.0	11.9	1.5	12.1	2.4	10.1	2.6	11.9	1.5	11.5	3.0
Total words recalled (Trials I-V)	55.8	5.7	53.5	5.2	55.3	6.0	51.8	7.6	54.2	6.4	55.2	10.3
Learning rate (V minus I)	6.1	1.7	6.4	1.9	7.1	1.3	6.3	2.0	5.7	1.2	6.1	1.8
Proactive interference (I minus B)	1.1	1.6	0.2	2.0	−0.1	2.4	1.0	1.8	0.6	2.1	1.6	2.1
Retroactive interference (V minus VI)	0.8	1.6	1.1	1.6	1.3	1.7	1.7	1.5	1.1	1.4	1.3	1.9
Forgetting (V minus VII)	0.7	2.2	0.9	1.4	1.5	1.9	2.7	1.8	1.0	1.2	1.9	2.2
RECOGNITION PHASE PERFORMANCE												
List A accuracy (number correct/15)	14.3	1.0	14.1	1.2	13.8	1.8	14.2	1.2	14.0	1.3	14.2	1.1
List B accuracy (number correct/15)	14.2	1.1	14.2	1.0	14.4	1.0	14.2	1.3	13.8	1.2	13.8	1.2
New accuracy (number correct/20)	18.9	1.1	18.9	1.3	19.3	0.7	18.8	1.4	19.0	1.0	18.5	1.9
List A RT (ms)	891.3	222.3	948.5	243.2	811.4	207.7	907.1	271.5	923.9	338.1	869.9	237.8
List B RT (ms)	802.7	153.2	939.1	281.3	824.7	293.1	912.0	218.7	937.6	325.7	890.2	204.8
New RT (ms)	864.3	232.9	977.2	250.9	792.5	178.1	973.6	227.4	883.0	284.2	915.2	283.5
PEAK COMPONENT AMPLITUDES												
Remembered P185†	4.1	3.0	3.4	2.3	2.5	2.0	3.2	2.4	2.7	1.6	3.3	2.2
Not Remembered P185†	3.2	3.4	2.7	2.5	2.4	1.4	2.6	2.7	2.8	2.4	2.5	3.1
List A N340†*	−5.7	4.7	−3.7	4.5	−5.9	6.2	−6.7	4.9	−1.2	7.1	−4.5	4.4
List B N340†*	−5.1	4.8	−3.5	4.3	−3.9	6.5	−6.9	4.4	−0.4	9.2	−3.8	4.2
New N340†*	−5.6	3.8	−2.6	3.5	−5.0	6.0	−4.9	3.7	−1.3	6.0	−4.0	3.2
List A P540†*	9.5	3.9	7.2	3.8	11.0	5.7	10.0	4.5	11.9	5.0	8.0	4.0
List B P540†*	4.1	2.7	1.5	4.4	5.6	4.3	3.4	4.4	3.2	4.4	2.4	3.2
New P540†*	2.7	3.3	0.9	2.9	3.5	2.8	2.3	3.0	4.3	3.0	1.5	1.8

†*N = 15 for female HD*
**N = 22 for male HD*

There was a non-significant trend to a greater linear increase over Trials I-V for the HD compared to the CU group ($F = 3.44$, $p = 0.067$). Further, a Group × Sex × Trial interaction approached significance ($F = 3.7$, $p = 0.056$, linear trend), such that male DNC and HD had similar learning over trials, while female HD actually had greater learning over trials than female DNC.

Participants remembered fewer words for Trial B than for Trial I ($F = 12.48$, $p = 0.001$), indicating proactive interference. Furthermore, a Group × Sex × Trial effect reached significance ($F = 4.55$, $p = 0.035$), such that for females, proactive interference was greater for DNC than HD ($d = 0.548$), but the opposite was true for males ($d = -0.402$). There were no significant differences between HD and CU groups (all $p > 0.236$, effect size across sexes $d = -0.277$). Participants also remembered significantly fewer words for Trial VI compared to Trial V ($F = 51.30$, $p < 0.001$), indicating retroactive interference. There were no main effects or interactions involving group or sex for retroactive interference (all $p > 0.125$).

Participants remembered significantly fewer words for Trial VII than for Trial V ($F = 58.54$, $p < 0.001$), indicating forgetting after a 20 min delay. Greater forgetting was apparent in HD compared to DNC ($F = 10.61$, $p = 0.002$, $d = -0.766$), and in males compared to females ($F = 4.27$, $p = 0.041$, $d = 0.404$). Forgetting was equivalent for HD and CU ($p > 0.190$, $d = 0.388$).

Regarding recognition performance, there were no significant differences between sexes or groups for accuracy to List A (all $p > 0.293$), List B (all $p > 0.093$) and New words (all $p > 0.228$). There was a significant sex difference in the RT to List A vs. New words ($F = 3.94$, $p = 0.050$), such that females were faster to respond to New than List A words, while males were slower to New than List A words. There were no interactions involving group.

Thus, it appears the performance of our sample is relatively normal and demonstrates the expected changes over trials, although, similar to Study 1, performance is slightly poorer than published norms (e.g., Carstairs et al., 2012). Overall, females did slightly (but non-significantly) better than males, consistent with previous reports of a slight verbal memory advantage for females (e.g., Andreano and Cahill, 2009; Carstairs et al., 2012). Further, there were tendencies for increased learning over trials in HD than CU, and in female HD than female DNC, although neither of these reached significance. However, the substantially greater forgetting after a 20 min delay in HD bears some discussion: HD lost an average of 2.2 words (1.5 for females and 2.7 for males). For comparison, females typically forget 1.0 word on average, while males forget 1.7 words (Carstairs et al., 2012); the increased forgetting is unlikely to be due to the modifications to RAVLT delivery in our study, since our DNC actually forgot fewer words than the normative samples (our female DNC = 0.7 words, male DNC = 0.9 words). Thus, our study highlights particular problems with forgetting/delayed recall in heavy drinkers, an effect which is reported sometimes (e.g., Waugh et al., 1989; Brown et al., 2000; Pitel et al., 2009) but not always (e.g., Kokavec and Crowe, 1999; Parada et al., 2011; Sanhueza et al., 2011; Solowij et al., 2011; Mota et al., 2013; Sneider et al., 2013; Winward et al., 2014).

The lack of significant deficits in CU is clearly in contrast to many previous studies which have reported significant memory deficits in cannabis users (e.g., Yücel et al., 2008; Solowij et al., 2011). We reference those two studies in particular because they utilized a similar approach as here, by controlling for alcohol use, which is itself associated with learning and memory deficits. Yücel et al. matched controls and cannabis users for alcohol use, while Solowij et al. recruited DNC, HD, and CU groups and reported all pairwise comparisons. It is unclear why we do not observe deficits associated with cannabis use (after controlling for alcohol use): it is not the case that, due to the smaller sample size of the current study, our statistical power was too low to detect cannabis-related deficits. Rather, the obvious deficit for CU relative to HD in Solowij et al. (e.g., total words recalled Cohen's $d = -0.748$) was absent in our study, with slightly *more* words recalled for CU than HD ($d = 0.199$). A more likely explanation concerns dose-dependent and possibly age effects: our sample consists of considerably lighter cannabis users than Yücel et al., and though it is more similar to the sample in Solowij et al., in terms of recruitment criteria, alcohol use (AUDIT scores), and duration and age of onset of regular cannabis use, the Solowij et al. (2011) sample were somewhat younger than ours (mean 18 vs. 20 years), as well as being more frequent users and possibly heavier users per occasion. Thus, it is possible that dose-dependent and/or age effects might explain our lack of significant memory disruption in cannabis users.

Recall ERPs

Grand mean ERPs in the Recall phase of the experiment can be observed in **Figure 4** (top), while topographic maps of activity can be seen in **Figure 5**. Generally similar waveform morphology is observed, compared to the adolescents in **Figure 2**. Again, a clear N1-P2 complex is observed, with an appearance of larger P2 amplitudes for Remembered than Not Remembered words, followed by a frontocentral negative wave around 400 ms, appearing larger for Not Remembered words.

Statistical analyses confirmed these observations: the PCA-identified P185 showed a frontal > parietal effect ($F = 27.59$, $p < 0.001$), and also larger amplitudes centrally than at frontal/parietal sites ($F = 40.40$, $p < 0.001$, $df = 1.102$). It was also larger in the midline than hemispheres ($F = 35.87$, $p < 0.001$). At frontal sites, a left > right effect was observed, which was reversed at parietal sites ($F = 4.21$, $p = 0.043$). Further, the midline > hemispheres effect was reduced at frontal compared to parietal sites ($F = 8.81$, $p = 0.004$).

P185 was marginally larger for Remembered than Not Remembered words ($F = 3.88$, $p = 0.051$), particularly at frontal sites ($F = 5.32$, $p = 0.023$). The midline > hemispheres effect was also larger for Remembered words ($F = 4.57$, $p = 0.035$). Remembered words showed a larger reversal of the parietal to frontal laterality effect than Not Remembered words ($F = 5.45$, $p = 0.022$).

The average of sites F1, Fz, F2, FC1, FCz, and FC2 were entered into the second MANOVA; means and SDs are presented in **Table 2** for each condition and group. The Type main effect was now significant ($F = 5.43$, $p = 0.022$, $df = 1.97$), again with larger amplitudes for Remembered words. However, no other main effects or interactions were significant (magnitude

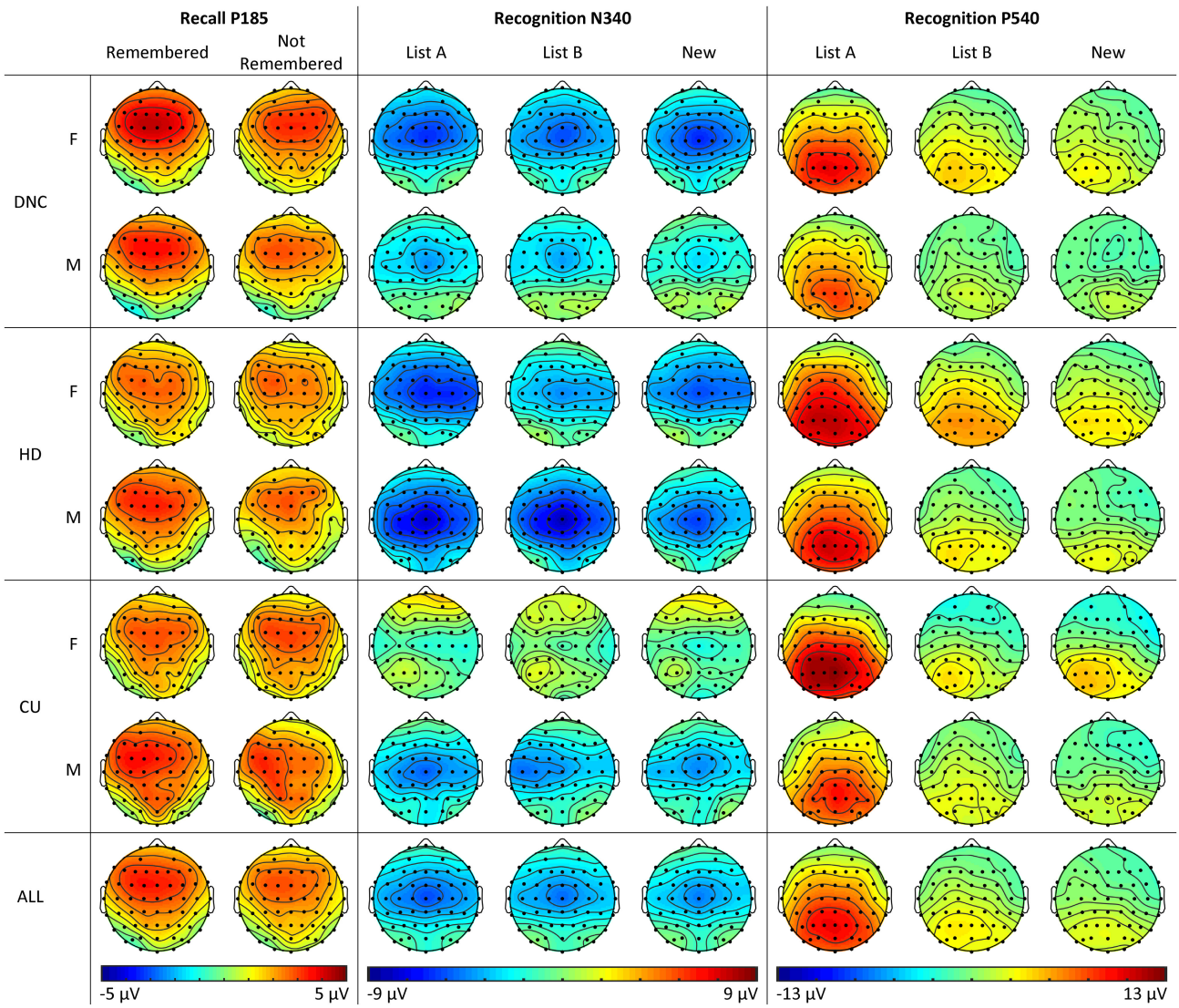

FIGURE 5 | Topographic plots of activity across sites, groups and conditions for P185 in the Recall phase, and N340 and P540 in the Recognition phase for female and male young adults (Study 2).

of Remembered > Not Remembered effect, difference between groups DNC vs. HD: $F = 1.19$, $p = 0.278$, $d = -0.216$; HD vs. CU: $F = 0.00$, $p = 0.990$, $d = -0.007$).

Recognition ERPs

Figure 4 (bottom) shows the grand mean waveforms for ERPs in the Recognition phase for List A, List B and New words for young adults. Again, the waveform morphology was similar to the adolescent group, and in line with expectations. A clear N1-P2 complex can be seen, followed by a frontal negativity peaking around 450 ms and appearing similar in amplitude for List B and New words for most groups, followed by a larger parietal late positivity peaking around 550 ms, largest for List A words. Statistical analyses of the PCA-identified N340 and P540 components are presented next.

N340

All topographic analyses for N340 and P540 have $df = 1.101$. N340 showed a frontal > parietal effect ($F = 13.14$, $p < 0.001$), and a central > frontal/parietal effect ($F = 252.30$, $p < 0.001$; see **Figure 5**). Amplitudes were more negative in the midline than hemispheres ($F = 53.03$, $p < 0.001$), particularly at central compared to frontal/parietal sites ($F = 34.25$, $p < 0.001$).

N340 was also more negative for words seen before (List A and List B) compared to New words ($F = 6.70$, $p = 0.011$). The midline > hemispheres effect was stronger for New than old words ($F = 4.98$, $p = 0.028$), particularly at parietal relative to frontal sites ($F = 8.74$, $p = 0.004$). For List A words, there was a small right > left effect frontally, but similar amplitudes parietally, while for List B words, there was a small left > right effect frontally, and a larger right > left effect parietally ($F = 5.18$, $p = 0.025$).

The average of sites FC1, FCz, FC2, C1, Cz, and C2 were entered into the second ANOVA, with $df = 1.96$ for both N340 and P540; means and SDs are presented in **Table 2** for each condition and group. There were no significant effects for List A vs. List B words. For New vs. old words, males showed larger amplitudes to old words while females showed larger amplitudes to new words ($F = 6.24$, $p = 0.014$). The N340 was smaller overall in CU relative to HD ($F = 5.60$, $p = 0.020$, $d = -0.586$).

P540

The P540 was more positive at parietal than frontal sites ($F = 143.39$, $p < 0.001$). Greater amplitudes were observed on the left than right ($F = 24.59$, $p < 0.001$) and in the midline compared to the hemispheres ($F = 19.79$, $p < 0.001$). This midline > hemispheres effect was stronger at parietal than frontal sites ($F = 17.23$, $p < 0.001$), and at central compared to frontal/parietal sites ($F = 5.56$, $p = 0.020$).

P540 was much larger for List A than Other words ($F = 268.97$, $p < 0.001$), particularly at parietal compared to frontal sites ($F = 52.27$, $p < 0.001$) and at central compared to frontal/parietal sites ($F = 17.20$, $p < 0.001$). Also, the midline > hemispheres was greater for List A than Other words ($F = 27.24$, $p < 0.001$). A slight left parietal dominance was observed for List A words, in line with previous research, although this did not reach significance ($F = 3.44$, $p = 0.067$): for List A words, the left > right effect was slightly greater at parietal than frontal sites, while for Other words, the effect was slightly greater frontally. The parietal > frontal × midline > hemispheres effect was greater for List A than Other words ($F = 6.31$, $p = 0.014$), as was the central > frontal/parietal × midline > hemispheres effect ($F = 5.52$, $p = 0.021$).

List B words were associated with greater positivity than New words ($F = 12.22$, $p = 0.001$), particularly at central sites relative to frontal/parietal ($F = 21.04$, $p < 0.001$). For List B words, a left > right effect was similar in magnitude frontally and parietally, while for New words, the left > right effect was much larger frontally ($F = 4.65$, $p = 0.033$).

The average activity from sites P3, P1, Pz, PO3, and POz were entered into the second MANOVA; means and SDs are presented in **Table 2**. A main effect of sex was significant ($F = 9.42$, $p = 0.003$), with larger P540 amplitudes in women than men, and amplitudes were also greater in HD relative to DNC ($F = 5.54$, $p = 0.021$, $d = 0.503$). P540 was substantially larger for List A vs. Other words ($F = 320.77$, $p < 0.001$), but no interactions with group or sex were significant. P540 was also larger for List B compared to New words ($F = 6.06$, $p = 0.016$). There was a tendency for a reduced List B > New effect for CU compared to HD, but this effect did not reach significance ($F = 3.44$, $p = 0.067$, $d = -0.432$). This effect did not differ between HD and DNC ($F = 0.73$, $p = 0.395$, $d = 0.173$).

Within-subject ERP results for the Recall P185 and the Recognition P540 were broadly in line with expectations for topographic and condition effects, and similar to Study 1. Additionally, the recognition N340 showed the expected frontocentral midline maximum. However, a sex difference was observed for the N340: males showed an unexpected increase in N340 amplitude to List A words, opposite to the females in this study, and reported in previous research (e.g., Rugg et al., 1998; Curran, 2000). Further, the effect is also different to the males in Study 1; it is possible that any of the differences between participants in Study 1 and 2 (e.g., age, location, education) might contribute to this result. Further research will be required to replicate and explain this observation.

The absence of group interactions for the Recall P2 suggests that this process is intact in HD and CU, although some differences were observed in the Recognition N340 and P540. For the N340, the increase in amplitude for male HD relative to DNC (not seen in females), and particularly the abnormal increase for List A and B words (see **Figure 5**), suggests some difficulties with familiarity-based recognition in this group. The HD also displayed a significant increase in P540 amplitude relative to DNC, possibly suggesting greater use of recollection-based recognition in this group.

Despite the lack of behavioral effects for CU relative to HD, we nonetheless observed some differences in their ERP components. The global reduction in N340 amplitude for CU relative to HD may be due to two factors: female CU appear to show an absence of this component (compare female CU with female HD and DNC in **Figure 5**), while male CU appear to show a normal amplitude in comparison with the abnormal increase in HD (again, compare male DNC, HD and CU in **Figure 5**). Lastly, although we note that the List B vs. New comparison for P540 is confounded with familiarity, the tendency for a smaller List B > New effect for this component in CU, relative to HD (who did not differ from DNC) suggests particular cannabis-related problems in the recollection component, independent of alcohol use. Further research will be required to confirm whether this as yet non-significant result can be replicated.

GENERAL DISCUSSION

A vast literature has investigated memory deficits using performance on the RAVLT in cannabis users and heavy drinkers. In two studies, we have extended the previous literature in reporting the first studies of event-related potentials in drug-naïve controls, let alone substance-using groups, and together with behavioral measures, examined the deficits associated with typical alcohol and/or cannabis use in young adults.

There are considerable differences between the samples collected, not only in age, but also in exposure to the drugs of interest, and location—relevant for both socioeconomic status and the recording settings in the individual laboratories, which necessitated some minor differences in early steps of ERP analysis. Despite this, we have confirmed some similarities in results between studies—notably, that while verbal memory performance in our modified RAVLT was slightly lower than published norms, the typical changes over trials remained, and demonstrably similar PCA components were extracted in each dataset. With the exception of the Recognition N340 in Study 2, these components displayed the expected topographies and condition effects. We thus have provided proof of concept that with a few modifications to the delivery of the task, the RAVLT, a widely-used, easy to administer, and normed test of learning

and memory, can be extended for use in psychophysiological contexts.

With regards to substance-related effects investigated in Study 2, both the ERP and behavioral measures suggest intact immediate recall processes (Trials I-VI), but problems in HD and CU groups concerning forgetting after a delay, and for ERP but not behavioral indices of (delayed) recognition memory. For the traditional behavioral measures (learning over Trials I-V, proactive and retroactive interference), we observed only non-significant trends for group effects (sometimes interacting with sex) in Study 2; in addition we observed no differences and small effect sizes for Recall P185 amplitudes between groups. In contrast, HD displayed significantly increased forgetting after a delay, and significantly increased amplitude of the recollection-based component (P540) despite intact recognition performance. CU displayed significantly reduced amplitude of the familiarity-based N340 component overall, and a non-significant tendency for reduced amplitude of the recollection-based P540 to List B words, also despite intact recognition performance. Thus, measurement of ERPs has added value to the study of memory processes in the RAVLT, being more sensitive than performance measures to alcohol-related impairments in recognition processes (specifically, recollection), and showing that cannabis use is associated with impairments in both recollection and familiarity-based recognition processes, again despite no statistically significant deficit on behavioral measures. The lack of memory deficits in CU is peculiar, given the robust deficits demonstrated elsewhere (e.g., Yücel et al., 2008; Solowij et al., 2011); we discussed this earlier as being possibly due to the lower level of cannabis exposure in our sample. Future research should urgently investigate ERPs in the RAVLT among a sample of heavier users of cannabis.

In summary, we have demonstrated the feasibility of measuring meaningful and reliable ERP components in the RAVLT, and its sensitivity in detecting alcohol- and cannabis-related deficits not apparent in performance measures. These studies invite replication of these methods in other laboratories, and lead the way for further ERP research investigating substance-related and other memory deficits, including the effects of age of onset, level of exposure, and interactions with sex.

AUTHOR CONTRIBUTIONS

JS and RM conceived of the study, with input from RB, AM, AF and NS. AM, RB, MD and TB collected the data for Study 1, while JS and JI collected the data for Study 2. JS and FD analyzed the ERP data and JS performed statistical analysis. All authors contributed to and approved of the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2017.02129/full#supplementary-material

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Electrophysiological Anomalies in Face–Name Memory Encoding in Young Binge Drinkers

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A growing body of evidence indicates that the intake of large amounts of alcohol during one session may have structural and functional effects on the still-maturing brains of young people. These effects are particularly pronounced in prefrontal and hippocampal regions, which appear to be especially sensitive to the neurotoxic effects of alcohol. However, to date, few studies have used the event-related potentials (ERPs) technique to analyze the relationship between binge drinking (BD) and associative memory. The objective of this study was to examine brain activity during memory encoding using the *Subsequent memory paradigm* in subjects who have followed a BD pattern of alcohol consumption for at least 2 years. A total of 50 undergraduate students (mean age = 20.6 years), i.e., 25 controls (12 females) and 25 binge drinkers (BDs; 11 females), with no personal or family history of alcoholism or psychopathological disorders, performed a visual face–name association memory task. The task used enables assessment of the *Difference due to memory effect* (Dm), a measure of memory encoding based on comparison of the neural activity associated with subsequent successful and unsuccessful retrieval. In ERP studies, study items that are subsequently remembered elicit larger positive amplitudes at midline parieto-frontal sites than those items that are subsequently forgotten. The Dm effect generally appears in the latency range of about 300–800 ms. The results showed a Dm effect in posterior regions in the 350–650 ms latency range in the Control group. However, in the BD group, no significant differences were observed in the electrophysiological brain activity between remembered and forgotten items during the encoding process. No differences between groups were found in behavioral performance. These findings show that young BDs display abnormal pattern of ERP brain activity during the encoding phase of a visual face–name association task, possibly suggesting a different neural signature of successful memory encoding.

Keywords: memory encoding, difference memory effect, face–name association, binge drinking, college students

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INTRODUCTION

Binge drinking (BD) is a pattern of alcohol consumption characterized by the intake of five or more drinks (four or more for females) on a single occasion within a 2-h interval, reaching blood alcohol concentration to 0.08 g/dL (1) at least once in the last month (2).

The most recent report of the World Health Organization (3) has highlighted that the highest rates of BD among young people occur in Europe (31.2%), the USA (18.4%) and the Western Pacific Region (12.5%). Furthermore, the rate reaches 41.8% in the 18–25 age range (4). BD has become a major

concern for public authorities because of its adverse impact on a wide range of personal, social, and health issues and also because of the associated economic cost.

Adolescence is a critical stage of development in which the brain undergoes processes of neuromaturation and reorganization (5), which extend into the third decade of life. In accordance with animal studies, this period is particularly sensitive to the effects of BD, which causes more brain damage in adolescent than in adult rats, especially in the prefrontal cortex and the hippocampus (6, 7). It has also been shown that these alterations can lead to long-lasting changes in the adult brain (8, 9).

To date, most of the relevant research in humans has focused on the consequences of this pattern of alcohol consumption on the still-maturing brain (10). Neuropsychological studies have shown that BDs display greater difficulties in processes such as working memory (11), inhibitory control (12), decision-making (13), or declarative memory (14). Functional magnetic resonance imaging (fMRI) studies have also reported abnormal brain activity in BDs during verbal learning tasks (15, 16), affective decision-making (17), working memory (18, 19), or inhibitory control (20). Furthermore, event-related potential (ERP) studies have demonstrated anomalies in BDs in different components related to processes such as attention (21), working memory (22, 23), inhibitory control (24, 25), emotional auditory processing (26), or reactivity to alcohol-related cues (27, 28).

Despite the growing evidence from research on the neurocognitive consequences of BD, few studies have examined brain activity related to associative memory processes in BDs. One type of associative memory, which has a key role in the social context, is the association between names and faces. Neuroimaging studies have shown that the encoding of face–name associations in intramodal (29–31) and intermodal tasks (32, 33) involves a network of brain structures, including the fusiform gyrus, the hippocampal formation and the dorsolateral prefrontal cortex. Scientific evidence regarding BD has reported alterations in regions such as the hippocampus and the prefrontal cortex, and it is, therefore, possible that associative memory may be impaired in BDs.

The *Subsequent memory paradigm*, in which the neural activity is recorded while individuals are explicitly or implicitly memorizing specific items, is a particularly powerful approach to studying memory encoding. The stimuli are classified on the basis of whether they were remembered or not in a subsequent memory test. In general, fMRI studies have revealed that medial temporal structures and prefrontal regions show greater activity for remembered than for non-remembered items, and this increased activity is assumed to reflect successful encoding processes. This effect, referred to as *difference due to memory effect* (Dm) or differential neural activity based on memory (34, 35), has been observed for a variety of stimuli, including faces, words, and objects (34).

Event-related potential approaches to studying declarative memory during encoding have also demonstrated the Dm effect. The ERPs elicited by study items that are subsequently remembered show larger positive amplitudes than ERPs elicited by subsequently forgotten items in midline parieto-frontal regions (36, 37). The Dm effect generally appears in the latency range of about 300–800 ms or even later, and it has been shown to be modulated by the type of encoding material (verbal vs non-verbal), task instructions (incidental vs intentional), and the type of encoding (deep vs shallow; associative vs non-associative) (35, 38). Furthermore, the effect is stronger when memory formation is intentional, associative, and requires free-recall judgments (35, 39).

In the present study, we recorded the ERPs elicited while participants performed a face–name pairs association task with subsequent memory testing, in order to shed further light on potential memory deficits associated with BD consumption in university students. We hypothesized that BD would impair face–name memory encoding at an electrophysiological and/or behavioral level because of the role of the hippocampus and the prefrontal regions in associative memory encoding, and taking into account previous reports of the influence of alcohol intake on these regions. The associative task used in this study is characterized by intentional encoding and cued-recall judgments and is, therefore, expected to elicit a clear Dm effect.

MATERIALS AND METHODS

Participants

The sample comprised 50 undergraduate students. The participants were selected from among first-year students at the University of Santiago de Compostela (Spain) who voluntarily filled in a questionnaire administered in class. The questionnaire included the Alcohol Use Disorders Identification Test (40) and other questions about substance use [for further details, see Ref. (41)]. From this initial screening, 164 subjects were enrolled in a longitudinal neurocognitive study, after undergoing a semi-structured interview in which more detailed inclusion and exclusion criteria were verified. Those participant who (1) drank six or more standard alcoholic drinks on the same occasion, one or more times per month, or (2) during these episodes, drank at a speed of consumption of at least three drinks per hour, were classified as BDs. Those who (1) drank six standard alcoholic drinks on the same occasion less than once per month and (2) drank at a maximum speed of consumption of two drinks per hour were classified as Controls. Exclusion criteria comprised non-corrected sensory deficits, any episode of loss of consciousness for more than 20 min, history of traumatic brain injury or neurological disorder, personal or familial (first-degree) history of psychopathological disorders (according to DSM-IV criteria), use of illegal drugs except cannabis, and scores above 20 in the Alcohol Use Disorders Identification Test. Two years (mean 22 months) after the first neurocognitive evaluation, participants were called for a follow-up. They were interviewed again, and those who continued to fulfill the inclusion and exclusion criteria completed a new neurocognitive assessment in which they carried out the face–name task reported here (as well as other tests). Twenty-five (11 females) subjects from the BD group and 25 (12 females) from the Control group participated in the present study (mean age 20.6 ± 0.66 years). The main demographic data and alcohol and drug use habits of the participants in the follow-up study are summarized in **Table 1**.

Informed consent was obtained from all subjects, who were paid for their voluntary participation in the study. The experiment study was undertaken in compliance with Spanish legislation and the Code of Ethical Principles for Medical Research Involving Humans Subjects outlined in the Declaration of Helsinki.

Procedure

Subjects were asked to abstain from consuming alcohol and other drugs for 24 h before the experiment to prevent effects of acute alcohol intake and to rule out withdrawal effects. In addition, they were instructed not to smoke or drink tea or coffee for at least 3 h before the assessments.

Participants were seated in an electrically shielded, sound attenuated, and dimly lit room at a viewing distance of 100 cm from a 21″ video CRT monitor (1,024 × 768 at 60 Hz). Each stimulus consisted of a face (2.9°× 3.4° visual angle) projected on a gray background and with a fictional first name printed underneath. The pictures, depicting 108 unfamiliar faces (half were female), were extracted from the AR Face Database (42). The images were cropped, resized, oval masked, and converted to gray level images using ImageMagick. All faces had a neutral expression.

TABLE 1 | Demographic and drinking characteristics of the Control and BD groups.

	Control	Binge drinkers	*p*-Value
Gender (M/F)	13/12	14/11	ns
Age	20.48 ± 0.58	20.76 ± 0.72	ns
Handedness (right/left)	23/2	22/3	ns
Caucasian ethnicity (%)	100	100	ns
Regular tobacco smokers	0	9	0.001*
Regular use of cannabis[a]	0	4	0.070
SCL-90-R: GSI percentile scores	37.20 ± 29.93	38.40 ± 31.61	0.891
Age of onset of drinking	15.52 ± 1.03	14.56 ± 1.36	0.011*
Total grams of alcohol in a standard week	39.3 ± 35.92	251.6 ± 136.66	0.001*
Speed of consumption: drinks per hour	0.90 ± 0.76	2.56 ± 0.82	0.001*
Number of drinks in a standard drinking episode	1.98 ± 1.28	5.62 ± 1.79	0.001*
Percentage of times became drunk when drinking	14.28 ± 21.19	58.40 ± 26.25	0.001*
Total AUDIT score	2.80 ± 2.35	11.68 ± 3.62	0.001*

[a]*Once or more a week.*

**p < 0.05.*

ns, non-significant; SCL-90-R, Symptom Checklist-90-Revised; AUDIT, Alcohol Use Disorders Identification Test.

During the study phase of the experiment, participants were asked to form associations between each face and the corresponding name and to try to memorize them. Face–name pairs were arranged in 18 encoding blocks (six pairs per block) presented for 1.5 s and followed by a 2–3 s randomly varying inter-stimuli interval.

Immediately after each encoding block, participants were presented with a recall block that consisted of a cued-recall test for names in which each of the six memorized face stimuli were presented (in a different order than in the learning block) for 1.5 s, followed by a question mark that remained in the center of the screen for 2 s. Participants were instructed to verbally recall the name that matched the face presented. Responses were allowed only after the face had disappeared from the screen, during presentation of the question mark (**Figure 1**).

Faces and names were never repeated during the encoding blocks of the experiment to ensure that the brain activation during this phase only reflected encoding processes and not automatic retrieval (recognition of familiar faces).

Electroencephalogram (EEG) Recording and Processing

The electroencephalogram was recorded with Brain Vision amplifiers (BrainAmp), using an Easycap with 32 synterized Ag–AgCl electrodes placed at AF3, AFz, AF4, F7, F3, Fz, F4, F8, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4, T7, T8, P7, P3, Pz, P4, P8, PO7, PO3, POz, PO4, PO8, O1, Oz, and O2 (according to the extended 10–20 International System). All active electrodes were referred to the nose tip and grounded with an electrode placed at Fpz. Vertical electrooculogram was recorded bipolarly from above and below the left eye to control eye movements and blinks. Electrode impedances were kept below 20 kΩ. EEG signals were continuously amplified and digitized at a rate of 500 Hz, and filtered on-line with a 0.01–100 Hz band pass filter.

Electroencephalogram data were off-line processed with Brain Vision Analyzer software (Version 2.0). Ocular artifacts were corrected by the procedure developed by Gratton et al. (43). The data were then digitally filtered with a 0.1–30 Hz bandpass filter (24 dB/oct) and segmented into epochs of 1000 ms, from 100 ms prestimulus to 900 ms post-stimulus. Those which exceeded ±90 μV were rejected and baseline-corrected.

Epochs recorded during encoding blocks were averaged separately according to the participant's memory judgments in the subsequent cued-recall test. Therefore, two conditions per group were computed: correctly encoded (CE) face–name pairs and incorrectly encoded (IE) pairs. There were no statistical

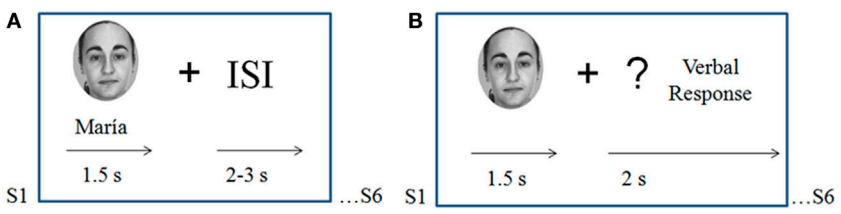

FIGURE 1 | Task design. **(A)** Study phase (encoding blocks): participants were asked to memorize novel face–name associations. Pairs were presented for 1.5 s each with a variable inter-stimulus interval of 2–3 s. **(B)** Recall blocks: the six faces memorized during the precedent encoding block were presented alone for 1.5 s; participants were instructed to verbally recall the name associated with each face when a question mark appeared on the screen.

differences in the number of averaged epochs between the groups for the CE (Controls: 51.04 ± 16.69; BD: 44.76 ± 14.36) or IE condition (Controls: 36.16 ± 15.49; BD: 39.84 ± 15.46).

Several measures were extracted for each averaged ERPs: (1) the Dm, an index of memory encoding that was the focus of this study, was quantified by comparing the mean ERP amplitudes elicited during encoding of pairs that were later remembered or forgotten in three separate latency intervals (200–350, 350–500, and 500–650 ms) at centroparietal (mean amplitude of the sites CP3, CPz, CP4, P3, Pz, and P4 at each latency interval), and parieto-occipital (mean amplitude of sites PO3, POz, PO4, O1, Oz, and O2) regions. These latency windows were selected to cover the deflection where Dm is apparent by visual inspection of the grand-averages and adjusted so that they comprised 150 ms equal length and covered all positive deflection. (2) N170 and vertex positive potential (VPP) were measured to confirm whether the task elicited the usual ERP pattern for perceptual processing of faces. N170 was identified as the mean amplitude in the 140–180 ms post-stimulus interval at P7, PO7, P8, and PO8 electrode sites; VPP was measured as the mean amplitude in the same latency interval at C3, Cz, and C4.

Data Analysis

Preliminary analysis considering Gender and Laterality (left vs right hemisphere) did not indicate any significant main effects and/or interactions of these factors, and therefore they were not included in subsequent analyses.

Behavioral performance was analyzed by using a Student's *t*-test to compare (Control vs BD) the percentage of hits (subsequently recalled names associated with faces).

Regarding the ERPs, analysis of variance (ANOVA) was conducted for the Dm effect in a 2 × 2 × 2 mixed-model design, with two within-subject factors, Condition (CE vs IE) and Region (Centroparietal vs Parieto-occipital), and one between-subject factor, Group (Control vs BD) for each of the three measured latency

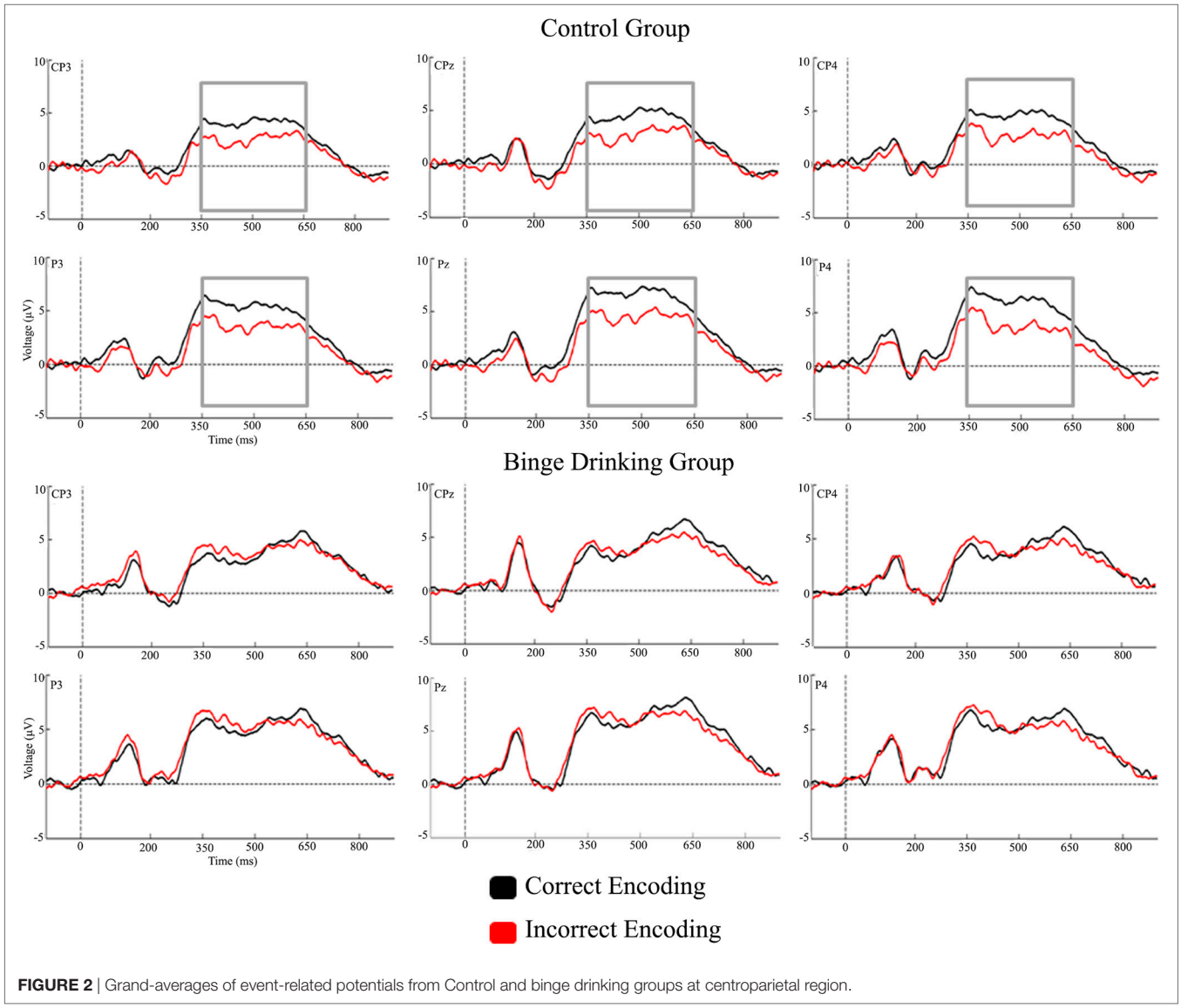

FIGURE 2 | Grand-averages of event-related potentials from Control and binge drinking groups at centroparietal region.

intervals. N170 was analyzed using a 2 × 4 × 2 mixed-model design with Condition (CE vs IE) and Electrode (P7, PO7, P8, and PO8) as within-subject factors, and Group (Control vs BD) as a between-subject factor, and VPP in a 2 × 3 × 2 mixed-model design with Condition (CE vs IE) and Electrode (C3, Cz, C4) as within-subjects factors, and Group (Control vs BD) as a between-subject factor.

Alpha levels were considered at 0.05 and the degrees of freedom were corrected, when appropriate, by the Greenhouse-Geisser estimate. *Post hoc* paired comparisons were performed with the Bonferroni adjustment for multiple comparisons.

RESULTS

Behavioral Performance

The percentage of correctly recalled names (Control = 58.59 ± 13.2%; BD = 55.55 ± 13.3%) was equivalent in the two groups [$t(48) = 0.808$, $p = 0.423$].

Event-Related Potentials

Figures 2 and **3** represent the grand-averages of the ERP at the centroparietal and parieto-occipital sites considered to evaluate the Dm. **Figure 4** represents the grand-averages corresponding to the electrode sites considered to evaluate N170 and VPP.

Table 2 presents the descriptive statistics of the amplitude values for the two groups and conditions at the three latency windows used to analyze the Dm.

With regard to the Dm effect, the analysis performed in the 200–350 ms interval did not reveal either a main effect or an interaction between Group and Condition factors. In the 350–500 ms latency window, the analysis revealed a significant difference between Regions [$F(1,48) = 56.37$, $p < 0.001$, $\eta_p^2 = 0.540$], with larger amplitudes at the parieto-occipital region. There was also a significant Condition by Group interaction [$F(1,48) = 5.01$, $p = 0.030$, $\eta_p^2 = 0.094$]; *post hoc* analysis indicated that differences

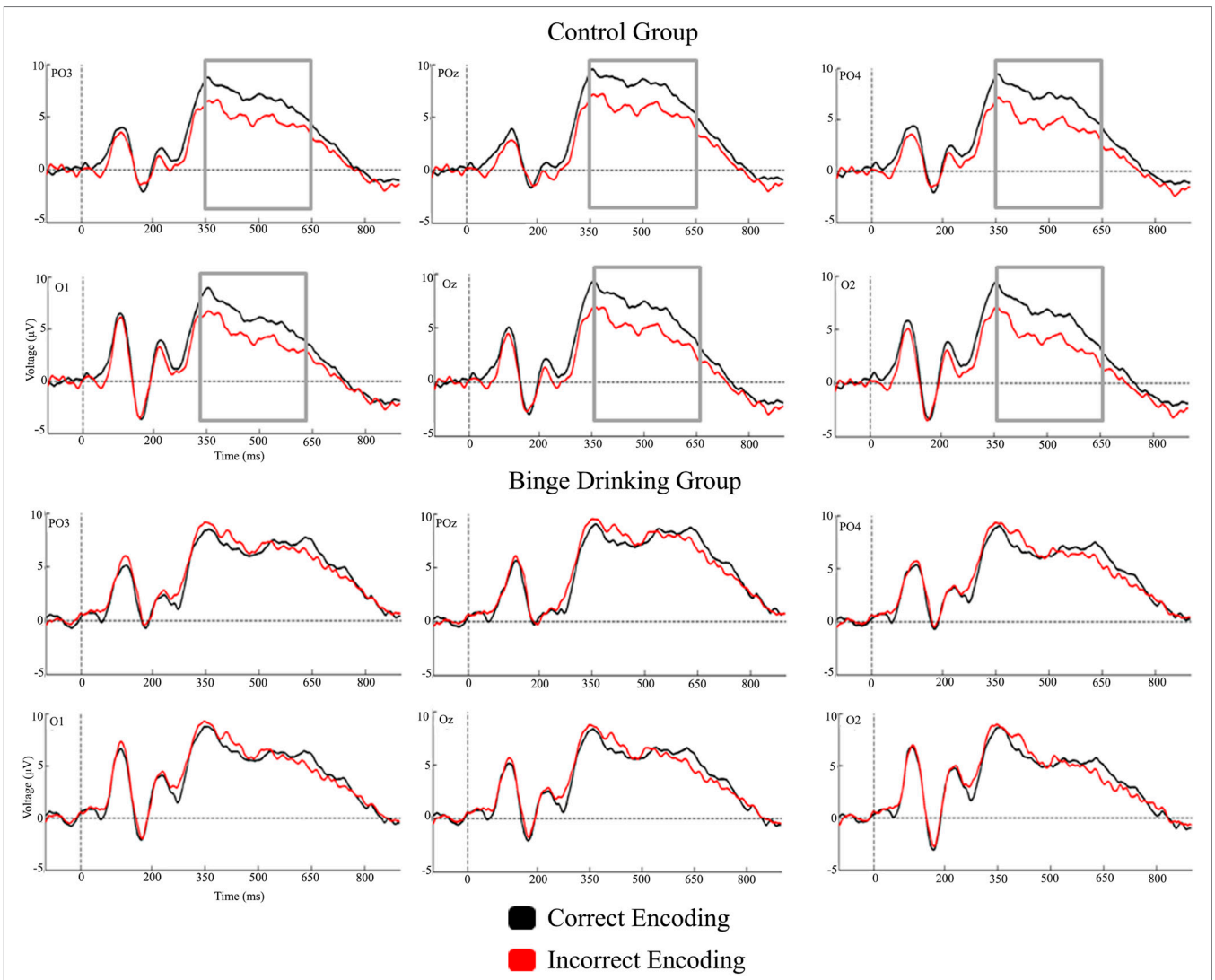

FIGURE 3 | Grand-averages of event-related potentials from Control and binge drinking groups at parieto-occipital region.

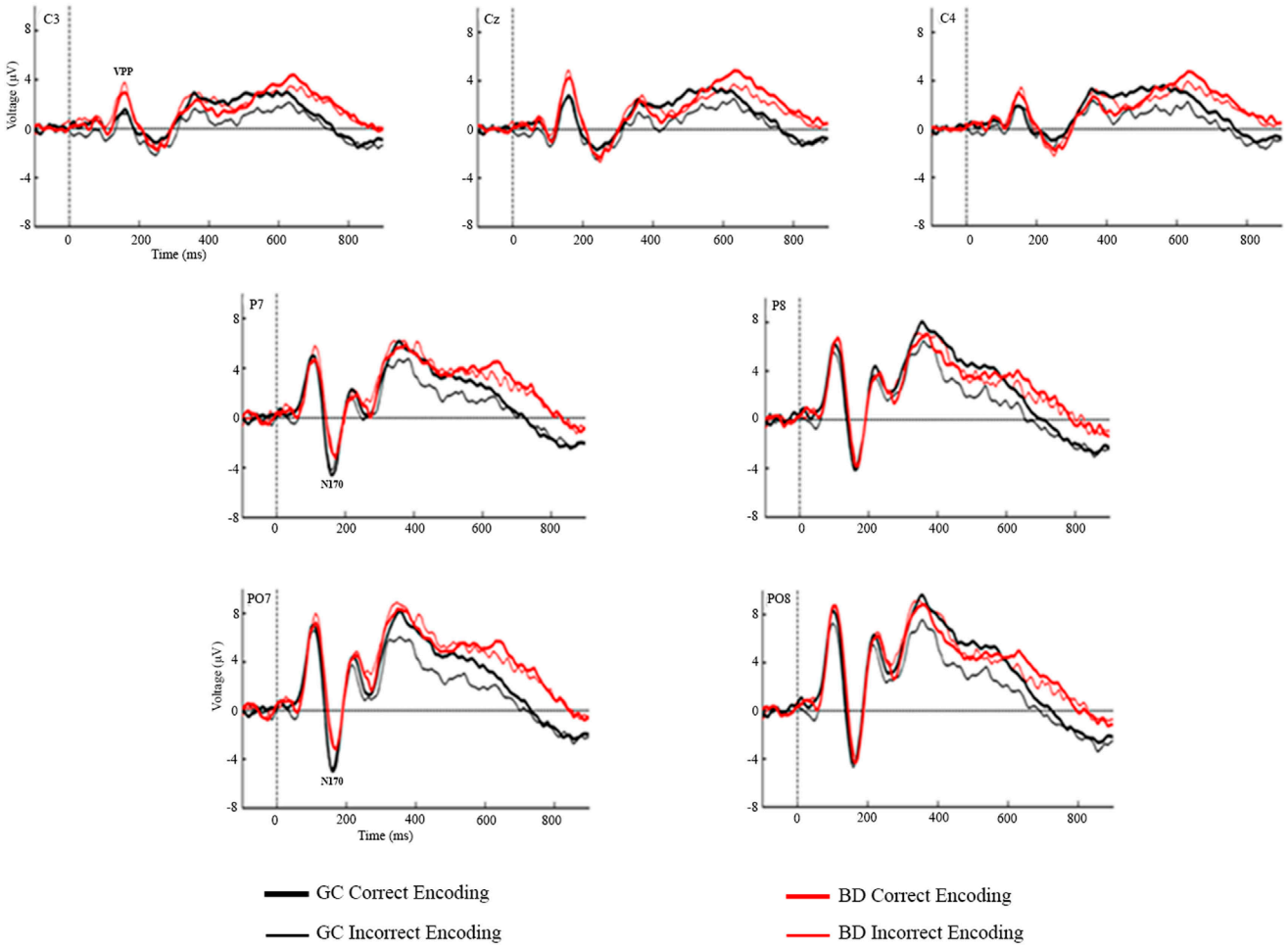

FIGURE 4 | Grand-averages of event-related potentials from Control and binge drinking groups at C3, Cz, C4 (VPP) and at P7, P8, PO7, and PO8 electrodes (N170).

between conditions (larger amplitude for CE than IE, i.e., Dm effect) were only significant in the Control group ($p = 0.012$). Analysis of the 500–650 ms interval revealed a significant main effect of Condition (Dm effect) [$F(1,48) = 4.83$, $p = 0.033$, $\eta_p^2 = 0.091$] and Region [$F(1,48) = 10.14$, $p = 0.003$, $\eta_p^2 = 0.174$] (larger amplitude at the parieto-occipital region). Although no significant Condition by Group interaction was detected, *post hoc* analysis revealed that differences between conditions were only significant in the Control group ($p = 0.028$).

Statistical analysis of the mean amplitudes in the N170 latency range did not reveal any significant main effects or interactions of the Group or Condition factors. Regarding the VPP component, the analysis revealed significant differences between groups [$F(1,48) = 4.56$, $p = 0.038$], with larger amplitudes in the BD (3.08 μV) than in the Control group (1.64 μV), there were also a main effects of the Electrode factor [$F(2,96) = 46.89$, $p < 0.001$, $\varepsilon = 0.89$, $\eta_p^2 = 0.494$] (larger amplitudes at the midline location) and Electrode by Group interaction [$F(2,96) = 3.46$, $p = 0.036$, $\eta_p^2 = 0.067$], *post hoc* analysis indicated significant differences between groups at C3 ($p = 0.015$) and Cz ($p = 0.031$) electrodes, with larger amplitudes in BD than Control group.

DISCUSSION

In the present study, ERPs were used to examine the effects of alcohol BD on declarative memory encoding among undergraduate students, using a subsequent memory paradigm with a visual face–name association memory task.

The results revealed that, despite the absence of behavioral differences between the groups (percentage of associations remembered), the Control and BD groups showed electrophysiological differences during memory encoding. The Control group displayed the classic Dm effect at the 350–500 ms latency window, with larger amplitudes for subsequently remembered face–name pairs than for those that were subsequently forgotten, whereas the BD group did not show this effect, and displayed similar neural activity for successful and unsuccessful encoding. The Dm appeared in the global sample at the 500–650 interval; however, *post hoc* analyses showed that it was only significant in the Control group.

TABLE 2 | Mean amplitude (μV) in the CE and IE conditions (mean ± SD) at the 12 electrodes analyzed in Control and BD groups at 200–350, 350–500, and 500–650 ms latency intervals.

	BD						CG					
	200–350 ms		350–500 ms		500–650 ms		200–350 ms		350–500 ms		500–650 ms	
	CE	IE	CE	IE	CE	IE	CE	IE	CE	IE	CE	IE
CP3	0.77 ± 2.94	1.31 ± 2.33	3.34 ± 3.61	3.92 ± 4.32	4.94 ± 3.48	4.46 ± 4.79	0.72 ± 3.27	−0.10 ± 4.23	4.00 ± 4.28	2.36 ± 5.34	4.29 ± 4.26	2.95 ± 4.72
CPz	0.58 ± 2.95	0.71 ± 2.48	3.68 ± 3.72	3.92 ± 4.22	5.83 ± 3.22	4.94 ± 4.57	0.40 ± 3.41	−0.41 ± 4.35	4.29 ± 4.68	2.52 ± 5.60	4.71 ± 4.66	3.25 ± 4.92
CP4	1.11 ± 2.72	1.35 ± 2.57	3.82 ± 3.58	4.27 ± 4.24	5.26 ± 3.03	4.48 ± 4.22	1.23 ± 3.33	0.60 ± 4.38	4.62 ± 4.53	2.90 ± 5.73	4.58 ± 4.33	2.84 ± 4.64
P3	2.25 ± 2.90	2.79 ± 2.76	5.31 ± 3.84	5.81 ± 4.92	6.24 ± 3.45	5.70 ± 5.11	1.81 ± 3.41	0.82 ± 4.66	5.67 ± 4.42	3.79 ± 5.49	5.22 ± 4.68	3.66 ± 5.10
Pz	1.97 ± 3.22	2.29 ± 2.76	6.02 ± 4.01	6.38 ± 4.84	7.49 ± 3.23	6.70 ± 4.85	1.78 ± 3.52	0.59 ± 4.75	6.77 ± 4.62	4.59 ± 5.76	6.49 ± 4.93	4.74 ± 5.12
P4	2.77 ± 2.87	3.05 ± 2.87	5.62 ± 3.80	6.01 ± 4.69	6.24 ± 3.04	5.47 ± 4.48	2.63 ± 3.60	1.58 ± 4.75	6.45 ± 4.55	4.20 ± 5.93	5.69 ± 4.68	3.56 ± 5.00
PO3	3.92 ± 3.66	4.45 ± 3.62	7.25 ± 4.02	7.73 ± 5.45	7.46 ± 3.60	6.88 ± 5.45	3.23 ± 3.75	2.15 ± 5.15	7.54 ± 4.71	5.55 ± 5.83	6.10 ± 5.20	4.48 ± 5.44
POz	3.30 ± 3.92	3.85 ± 3.72	7.83 ± 4.13	8.38 ± 5.52	8.44 ± 3.31	7.97 ± 5.43	2.85 ± 4.00	1.64 ± 5.14	8.64 ± 4.57	6.34 ± 5.88	7.32 ± 5.30	5.49 ± 5.36
PO4	4.43 ± 3.49	4.92 ± 3.52	7.29 ± 4.18	7.81 ± 5.19	7.13 ± 3.13	6.44 ± 4.79	3.77 ± 3.87	2.56 ± 5.08	8.00 ± 4.25	5.59 ± 5.95	6.36 ± 4.84	4.26 ± 5.18
O1	4.70 ± 4.57	5.18 ± 4.90	7.07 ± 4.15	7.47 ± 5.74	6.39 ± 3.97	5.89 ± 5.87	4.03 ± 4.06	3.03 ± 5.40	7.02 ± 4.95	5.18 ± 5.83	4.99 ± 5.31	3.42 ± 5.56
Oz	3.61 ± 4.37	4.15 ± 4.58	6.85 ± 4.32	7.30 ± 5.68	6.54 ± 3.94	5.97 ± 5.65	3.22 ± 4.23	2.00 ± 5.27	7.89 ± 4.90	5.76 ± 5.90	5.94 ± 5.20	4.18 ± 5.42
O2	4.83 ± 3.94	5.32 ± 4.40	6.65 ± 4.48	7.04 ± 5.45	5.64 ± 3.44	5.06 ± 4.96	4.14 ± 4.35	2.88 ± 5.14	7.58 ± 4.64	5.25 ± 6.06	5.47 ± 4.83	3.48 ± 5.34

BD, binge drinking; CG, Control group; CE, correct encoding; IE, incorrect encoding.

The literature about Dm effect has described significant differences in ERPs between conditions (remembered and unremembered stimuli) during the encoding of verbal and non-verbal material in young healthy people (37, 44, 45). In the present study, significant differences were observed in the Control group, whereas the BD group showed a lack of electrophysiological differences between successful and unsuccessful memory encoding. The absence of differences in neural activity would indicate anomalous processing during this memory stage in young BD subjects that seems to mask the expected Dm effect.

Studies focusing on alcoholic patients have suggested that face–name association learning is impaired in this population (46, 47). Pitel et al. (48) used magnetic resonance imaging with a face–name association task to assess different memory processes, such as face–name memory encoding with different levels of processing (i.e., shallow and deep encoding), showing poorer associative and single-item recognition in alcoholics than in controls.

Regarding BD, neuropsychological (14, 49–51), and fMRI studies (15, 16, 52) have reported impairments in declarative memory among BDs. However, to our knowledge, no previous studies have used ERPs to assess this type of memory in young BDs.

Two previous studies used fMRI to evaluate neural activity during declarative memory in BD subjects. Schweinsburg et al. (15, 16) reported that BDs exhibited increased BOLD activity in frontal and parietal regions and decreased activity in frontal and occipital cortex during memory encoding of new words; however, they did not differentiate items according to subsequent recall. Dager et al. (52) used the subsequent memory paradigm to assess the Dm effect during encoding of visual abstract stimuli. They found that heavy drinkers displayed increased BOLD activity during successful encoding in frontal, posterior parietal, and medial temporal regions, together with less left inferior frontal activation and greater precuneus deactivation during incorrect encoding. Dager et al. (52) suggested that heavy drinkers could show compensatory hyperactivation during correct encoding and greater deactivation of default mode regions during incorrect encoding, which would mean that this population would use different encoding strategies. These results are not in line with our ERP study. However, it should be noted that there were technical and experimental differences between both studies, as they analyzed BOLD activity and they used different stimuli. Moreover, in the study of Dager et al. (52), the sample characteristics were also different, as these authors did not exclude subjects with alcohol use disorder (39.1% of their Heavy Drinkers Group met criteria for this disorder). The results of the two studies are not, therefore, directly comparable.

Previous ERP and fMRI studies have also found neural hyperactivation associated with BD during different cognitive processes, such as working memory (19, 53, 54), inhibitory processes (20, 24, 25), decision-making (17, 55), or reactivity to alcohol-related cues (27, 28). These authors have suggested that the increased activity may be related to the recruitment of additional resources to compensate for underlying neurocognitive deficits in BD. On the contrary, a few other studies have reported smaller amplitudes of ERP components related to perceptual and attentional processes (56) and working memory (23). Accordingly,

these authors have suggested that BDs show some neurocognitive anomalies that have been found to be similar in alcoholics, and they have proposed that the maintenance of a BD pattern could be considered a first step toward the development of alcoholism.

In the present study, it is not possible to relate the absence of the Dm effect in the BD group with neural hyper- or hypoactivation, because differences between groups were not significant for the CE or the IE ERP amplitudes; however, they point out to an anomalous activity in regions involved in memory encoding that prevents the emergence of the Dm effect observed in normal population. Further studies are necessary to replicate these results and to clarify whether the absence of Dm is due to abnormal unspecific hyperactivation when encoding fails or to decreased activity when it is successful.

Regarding the inconsistency between behavioral and neural results, most ERP and fMRI studies on BD have found anomalies in neural activity with no behavioral differences between groups (15, 16, 18, 19, 22–24, 26, 27, 53, 54, 56, 57). It has been argued that college BDs who did not develop alcohol dependency manifest subtle deficits that go unnoticed at the behavioral level, but are detected by ERP or neuroimaging techniques. It is possible that subjects who maintain the BD pattern of consumption for a long time may begin to show similar behavioral impairments to those described in patients with alcohol use disorder following after several years of BD.

Although this study focused on components associated with memory encoding, the N170 and VPP were assessed because they are specifically related to perceptual processing of faces (58, 59). Moreover, it should be noted that very few studies on BD have reported anomalies in perceptual ERP components (26, 27, 56). Regard face perception processes, only Maurage et al. (56), in an oddball task using faces as stimuli, reported lower N170 amplitude in high BDs in comparison with light BDs, daily drinkers, and controls. The VPP component was not assessed in that work, and the reported N170 effect was not replicated in the present study. Our results revealed significant differences between groups in the VPP component, with larger amplitudes in BD than Control group. However, in this task each stimulus consisted of a face with a name written below, and face–related and name-related visual ERP components may, therefore, have overlapped. In this sense, these results should be interpreted with caution because we cannot be sure whether the central positive component reflects only face perceptual processes.

In summary, the results of the present study indicate the presence of electrophysiological differences between young college student BDs and controls during the memory encoding process in a visual face–name associative memory task, with an absence of the Dm effect in the BDs. Although the neural significance of these results is not clear, it points, as neuropsychological and fMRI previous evidence, that encoding on declarative memory could be affected by BD in young population. Further studies with larger samples are required to replicate these findings and to further inquiry in its meaning.

ETHICS STATEMENT

The protocol was approved by the Bioethics Committee of the Universidade de Santiago de Compostela. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

FC and SRH designed the general study, including sample selection criteria. PP-A implemented the task and wrote a preliminary draft. AC and EL-C collected the data. PP-A, RF-A, and SRH analyzed the data. FC, PP-A, RF-A, and SRH interpreted the data. RF-A wrote the manuscript. All authors have critically revised the manuscript for intellectual content. The final version was approved for publication by all authors.

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The Burden of Binge and Heavy Drinking on the Brain: Effects on Adolescent and Young Adult Neural Structure and Function

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Introduction: Adolescence and young adulthood are periods of continued biological and psychosocial maturation. Thus, there may be deleterious effects of consuming large quantities of alcohol on neural development and associated cognition during this time. The purpose of this mini review is to highlight neuroimaging research that has specifically examined the effects of binge and heavy drinking on adolescent and young adult brain structure and function.

Methods: We review cross-sectional and longitudinal studies of young binge and heavy drinkers that have examined brain structure (e.g., gray and white matter volume, cortical thickness, white matter microstructure) and investigated brain response using functional magnetic resonance imaging (fMRI).

Results: Binge and heavy-drinking adolescents and young adults have systematically thinner and lower volume in prefrontal cortex and cerebellar regions, and attenuated white matter development. They also show elevated brain activity in fronto-parietal regions during working memory, verbal learning, and inhibitory control tasks. In response to alcohol cues, relative to controls or light-drinking individuals, binge and heavy drinkers show increased neural response mainly in mesocorticolimbic regions, including the striatum, anterior cingulate cortex (ACC), hippocampus, and amygdala. Mixed findings are present in risky decision-making tasks, which could be due to large variation in task design and analysis.

Conclusions: These findings suggest altered neural structure and activity in binge and heavy-drinking youth may be related to the neurotoxic effects of consuming alcohol in large quantities during a highly plastic neurodevelopmental period, which could result in neural reorganization, and increased risk for developing an alcohol use disorder (AUD).

Keywords: binge drinking, heavy drinking, adolescence, young adulthood, MRI and fMRI

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INTRODUCTION

Magnetic resonance imaging (MRI) studies have highlighted ongoing brain maturation through young adulthood (Gogtay et al., 2004). Decreases in cortical gray matter (GM) from ages 10–12 through adulthood have been attributed to synaptic pruning, a process that prioritizes efficiency and strengthening of connections via proliferation of myelin over the creation of new synaptic

connections that occurs in childhood (Amlien et al., 2016). White matter (WM) volume increases linearly through young adulthood, which yields relatively stable total brain volumes after puberty (Giedd et al., 2009). This period of significant cortical modification coincides with increases in behavioral risk taking including the use of alcohol and other substances.

Alcohol use has negative effects on cognition and the brain (Jacobus and Tapert, 2013) and on health and safety (Nhtsa, 2014), yet drinking in high quantities increases during adolescence as nearly 25% of high school seniors report getting drunk in the last 30 days (Johnston et al., 2017). Binge or heavy episodic drinking (i.e., 4 or more standard drinks within a 2 h drinking session for females, 5 or more drinks for males) (NIAAA, 2004)[1] leads to increased risk for negative acute effects, such as drunk driving, unsafe sex, and other substance use (Miller et al., 2007). Long-term, adolescent alcohol use is related to serious psychosocial problems, including comorbid psychopathology (Deas and Thomas, 2002), poorer academic success (Kristjansson et al., 2013), and detrimental neurocognitive consequences (Jacobus and Tapert, 2013). Furthermore, binge drinking patterns initiated during late adolescence often persist into early adulthood (Degenhardt et al., 2013) and initiating heavy drinking at an early age significantly increases risk for subsequent adult alcohol use disorders (AUD) and related problems (Hingson et al., 2006).

Given the increase of binge and heavy drinking during adolescence when protracted brain maturation is still underway, understanding the potentially harmful effects of consuming large quantities of alcohol on neural development and associated cognition is of central importance. The purpose of this mini review is to highlight associations that may reflect deleterious effects of binge drinking and also to inform future investigations into the effects of binge drinking on brain development and functioning in young binge/heavy episodic drinkers (BD/HD). Thus, we excluded samples based on diagnostic criteria (e.g., alcohol abuse or AUD), treatment studies, and those that characterized drinking based on non-binge or heavy-drinking criteria (e.g., lifetime alcohol use days).

STRUCTURAL BRAIN IMAGING

Structural MRI assesses the metrics (e.g., thickness, surface area, and volume) of specific brain tissues at the macrostructure level. Additional techniques utilize the diffusion of water molecules [e.g., diffusion tensor imaging (DTI)] to characterize the microstructure of GM and WM. The majority of studies present cross-sectional data using retrospective reports of drinking experience, while a few recent studies have reported longitudinal changes in brain structure associated with binge drinking (**Table 1**).

GM and WM Macrostructure

Several cross-sectional studies have examined brain structure and binge and heavy-drinking histories of varying lengths in young drinkers, and the majority have highlighted regions of interest where alcohol-related deficits have been identified in chronic alcoholics (Pfefferbaum et al., 1998). Many studies report smaller volumes or thinner tissue distributed across neocortical regions primarily in frontal cortices, but also in temporal and parietal cortices (see **Table 1**). For example, a study that followed drinking patterns of young adults for 10 years reported HD exhibited reduced GM volume in the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), temporal gyrus, and insular cortex compared to light drinkers (LD) (Heikkinen et al., 2017). One study targeting the ACC also reported decreased cortical thickness among BD compared to LD (Mashhoon et al., 2014), while another study found that BD exhibited larger ACC volumes (Doallo et al., 2014). A large cross-sectional study reported that BD ($n = 134$) exhibited smaller volumes and thinner cortical tissue in total, frontal, and temporal GM as well as thinner cingulate cortex compared to controls ($n = 674$). In addition, within the BD group the number of binges in the previous year was negatively related to frontal and parietal cortical thickness (Pfefferbaum et al., 2016).

Subcortical regions including the hippocampus, diencephalon, cerebellum and brain stem also exhibit decreased volume among BD. For example, smaller left hippocampal volume in conjunction with greater hippocampal asymmetry in BD compared to controls has been found (Medina et al., 2007). Other studies reported brain stem volumes were smaller in HD compared to LD (Squeglia et al., 2014), and binge drinking episodes were inversely related to cerebellar volume (Lisdahl et al., 2013). Conversely, one study reported increased volume in the ventral striatum and thalamus among BD compared to controls (Howell et al., 2013). Interestingly, two studies found no differences between BD compared to controls/LD, but discovered a BD by sex interaction such that male BD exhibited smaller volumes compared to male controls/LD in several frontal, temporal, and subcortical regions, while female BD had larger volumes than female controls/LD in the same regions (Squeglia et al., 2012b; Kvamme et al., 2016).

Two longitudinal studies were able to examine structural MRI changes in adolescents who had a pre-drinking baseline measure. One reported greater-than-expected decline in cortical thickness in the middle frontal gyrus (MFG) associated with the onset of binge drinking (Luciana et al., 2013), as well as greater increases in several distributed WM regions over 2 years in non-drinkers compared to BD (Luciana et al., 2013). In a larger sample similar accelerated declines in frontal and temporal cortical volumes in BD and slower increases in WM were reported (Squeglia et al., 2015). A co-twin study attempted to parse out effects of drinking from genetic (or other) pre-existing vulnerabilities by examining co-twin deviations, and reported that reduced volume of the ventral diencephalon and middle temporal gyrus could be attributed to drinking, while reduced volume of the right

[1]While the definition of a standard drink differs by location outside of the United States (Mongan and Long, 2015). binge drinking episodes result in blood alcohol concentrations (BAC) near.08 gram percent (i.e., minimum of 2–3 ounces or 60–85 grams of pure alcohol).

TABLE 1 | Structural MRI findings in binge/heavy-drinking adolescents and young adults.

Study	Population (N)	Age (Mean ± SD)	BD/HD criteria	LD/controls criteria	Main findings[a]
GRAY/WHITE MATTER MACROSTRUCTURE					
Banca et al., 2016	BD: 30	BD: 21.9 ± 3.3	BDE at least once a week for the last 3 months	Drinking threshold not specified; Drinks per week = 4.8 ± 2.4	No between group differences in ROIs [cerebellum, DLPFC, inferior parietal, or thalamus] selected due to negative correlation with impulsivity
	C: 30	C: 22.2 ± 3.4			
Doallo et al., 2014	BD: 11	BD: 22.2 ± 1.1	Either (1) weekly six or more alcoholic drinks (10 g of alcohol)[e], OR (2) monthly six or more alcoholic drinks (10 g of alcohol) with pace of 3 drinks per hour, for ≥3 years	Less than monthly drinking six or more alcoholic drinks (10 g of alcohol) and pace of no more than 2 drinks per hour, for ≥3 years	BD ↑ volume mid-DLPFC (BA46 and BA9) and ACC in ROI analysis; Speed and quantity of alcohol consumption ↑ correlation with mid-DLPFC volume; also ↑ volume in MOG (BA 19), ACC/MeFG (BA32), Precentral Gyrus/MFG (BA6), and MCG (BA24) in uncorrected whole brain analysis
	C: 21	C: 22.4 ± 1.0			
Heikkinen et al., 2017	HD:35	[b]HD: 21.9 ± 3.3	AUDIT-C score ≥4 (males) and ≥3 (females) over 10 years	AUDIT-C score ≤2 over 10 years	No group differences in whole-brain VBM analysis; HD ↓ volume in subgenual ACC, OFC, STG and IC in ROI analyses
	LD:27	[b]LD: 22.2 ± 3.4			
Howell et al., 2013	BD: 19	BD: 21.9 ± 3.3	BDE at least once a week for the last 3 months	Drinking threshold not specified; AUDIT Scores = 3.2 ± 2.7	BD ↑ volume VS, thalamus, and lingual gyrus; BD ↓ volume right precuneus
	C: 19	C: 22.2 ± 3.4			
Kvamme et al., 2016	BD: 30	BD: 21.1 ± 1.8	BDE at least once a week for the last 6 months	Drinking threshold not specified; AUDIT Scores = 4.0 ± 2.6	No main effect of group; Group × Sex interaction [male: BD < C/female: BD > C] fusiform gyrus, SMA, temporal middle lobe, frontal inferior operculum, postcentral gyrus, precuneus, caudate, and VS
	C: 46	C: 20.3 ± 1.3			
Lisdahl et al., 2013	BD: 46	BD: 18.0 ± 0.8	BDE at least once in the last 3 months	No BDE in the last 3 months	BD: Number of BDE was inversely related to cerebellar volume of gray and white matter
	C: 60	C: 17.7 ± 1.0			
Luciana et al., 2013	AI: 30	[b]AI: 19.2 ± 1.4	Initiated alcohol consumption over 2 year follow-up period	No alcohol consumption	AI ↓ cortical thickness in MFG; AI ↓ WM volume in precentral, lingual, cingulate gyri, and MFG
	C: 25	[b]C: 18.6 ± 1.3			
Mashhoon et al., 2014	BD: 23	BD: 22.0 ± 1.2	≥3 BDEs per month for last 3 months	1 to 2 drinks per week and no BDE in past 3.5 years	BD ↓ cortical thickness in ACC and PCC; BD: negative correlation between drinks per week and ACC cortical thickness
	LD: 31	LD: 21.5 ± 1.6			
Medina et al., 2007[c]	HD: 16	HD: 16.9 ± 0.7	Monthly drinking; Alcohol as only substance of use	<60 lifetime alcohol use days; no abuse/dependence diagnosis	HD ↓ left Hip volume and ↑ right/left Hip asymmetry
	C: 21	C: 17.5 ± 1.1			

(Continued)

TABLE 1 | Continued

Study	Population (N)	Age (Mean ± SD)	BD/HD criteria	LD/controls criteria	Main findings[a]
Pfefferbaum et al., 2016	BD: 134	BD: 18.6 ± 2.0	At least 1 past year BDE	No lifetime BDE	BD ↓ volume in frontal and temporal cortices; BD ↓ thickness in frontal, temporal, and cingulate cortices; BD: past year binges negatively related to frontal and parietal cortical thickness
	LD: 674	LD: 15.2 ± 2.4			
Squeglia et al., 2012b	BD: 29	BD: 18.2 ± 0.8	≥1 BDE in past 3 months	<3 drinks total in the past 3 months; no lifetime BDE	No main effect of group; Group × Sex interaction [male: BD < C/female: BD > C] in frontal pole, left pars orbitalis, left medial OFG, and left rostral ACC
	LD: 30	LD: 18.0 ± 1.1			
Squeglia et al., 2014	HD: 20	[b]HD: 18.0 ± 2.0	See Figure 1 in (Squeglia et al., 2012a) for full criteria	Drink <1x/month with 1–2 drinks on average, <5 drinks maximum ever on one occasion	HD ↓ volume left VDC, ITG, MTG, caudate, and brain stem; HD: ↑ alcohol use days, ↓ caudate, brain stem volume
	C: 20	[b]C: 17.2 ± 1.6			
Squeglia et al., 2015	HD: 75	[b]HD: 19.6 ± 1.9	See Figure 1 in (Squeglia et al., 2015) for full criteria	Drink <1x/month with 1–2 drinks on average, <5 drinks maximum ever on one occasion	HD ↓ volume frontal, lateral frontal, and temporal cortices; HD = less increase in pons and CC WM
	C: 59	[b]C: 17.3 ± 2.0			
(Wilson et al., 2015)	96[d]	[b]16.4 ± 0.9	Drinking treated as continuous variable; 10% reported past year BDE at follow up		Drinking ↓ volume right MFG, right pars triangularis, left and right MTG, left and right ITG, Amyg and left VDC; Drinking ↑ volume cerebellum; Drinking ↓ thickness right SFG, right MFG, right pars triangularis, and left and right MTG;
DIFFUSION TENSOR IMAGING MICROSTRUCTURE					
Jacobus et al., 2009[c]	BD: 14	BD: 18.1 ± 0.7	≥1 BDE in past 3 months	<3 drinks total in the past 3 months	BD ↓ FA in right ILF, left IFOF, left middle cerebellar peduncle, left SLF, and 4 clusters in left SCR
	C: 14	C: 17.3 ± 0.8			
Jacobus et al., 2013[c]	BD: 17	[b]BD: 20.9 ± NR	≥3 BDE in past year	Minimal drinking experience and no history of BDE	BD ↓ FA in splenium, genu, IFOF, anterior thalamic radiations, uncinate fasciculus, SLF, anterior limb internal capsule, ACR, SCR, and posterior limb internal capsule; BD: FA decreased across 3 years (~18–21 years old)
	C: 16	[b]C: 20.9 ± NR			

(Continued)

TABLE 1 | Continued

Study	Population (N)	Age (Mean ± SD)	BD/HD criteria	LD/controls criteria	Main findings[a]
Luciana et al., 2013	AI: 30	[b]AI: 19.2 ± 1.4	Initiated alcohol consumption over 2 year follow-up period	No alcohol consumption	AI ↓ FA in dorsal caudate and IFOF
	C: 25	[b]C: 18.6 ± 1.3			
Mcqueeny et al., 2009	BD: 14	BD: 18.1 ± 0.7	≥1 BDE in past 3 months	Minimal drinking experience and no history of BDE	BD ↓ FA in ACR, CC, SLF, posterior limb of internal capsule, external capsule, fornix / stria terminalis, inferior cerebellar peduncle, superior cerebellar peduncle, PCR, and ILF (18 clusters total)
	C: 14	C: 18.0 ± 0.9			
Morris et al., 2017	BD: 28	BD: 22.0 ± 4.5	BDE at least once a week for the last 6 months	No BDE in past 6 months	BD ↓ ODI in frontal cortical GM and ↑ ODI in parietal GM; BD ↑ neurite density in cortical WM in adjacent regions of lower ODI; BD: ↑ VS ODI positively correlated with binge history
	C: 38	C: 23.7 ± 3.9			

ACC, anterior cingulate cortex; ACR, anterior corona radiata; AI, alcohol initiators; Amyg, amygdala; AUDIT, alcohol use disorders identification test; AUDIT-C, alcohol use disorder identification test – 3 item short form; BA, Brodmann's Area; BD, binge drinkers; BDE, binge drinking episode, defined as ≥5 drinks/occasion for males, ≥4 drinks/occasion for females; C, controls; CC, corpus callosum; DLPFC, dorsolateral prefrontal cortex; FA, fractional anisotropy; GM, gray matter; HD, heavy drinkers; Hip, hippocampus; IC, insular cortex; ILF, inferior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; ITG, inferior temporal gyrus; LD, light drinkers; MCG, middle cingulate gyrus; MOG, middle occipital gyrus; MFG, middle frontal gyrus; MeFG, medial frontal gyrus; MTG, middle temporal gyrus; ODI, orientation dispersion index; OFG, orbital frontal gyrus; PCC, posterior cingulate cortex; PCR, posterior corona radiata; ROI, region of interest; SCR, superior corona radiata; SFG, superior frontal gyrus; SLF, superior longitudinal fasciculus; SMA, supplementary motor area; STG, superior temporal gyrus; VDC, ventral diencephalon; VS, ventral striatum; WM, white matter; ↓, less or decreased; ↑, greater or increased.

[a] *Relative to LD/controls, unless otherwise specified.*

[b] *Age at final assessment time point.*

[c] *A group with combined heavy alcohol and marijuana use is not included in the current summary.*

[d] *Study consists of 48 monozygotic twin pairs followed for 2 years.*

[e] *Six drinks with 10 g of alcohol is similar to NIAAA guidelines of 5 or more drinks with 0.6 ounces (~14 grams) of pure alcohol per drink.*

TABLE 2 | fMRI findings in binge/heavy-drinking adolescents and young adults.

Study	Population (N)	Age (Mean ± SD)	BD/HD criteria	LD/controls criteria	Main findings[a]
INHIBITORY CONTROL					
Ahmadi et al., 2013	56 HD	HD: 19.0 ± 0.5	AUD or drank >half the weeks in preceding 6 months with BD pattern[b]	No current or past AUD; drank <half the weeks in preceding 6 months	HD: ↓ ACC, SMA, parietal, hippocampal, MFG, STG activity during correct NoGo
	36 LD	LD: 18.8 ± 1.0			
Ames et al., 2014	21 HD	HD: 20.2 ± 1.4	Males: ≥15 drinks/week	Expected to drink <3 times/week and consume ≤2 drinks/occasion	HD: ↑ DLPFC, ACC/MeFG, anterior insula activity during correct NoGo
	20 LD	LD: 20.8 ± 1.1	Females: ≥8 drinks/week BD ≥twice/week[b]		
Campanella et al., 2016	19 HD	HD: 24.7 ± 3	≥8 on AUDIT	≤7 on AUDIT	HD: ↑ occipital lobe, amygdala activity during failed NoGo
	17 LD	LD: 25.8 ± 4.2			
Wetherill et al., 2013	20 HD	Baseline HD: 14.7 ± 1.1	See Figure 1 in Wetherill et al., 2013	See Figure 1 in Wetherill et al., 2013	HD: ↑ fronto-parietal and cerebellar activity at follow-up, but less at baseline for NoGo vs. Go
	20 LD	Baseline LD: 14.1 ± 1.2 Follow-up HD: 18.5 ± 1.8 Follow-up LD: 17.6 ± 1.2			
WORKING MEMORY					
Campanella et al., 2013	16 BD	BD: 20.9 ± 1.8	≥6 drinks/occasion at speed of ≥2 drinks/hour, <2–3 times/week	Drank 1–30 days/month, ≤5 drinks/occasion at speed ≤2 drinks/hour	BD: ↑ pre-SMA during working memory
	16 C	C: 21.6 ± 2.6			
Squeglia et al., 2011	40 BD	BD Males: 18.1 ± 0.7	BD pattern ≥once in 3 months before scan	<3 drinks in past 3 months	Female BD vs. Female C: ↓ frontal, cerebellar, temporal during SWM Male BD vs. Male C: ↑ frontal, cerebellar, temporal during SWM
	55 C	BD Females: 17.8 ± 1.0 C Males: 17.7 ± 1.0 C Females: 18.1 ± 0.9			
Squeglia et al., 2012a	20 HD	Baseline HD: 15.1 ± 1.3	See Figure 1 in Squeglia et al., 2012a	See Figure 1 in Squeglia et al., 2012a	HD: ↑ fronto-parietal activity from baseline to follow-up during VWM
	20 C	Baseline LD: 14.7 ± 1.1 Follow-up HD: 18.5 ± 1.9 Follow-up LD: 17.7 ± 1.4			
VERBAL LEARNING/MEMORY					
Schweinsburg et al., 2010	12 BD	BD: 18.1 ± 0.7	Typical BD pattern[b]	No drinking past three months (See details in Table 1 in Schweinsburg et al., 2010)	BD: ↑ SFG/MFG/SPL/IPL, ↓ occipital activity during novel encoding
	12 C	C: 17.6 ± 0.8			

(Continued)

TABLE 2 | Continued

Study	Population (N)	Age (Mean ± SD)	BD/HD criteria	LD/controls criteria	Main findings[a]
Schweinsburg et al., 2011	16 BD	BD: 18.2 ± 0.8	Typical BD pattern[b] in last three months	≤5 lifetime marijuana uses; ≤50 lifetime alcohol uses	BD: ↑ fronto-parietal, ↓ precuneus, cingulate, inferior frontal gyrus activity during novel encoding
	22 C	C: 17.8 ± 0.9			
Dager et al., 2014b	23 HD	HD: 18.9 ± 0.6	AUD or drank >half the weeks in preceding 6 months with BD pattern[b]	No current or past AUD; drank <half the weeks in preceding 6 months	BD: ↑ DLPFC, posterior parietal, IFG, hippocampal activity during correct encoding BD: ↓ insula during correct recognition
	33 LD	LD: 18.7 ± 0.4			
DECISION MAKING/REWARD PROCESSING					
Xiao et al., 2013	14 BD	BD: 17.3 ± 0.5	≥5 drinks/occasion at least once in past month	Alcohol-naïve	BD: ↑ amygdala and insula activity during decision making in IGT
	14 C	C: 17.1 ± 0.7			
Jones et al., 2016	13 BD	Baseline BD: 14.9 ± 1.2	≥one BD pattern and ≥3 total occasions of ≥4 drinks within the last 90 days	Alcohol and substance-naïve	BD: ↓ dorsal striatal activity at follow-up, ↓ fronto-parietal and temporal activity at baseline and revisit during risky vs. safe decision making
	13 C	Baseline C: 14.9 ± 1.1 Follow-up BD: 17.7 ± 1.2 Follow-up C: 17.0 ± 1.1			
Worbe et al., 2014	19 BD	BD: 23.2 ± 3.5	>8 drinks for males (>6 for females) in a 2-h period, at least once a week, over a period of 3 months	Not described	BD: ↑ IFG activity associated with decrease in risky choices when feedback presented during risky-choice task
	21 C	C: 24.1 ± 3.1			
Cservenka et al., 2015	17 BD	Baseline BD: 14.9 ± 1.1	≥one BD pattern and ≥2 total occasions of ≥4 drinks within the same 90 day period	Alcohol and substance-naïve	BD: ↓ cerebellar activity during win vs. no win reward processing
	17 C	Baseline C: 14.8 ± 0.8 Follow-up BD: 16.9 ± 1.3 Follow-up C: 16.7 ± 1.2			
ALCOHOL CUE REACTIVITY					
Dager et al., 2013	35 HD	FHP HD: 19.3 ± 0.8	AUD or drank >half the weeks in preceding 6 months with BD pattern[b]	No current or past AUD; drank <half the weeks in preceding 6 months	BD: ↑ limbic, visual, frontal, and insular activity to alcohol vs. non-alcohol cues
	30 LD	FHN HD: 19.2 ± 0.7 FHP LD: 18.9 ± 1.0 FHN LD: 19.4 ± 0.6			
Kreusch et al., 2015	12 HD	21.3 ± 2.1	15 drinks/week on average ≥1 binge (i.e., 6 or more standard Dutch units of alcohol of 10 g each on 1 occasion) per week	N/A	HD: ↑ VTA activity in presence of task-irrelevant alcohol vs. soft-drink cues

(Continued)

TABLE 2 | Continued

Study	Population (N)	Age (Mean ± SD)	BD/HD criteria	LD/controls criteria	Main findings[a]
Dager et al., 2014a	16 HD ➔ HD	HD ➔ HD: 18.7 ± 0.8	HD: BD pattern[b] ≥13 of the past 26 weeks, and averaging ≥30 drinks/month (7 drinks/week) in the 6 months before scanning. MD: BD pattern <13 of the previous 26 weeks, averaging ≤30 drinks/month, and never meeting criteria for AD.	N/A	MD ➔ HD: ↑ fronto-striatal and insular activity to alcohol vs. non-alcohol cues
	14 MD ➔ HD	MD ➔ HD: 18.2 ± 0.4			
	13 MD ➔ MD[c]	MD ➔ MD: 18.5 ± 0.9			
Brumback et al., 2015	32 HD	HD: 17.9 ± 0.7	≥100 lifetime drinking episodes, ≥3 past month BD pattern[b] (≥1 in 2 weeks before study), and ≥1 recent alcohol withdrawal symptoms	<5 lifetime drinking episodes, no history of BD pattern or alcohol withdrawal symptoms	HD: ↓ differences in ACC and cerebellar activity to alcohol vs. non-alcohol cues after 1 month of abstinence
	19 C	C: 17.4 ± 0.7			
SOCIO-COGNITIVE/SOCIO-EMOTIONAL PROCESSING					
Maurage et al., 2013	12 BD	BD: 24.2 ± 4.5	>5 doses of 10 g of pure ethanol on drinking day; >3 occasions/week; >2 doses/hour	<2 doses of 10 g of pure ethanol on drinking day; <1 occasion/week; <1 dose/hour	BD: ↓ in bilateral STG, ↑ in right MFG
	12 C	C: 23.4 ± 4.2			

ACC, anterior cingulate cortex; AD, alcohol dependence; Amyg, amygdala; AUD, alcohol use disorder; AUDIT, alcohol use disorders identification test; BD, binge drinkers; BOLD, blood oxygen level-dependent; C, controls; DLPFC, dorsolateral prefrontal cortex; FHN, family history negative; FHP, family history positive; HD, heavy drinkers; IFG, inferior frontal gyrus; IGT, Iowa Gambling Task; IPL, inferior parietal lobule; LD, light drinkers; MD, moderate drinkers; MFG, middle frontal gyrus; MeFG, medial frontal gyrus; MTG, middle temporal gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; SPL, superior parietal lobule; STG, superior temporal gyrus; SWM, spatial working memory; VTA, ventral tegmental area; VWM, verbal working memory; ↓, less or decreased; ↑, greater or increased

[a] *Relative to the LD/controls, unless otherwise specified.*

[b] *BD pattern, ≥5 drinks/occasion for males, ≥4 drinks/occasion for females.*

[c] *Three groups included participants who started as heavy drinkers at baseline and remained heavy drinkers at follow-up (HD ➔ HD), participants who were moderate drinkers at baseline and transitioned into heavy drinking at follow-up (MD ➔ HD), and participants who started as moderate drinkers at baseline and remained moderate drinkers at follow-up (MD ➔ MD).*

amygdala and increased volume of the left cerebellum appeared to be pre-existing vulnerability for the onset of drinking (Wilson et al., 2015).

Taken together, binge drinking appears to be largely associated with decreased volume and accelerated thinning in the frontal and prefrontal cortices and slowing of expected WM increases. Allocortical and subcortical regions may reflect some specific positive associations with binge drinking (e.g., ventral striatum), and there is some evidence that male and female BD may exhibit an inverse relationship in some frontal and subcortical regions.

GM and WM Microstructure

Among alcohol dependent adults WM integrity tends to be weakened (Pfefferbaum et al., 2006), but fewer studies have examined the effects of binge drinking on WM and GM microstructure (see **Table 1**). Each study among non-dependent BD has reported WM integrity deficits compared to LD/controls across the majority of WM tracts (Jacobus et al., 2009; Mcqueeny et al., 2009; Bava et al., 2013). Longitudinal studies also support decreased WM integrity among individuals who initiate or increase binge drinking, showing additional declines in fractional anisotropy over time (Jacobus et al., 2013; Luciana et al., 2013). A recent study examining both GM and WM microstructure utilizing orientation dispersion index (ODI) reported that BD had lower ODI in frontal GM but higher ODI in parietal GM and in the ventral striatum (Morris et al., 2017). Thus, overall it appears that binge drinking is associated with decreased WM microstructural integrity, but may be selectively related to increases in microstructural GM in a brain region associated with reward seeking.

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)

As structural abnormalities have been related to heavy alcohol use during neuromaturation, it is important to understand whether these findings translate to alterations in the functioning of brain systems across different cognitive domains. We discuss six areas that have included studies of BD/HD: response inhibition, working memory, verbal learning and memory, decision making and reward processing, alcohol cue reactivity, and socio-cognitive/socio-emotional processing (**Table 2**). Further, in order to focus this section of the mini review on task-related functional magnetic resonance imaging (fMRI) studies, we excluded discussion of functional connectivity (Gorka et al., 2013; Weiland et al., 2014; Morris et al., 2016), acute alcohol administration (Filbey et al., 2008), machine learning (Squeglia et al., 2017), treatment (Feldstein Ewing et al., 2016), and neurofeedback (Kirsch et al., 2016) studies that included young BD/HD, as well as studies where binge drinking was examined, but was not the main variable of interest (Glaser et al., 2014).

Response Inhibition

The ability to inhibit a pre-potent response or have self-control over impulsive actions is a central facet of executive functioning (Diamond, 2013). Several studies have identified deficits in response inhibition and its neural correlates in individuals with AUD (Lawrence et al., 2009), and these investigations have extended to adolescent and young adult BD/HD, most of which have used Go/NoGo tasks. For example, in a study of 18–20 year old college students, HD showed slower reaction times on both correct Go hits and incorrect NoGo false alarms (Ahmadi et al., 2013). LD had greater response in ACC, supplementary motor area (SMA), MFG, parietal lobe, hippocampus, and superior temporal gyrus (STG) than HD during NoGo correct rejections, suggesting decreased inhibitory control brain activity in HD in a set of brain regions that underlie cognitive and impulse control (Ahmadi et al., 2013).

Variations of the Go/NoGo task have used alcohol-related images as NoGo stimuli and non-alcoholic beverages as Go stimuli. Ames et al. (2014) demonstrated that compared with HD, LD had better Go/NoGo task performance as indexed by *d*-prime. HD had greater activity in the dorsolateral prefrontal cortex (DLPFC), ACC, and the anterior insula than LD during NoGo trials, suggesting greater reliance on executive functioning, error monitoring, and emotional interoception regions during inhibitory control (Ames et al., 2014). Another task presented the traditional letters used in Go/NoGo tasks overlaid onto black, neutral picture, and alcoholic photo backgrounds. While there were no effects of background context, college HD displayed greater activity in visual and emotional processing regions, such as the amygdala and occipital lobe during *failed inhibitions* compared with LD (Campanella et al., 2016).

In one longitudinal investigation, HD had greater fronto-parietal and cerebellar activity during response inhibition relative to controls at follow-up but reduced activity in these same regions at baseline, suggesting both markers of vulnerability toward heavy drinking and altered executive functioning activity after the initiation of heavy alcohol use (Wetherill et al., 2013). Task-related fMRI studies have largely reported that HD/BD have increased fronto-parietal and cerebellar response during successful inhibitory control and increased emotional and visual response during unsuccessful response inhibition (except for Ahmadi et al., 2013).

Working Memory

Another key component of executive functioning is working memory (WrkM), the ability to maintain and manipulate information during a short time span (Diamond, 2013). WrkM has been linked with adaptive decision making and deficits in WrkM are associated with vulnerability toward addiction (Nagel et al., 2012). An fMRI n-back task of WrkM was completed by university BD, who showed larger pre-SMA WrkM-related activity than controls, suggesting greater attentional resources devoted to performing the task by the BD to maintain equal performance with the control group (Campanella et al., 2013).

Some studies have reported that sex differences may also be present in WrkM-related activation between male and female BD. Female BD had less spatial WrkM activation in several frontal, temporal, and cerebellar regions compared to female controls and this was linked to poor behavioral performance in the BD, a pattern opposite to what was seen in male BD relative to male controls (Squeglia et al., 2011). The authors argue that this may suggest female vulnerability toward the neurotoxic effects of binge drinking during active periods of neuromaturation.

While longitudinal research is sparse among fMRI studies of BD/HD youth, one study reported reduced baseline fronto-parietal activity in adolescents who later transitioned into heavy drinking. However, HD showed significantly increased activity in these areas at a 3-year follow-up relative to baseline brain response (Squeglia et al., 2012a). Overall, these studies suggest mostly greater WrkM-related brain activity across fronto-parietal regions in BD/HD relative to controls, but some exceptions may be present when examining sex differences and pre-drinking vulnerability.

Learning and Memory

Deficits in learning and memory have been previously reported in individuals with AUD (Pitel et al., 2014), and in investigations of BD youth (Carbia et al., 2017). In the first of three studies examining neural response during verbal or figural encoding, Schweinsburg et al. (2010) found that while learning novel word pairs, BD showed elevated superior frontal and posterior parietal activity compared with controls, a finding that was closely replicated in a subsequent study where BD had greater fronto-parietal activity during novel encoding, with some areas displaying reduced activity relative to controls, such as the inferior frontal gyrus (IFG), precuneus, and ACC (Schweinsburg et al., 2011). These findings suggest some degree of neural reorganization in BD that results in increased reliance on fronto-parietal regions while learning novel word pairs, and decreased activity in other regions.

Pictorial as opposed to verbal stimuli were used in a study of college HD who demonstrated similar patterns of brain activity to previous studies of adolescents, namely greater fronto-parietal activity during encoding of novel stimuli, as well as greater hippocampal response relative to LD (Dager et al., 2014b). This study also examined brain activity associated with recognition for the first time, and found less insular activity during correct recognition in HD vs. LD, a finding the authors believed could reflect less arousal during correct recognition or a different task approach that resulted in similar task performance (Dager et al., 2014b).

Decision Making and Reward Processing

A number of studies have investigated the neural correlates of risky decision making and reward processing across monetary decision making tasks in young BD. A study using the Iowa Gambling Task found that compared with their peers, adolescent BD had greater insular and amygdala activity, suggesting greater emotion-driven decision making in the BD (Xiao et al., 2013), but this task did not permit the dissociation of decision making-related activation from reward processing. A subsequent longitudinal study used a modified Wheel of Fortune Task, in which BD showed reduced dorsal striatum activity during risky vs. safe decision making, and similar to previous studies, reductions in fronto-parietal activity preceded the onset of heavy drinking (Jones et al., 2016). It is possible that feedback during risk taking could modify behavior and cognitive control as young adult BD decreased their risk taking when they were presented with information about potential monetary losses, and this was associated with increased recruitment of IFG (Worbe et al., 2014). Finally, processing of reward receipt was related to decreased cerebellar activity in a longitudinal study of BD, suggesting blunted reward and affect-related responses as a result of heavy episodic drinking (Cservenka et al., 2015). Based on these results, a general pattern that is emerging is related to alterations in cognitive control and emotional processing brain regions that may be modifiable when feedback about the consequences of risk taking are presented.

Alcohol Cue Reactivity

Alcohol cue reactivity studies have found greater neural response in reward and emotional processing brain regions among individuals with AUD (Heinz et al., 2009). Alterations in motivational neurocircuitry are associated with AUD (Koob and Volkow, 2010) and have thus been investigated in young adult and adolescent BD/HD. Dager et al. (2013) reported that young adult HD had greater neural activity in response to alcohol-related images in widespread areas comprised of limbic, visual, frontal, and insular regions compared with LD. Further, in a task where participants were instructed not to focus on alcohol cues, ventral tegmental area activation was elevated in young adult HD compared with neural response seen to soft drink cues, suggesting automatic processing of alcohol-related stimuli that may increase motivational drive in mesolimbic circuitry (Kreusch et al., 2015). Interestingly, response to alcohol cues may be used to predict drinking behavior in young adult HD as those who showed elevated response in fronto-striatal areas and the insula subsequently transitioned into heavy drinking (Dager et al., 2014a). A longitudinal study of adolescent HD showed that increased brain activity to alcohol cues in HD vs. controls diminishes with abstinence from alcohol, indicating that a decline in risky drinking may modify brain activity in response to alcohol-related stimuli (Brumback et al., 2015). Across these studies, there is evidence that mesolimbic and motivational circuitry may be important targets for studies designed to reduce response to alcohol cues in adolescent and young adult HD.

Socio-Cognitive and Socio-Emotional Processing

Research on the effects of binge and heavy drinking on the developing brain are limited in other domains, such as socio-cognitive and socio-emotional processing. While recent meta-analyses highlight deficits in social cognition in individuals with AUD (Onuoha et al., 2016; Bora and Zorlu, 2017), there are a lack of fMRI studies in this area within young BD/HD. In one study, young adult BD categorizing vocal affective stimuli had less activity in STG, but more activity in MFG compared with their peers (Maurage et al., 2013). Given the large gap in the literature specifically focused on socio-cognitive processing in young BD/HD, future research should further investigate this domain.

CONCLUSIONS

Binge drinking among youth is associated with smaller/thinner cortical and subcortical structures and decreased WM integrity. Consistent across many fMRI studies of cognitive control,

WrkM, and verbal learning, young BD and HD show greater reliance on fronto-parietal systems while performing these tasks (Schweinsburg et al., 2010, 2011; Squeglia et al., 2012a; Wetherill et al., 2013; Dager et al., 2014b). Executive functioning and emotional processing systems are important networks for future investigations related to decision making and reward processing (Xiao et al., 2013; Worbe et al., 2014; Cservenka et al., 2015; Jones et al., 2016), while mesolimbic circuitry is likely involved in the elevated response to alcohol cues in young BD/HD (Dager et al., 2013, 2014a; Brumback et al., 2015; Kreusch et al., 2015). These findings suggest there may be neural alterations as a result of heavy alcohol use or neural risk markers related to vulnerability toward heavy drinking during adolescence and young adulthood. While some findings have been replicated, greater efforts are needed for consistency across task variations, analyses reported, inclusionary criteria for BD/HD, as well as longitudinal studies of this topic.

AUTHOR CONTRIBUTIONS

AC conducted literature searches, wrote, edited, and revised the section on fMRI findings, wrote the conclusions, and created the table of fMRI findings. TB conducted literature searches, wrote, edited, and revised the section on structural MRI findings, wrote the introduction, and created the table of MRI structural findings. AC edited the final version of the manuscript and wrote the abstract.

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Gray Matter Abnormalities in the Inhibitory Circuitry of Young Binge Drinkers: A Voxel-Based Morphometry Study

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Binge drinking (BD) is defined as a pattern of high alcohol intake in a short time followed by periods of abstinence. This behavior is very common in adolescence, a developmental stage characterized by the maturation of the prefrontal and striatal networks, important circuits underlying the capacity to control and regulate the behavior. In this study, we conducted a voxel-based morphometry (VBM) analysis, using a region of interest (ROI) analysis of brain regions associated with inhibitory control and self-regulatory processes, in a group of 36 young college students, 20 binge drinkers (BDs) and 16 alcohol abstinent controls (AAC). Results showed increased gray matter (GM) densities in the left middle frontal gyrus in BDs, when compared with alcohol abstinent controls. Additionally, a ROI-based Pearson analysis documented positive correlations between the left middle frontal gyrus GM densities and the self-control subscale of the Barratt Impulsiveness Scale (BIS), in the BD group. These findings highlight abnormalities in core brain regions associated with self-regulatory processes in the BD group.

Keywords: binge drinking, gray matter, inhibitory control, self-regulation, impulsivity, adolescence, college-students, voxel-based morphometry

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INTRODUCTION

Binge drinking (BD) is a common pattern of consumption among college students and is characterized by repeated episodes of large amounts of alcohol intake. In order to be considered BD, an alcohol ingestion episode requires a minimum consumption of four drinks for women and five for men, in a brief period of time (±2 h) at least once per month, being followed by periods of abstinence (see Parada et al., 2011; Substance Abuse and Mental Health Services Administration [SAMHSA], 2016a for a review). This pattern of high alcohol consumption increases the individual's susceptibility to engage in several risky behaviors (Courtney and Polich, 2009; Substance Abuse and Mental Health Services Administration [SAMHSA], 2015).

Abbreviations: AAC, alcohol-abstinent control; AACs, alcohol-abstinent controls; AUDIT, Alcohol Use Disorder Identification Test; BD, binge drinking; BDs, binge drinkers; BIS, Barratt Impulsiveness Scale; DLPFC, dorsolateral prefrontal cortex; GM, gray matter; ROI, regions of interest; VBM, voxel-based morphometry.

According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), nearly 60% of US college students (age range 18–22 years) reported alcohol consumption and 40% exhibited a BD pattern in the past month. This behavior is seriously harmful affecting several domains of the individuals' life such as social, academic and health, being associated with the death of approximately 1,825 US college students each year (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2015; Substance Abuse and Mental Health Services Administration [SAMHSA], 2016b). In Europe, a growth of this abusive pattern of consumption among young people was noted between the years 1995 and 2000, with the prevalence rate being quite unchangeable over the past two decades (Kraus et al., 2016). The percentage of frequent BD (at least a BD episode per week) is higher in the youngest individuals (age range: 15–24 years) with 33% reporting BD. Additionally, in terms of gender prevalence, the proportion of frequent BD is higher in men (36%) than in women (19%). (Eurobarometer, 2010).

The adolescence is a critical period for the beginning of abusive alcohol consumption (Crews and Boettiger, 2009; Casey and Caudle, 2013). In fact the onset of BD among youths seems to be around age 12, but the largest percentage of BD episodes is observed in older adolescents (age range: 16–17) (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2015). In this particular developmental period individuals tend to increasingly engage in social behaviors, such as recreational drinking, in order to attain social conformity. Additionally, adolescents tend to use alcohol as a coping strategy to deal with negative emotions and achieving an illusive state of well-being, induced by large doses of alcohol (Lorant et al., 2013; Laghi et al., 2016). At the neuromaturational level, adolescence is a period of great physiological changes including intracellular events such as loss of overproduced synapses and increase of myelin sheaths, particularly in the prefrontal cortex, limbic system, and white matter association and projection fibers, essential to brain maturation. In addition, these neuromaturational changes are linked with advancements in complex cognitive functions as inhibitory control and self-regulation, which also occur in this developmental stage (Bava et al., 2010), allowing individuals to deal with risk-taking choices (Casey and Caudle, 2013). In accordance, the lower adolescent's proficiency in regulating their own behavior and suppress inappropriate emotions or actions has been associated with the structural immaturity of several cortical and subcortical regions (Crews and Boettiger, 2009; Bava and Tapert, 2010; Bari and Robbins, 2013), hence, the immature prefrontal-striatal regions in association with the underdeveloped self-regulation seem to let individuals more prone to risky environmental factors such as drugs or alcohol misuse, and to engage in impulsive behaviors.

Research on the putative neuropsychological abnormalities in BD documented a multiplicity of deficits underlying these executive function and self-regulatory abilities, as attention, cognitive flexibility, working memory, planning, decision-making and inhibitory control. These functional impairments have been associated with atypical functioning of several brain regions, including the dorsolateral prefrontal cortex (DLPFC), the inferior, middle and superior frontal gyri, the anterior cingulate cortex and the parietal and the temporal lobes, revealed by electrophysiological, structural and functional neuroimaging studies (see Hermens et al., 2013 and Lopez-Caneda et al., 2014 for a review). In particular, morphometric studies reported regions of enlarged gray matter (GM) such as the striatum (age range: 18–28; Howell et al., 2013), the DLPFC (age range: 20–24; Doallo et al., 2014), the cingulate cortex and the temporal gyri (age range: 22–28; Heikkinen et al., 2017), while some studies showed decreased GM in the temporal gyri, the superior and middle frontal gyri and the pars triangularis (age range: 14–19) (Luciana, et al., 2013; Wilson, et al., 2015).

Overall, while some of the authors related their results to a neurotoxic effect of alcohol (e.g., Luciana et al., 2013; Doallo et al., 2014), others suggested that premorbid changes in the brain structure were present before alcohol initiation, which were possibly related with future alcohol misuse (Cheetham et al., 2014, 4 year follow-up; Squeglia et al., 2014, 2017, 3 year follow-up; Wilson et al., 2015, 1 year follow-up). Therefore, the data gathered in the BD field suggests that the brain abnormalities found in the young BDs might be related with disruptions in the normative brain development that occur previously to the drinking onset, whereas others suggest that alteration of the optimal brain maturation and integrity is a consequence of BD.

Taking this developmental, neurofunctional and neurocognitive findings into consideration, we hypothesized that BDs would show morphological alterations within core brain regions associated with self-regulatory processes (i.e., superior, middle and inferior frontal gyri, orbitofrontal cortex, anterior cingulate, nucleus accumbens and caudate), when compared with AAD. In order to test this hypothesis, we performed a voxel-based morphometry (VBM) study in a group of young college students that met the criteria for binge alcohol consumption and a group of AACs employing a region of interest (ROI) analysis of brain regions associated with inhibitory control and self-regulatory processes (Crews and Boettiger, 2009; Koob and Volkow, 2010).

MATERIALS AND METHODS

Participants

Participants were recruited through an online survey with college students, which included items regarding the use of alcohol (frequency of alcohol consumption, number of drinks consumed on each day of the past week, speed of drinking, etc.) and other drugs (type of drug, frequency of consumption, etc.). Then, participants with BD or AAC criteria were selected to participate and invited to a clinical structured interview. The interview covered several aspects related to alcohol and drug consumption, personal and family history of alcoholism, medical or psychopathological disorders, as well as the assessment of their laterality, impulsivity and psychopathological symptomatology. The sample included 36-college students ranging in age between 18 and 23 years old, with 20 participants with BDs (10 women) and 16 AACs (10 women). Participants were classified as BDs if

they consumed a minimum of four drinks or five for men in a brief period of time (∼2 h), at least once per month, for the last 10 months (minimum). Participants assigned to the AAC group were completely alcohol abstinent, i.e., do not drink alcohol at all, neither now nor in the past. The demographic and drinking characteristics of both groups are shown in **Table 1**.

Exclusion criteria for both groups were defined as the following: be left-handed; scores ≥ 20 in the AUDIT; GSI ≥ 90 or scoring in at least 2 symptomatic dimensions of the SCL-90-R; uncorrected sensory deficits; personal history of traumatic brain injury or neurological disorder; regular (i.e., on a weekly basis) consumption of cannabis, personal history of regular or occasional use of other drugs (opiates, hallucinogens, cocaine, ecstasy, amphetamine compounds or medically prescribed psychoactive substances); Alcohol Use Disorder (AUD), i.e., alcohol abuse/dependence, based on DSM-IV-R criteria; personal and/or family history of any neurological or DSM-IV axis I disorder in first-degree relatives, family history of alcoholism in first-degree relatives; and magnetic resonance imaging (MRI) contraindications.

Clinical and Neuropsychological Assessment

Personal and family history of alcoholism plus medical or psychopathological disorders information was collected through a semi-structured interview including: a Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), Individual Assessment Module (IAM) and Family History Assessment Module (FHAM), designed by the Collaborative Study on the Genetics of Alcoholism (Bucholz et al., 1994). In addition, in order to assess the psychopathological symptomatology, the Portuguese version of the Symptom Checklist-90-Revised (SCL-90-R) (Derogatis, 2002; Almeida, 2006) was used. This self-report questionnaire is used to evaluate a range of current psychological symptoms and distress providing a Global Score index (GSI), which is a measure of the overall psychological distress and nine primary symptom dimensions (interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism).

Sociodemographic and substance use data were collected through a questionnaire that, besides sociodemographic information, included items 10, 11 and 12 from the Alcohol Use Questionnaire (AUQ) (Townshend and Duka, 2002), assessing speed of drinking (average number of drinks consumed per hour), number of times getting drunk in the past 6 months, and percentage (average) of times getting drunk during drinking episodes.

Additionally, a diary of alcohol ingestion, questions about consumption of alcohol and other psychoactive substances (type of substance, frequency of consumption, etc.) and the Portuguese version of the Alcohol Use Disorder Identification Test (AUDIT) (Cunha, 2002) were administered. Total AUDIT score reflects the subject's level of risk due to harmful alcohol intake: scores in the range of 8–19 reveal hazardous drinking, while scores of 20 or above warrant further diagnostic evaluation for alcohol dependence (Babor et al., 2001).

Impulsivity was assessed through the Barratt Impulsiveness Scale 11 (BIS11) (Patton et al., 1995). BIS is a self-report questionnaire intended to evaluate personality and behavioral aspects of impulsiveness providing a full-scale score plus second and first order subscores reflecting subtraits of impulsiveness. The Portuguese version was used (Cruz and Barbosa, 2012, Unpublished). Likewise, the Edinburg Handedness Inventory (Oldfield, 1971) was used to assess participants' laterality.

Procedure

All the participants (regardless of whether they had been pre-classified as BDs or AACs) underwent the same clinical, neuropsychological and neuroimaging assessment protocol. Prior to the MRI assessment, participants were asked to abstain from BD during the three preceding days, consuming drugs and alcohol 12 h before the scanning and to avoid smoking and drinking tea or coffee for at least 3 h in advance. All participants gave written informed consent after the procedure had been carefully explained and received a financial stipend for their participation. The research was conducted in accordance to the ethical principles for medical research involving human subjects of the World Medical Association present in the Declaration of Helsinki (Williams, 2008). The Bioethics Committee of the University of Minho approved the protocol.

Magnetic Resonance Image Acquisition

The neuroimaging assessment was conducted with clinically approved Siemens Magneton TrioTim 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a 32-channel receive-only head coil. Sagittal high-resolution 3D T1 weighted anatomical images were acquired using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: repetition time (TR) = 2700 ms, echo time (TE) = 2.33 ms, flip angle (FA) = 7°, 192 slices with 0.8 mm thickness, in-plane resolution = 1×1 mm^2, and 256 mm field of view (FoV).

Image Processing

Before running the postprocessing protocol, all MRI scans were visually controlled to discard for critical head motion or brain lesions. All the images were normalized to the ICBM 152 average SPM template in Montreal Neurological Institute (MNI) space. Data was processed using SPM12 pipeline and statistical tools (Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom[1]) executed in Matlab R2015a (MathWorks, Natick, MA, United States) with the VBM module. VBM is an automated processing technique applied to the entire brain allowing the characterization of shape and neuroanatomical configuration of different brains. Local composition of brain tissues is compared based in a voxelwise approach (Ashburner and Friston, 2000; Mechelli et al., 2005). Images were segmented into GM, white matter and cerebrospinal fluid using an extension of the standard unified segmentation model in SPM12. White and GM segmentations were co-registered across participants using the DARTEL algorithm (Diffeomorphic Anatomical

[1]http://www.fil.ion.ucl.ac.uk/spm/

TABLE 1 | Demographic and behavioral data for BDs and AACs.

	BD Mean ± SD	AAC Mean ± SD	*t* (34)
N (females)	20 (10)	16 (10)	
Caucasian ethnicity (%)	100	100	
Age (range)	20.45 ± 1.60 (18–23)	21.00 ± 1.71 (18–23)	0.99
Age of onset of BD	17.45 ± 1.08	–	
AUDIT (total score)	11.20 ± 3.25	0.62 ± 1.20	−13.43***
Number of times of BD per month	3.57 ± 1.87	0	−8.54***
Number of months with BD pattern	35.90 ± 14.03	0	−11.44***
Grams of alcohol consumed per week	151 ± 44.27	0	−14.78***
Speed of drinking (gr/h during BD episodes)	34.50 ± 8.26	0	−18.69***
Percentage of times getting drunk when drinking	43.25 ± 20.41	0	−9.48***
Tobacco smokers	7 (4 ♀)	0	
Occasional users of cannabis	2 (2 ♀)	0	
BIS (Total Score)	64.80 ± 5.83	63.56 ± 6.05	−0.62
BIS (Attention)	10.65 ± 2.23	10.63 ± 2.16	−0.03
BIS (Cognitive Instability)	6.10 ± 1.41	5.50 ± 1.51	−1.23
BIS (Motor)	11.80 ± 2.76	10.00 ± 2.03	−2.17*
BIS (Perseverance)	7.05 ± 1.05	7.31 ± 1.40	0.64
BIS (Self-control)	16.50 ± 2.46	17.38 ± 2.58	1.04
BIS (Cognitive complexity)	12.70 ± 1.95	12.75 ± 1.88	0.08

*AUDIT, Alcohol Use Disorders Identification Test; BIS, Barratt Impulsiveness Scale; BD, Binge Drinking; AAC, alcohol-abstinent control; SD, standard deviation. All p-values reported are for two-tailed independent samples t-tests. *P ≤ 0.05. ***P ≤ 0.000.*

Registration Through Exponentiated Lie Algebra; Ashburner, 2007; Ashburner and Friston, 2009) and smoothed with a 8 mm FWHM Gaussian filter to reduce errors from between-subject variability in local anatomy and to improve the normality of the data. For the purpose of this study only GM segmentations were analyzed.

Region of Interest Definition (ROI)

For this purpose, a review on the prefrontal-striatal network underlying self-regulatory mechanisms involved in the addiction circuitry (Crews and Boettiger, 2009; Bava and Tapert, 2010; Koob and Volkow, 2010; Goldstein and Volkow, 2011; Koob, 2011; Bari and Robbins, 2013) was performed. The identified brain regions were the superior, middle and inferior frontal gyri, the frontal superior orbital gyrus, the anterior cingulum, the caudate nucleus and the nucleus accumbens. Therefore, a mask was generated with the WFUpickatlas toolbox version 3.0.5b[2] based on the Talairach Daemon database running on MatLab R2015a (MathWorks, Natick, MA, United States) that included both cortical and subcortical areas of these brain regions, known to be involved in the inhibitory circuitry (see **Figure 1**).

Statistical Analysis

For statistics, two-way analysis of variance was performed. Gender and Group were included as between subject factors and age was used as a covariate. Total intracranial volume of each subject was included in the statistical model. For statistical threshold criteria significant results were considered after Monte Carlo correction for multiple comparisons $p < 0.05$. The correction was determined over 1000 Monte Carlo simulations using AlphaSim tool, distributed with REST toolkit (Song et al., 2011)[3] and mask set to the corresponding ROI previously generated. Anatomical labeling was obtained using the anatomical automatic labeling atlas (AAL), (Tzourio-Mazoyer et al., 2002).

In addition, Pearson correlations (with bootstrap corrections, 5000 iterations and 95% confidence interval) were performed to analyze the relationship between GM densities and both alcohol-related measures only in the BD group: number of times of binge drinking per month, number of months with BD pattern, grams of alcohol consumed per week, speed of drinking (grams/h during BD episodes), AUDIT scores, and BIS scores: total score, and subscales: attention, cognitive instability, motor control, perseverance, cognitive complexity and self-control. Additionally Pearson correlations between GM densities and the BIS scale and subscales scores were also calculated for both groups.

RESULTS

ROI-Based Analysis

Increased GM densities in the left middle frontal gyrus were observed in the BDs (MNI coordinates: −45, 24, 33; $K = 315$, $z = 3.98$, $p < 0.0001$ uncorrected; AlphaSim correction, $p < 0.05$, cluster size > 29), when compared to the AACs. **Figure 2** illustrates the regions where significant differences in peak-level densities were observed between BDs and AACs.

A group-by-gender interaction effect was observed in the left middle frontal gyrus (MNI coordinates: −42, 51, 15; $K = 81$, $z = 3.40$, $p < 0.001$ uncorrected; AlphaSim correction, $p < 0.05$,

[2]http://www.ansir.wfubmc.edu

[3]http://resting-fmri.sourceforge.net/

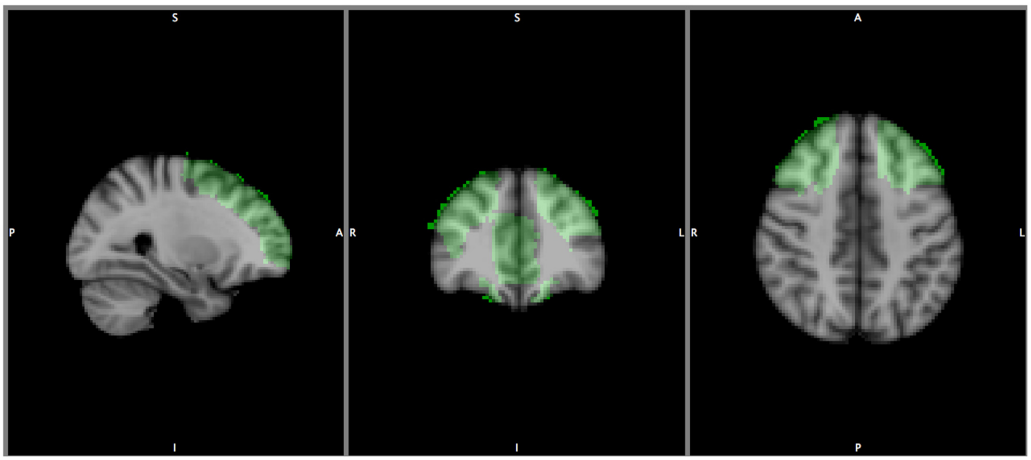

FIGURE 1 | Represents the areas of the inhibitory circuitry.

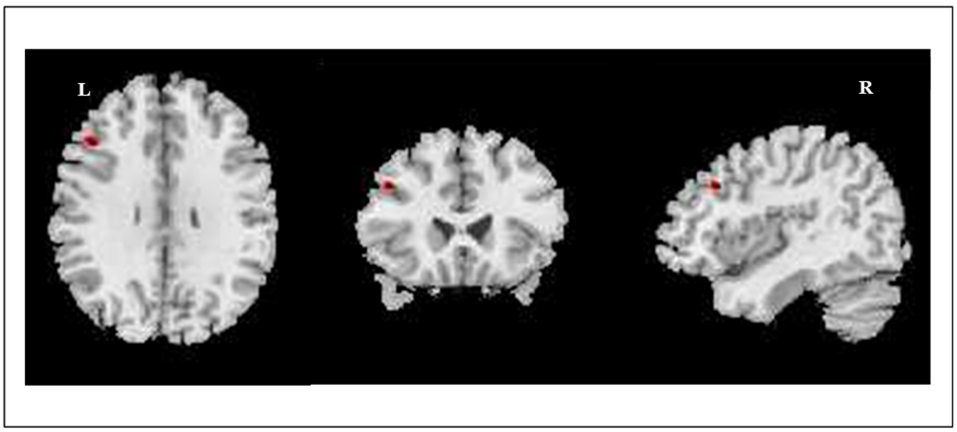

FIGURE 2 | Image illustrates the regions where significant differences in GM densities (peak-level) were observed between BDs and AACs. BDs > AACs. Left middle frontal gyrus, MNI coordinates: –45, 24, 33; $K = 315$, $p < 0.0001$. Voxel size: 1.5 mm^3.

cluster size > 29). *Post hoc* tests revealed that BDs males displayed higher GM densities than AACs males in the left middle frontal gyrus (MNI coordinates: −44,26,33; $K = 333$, $z = 3.86$, $p < 0.001$ uncorrected); and BDs females displayed higher GM densities in the left middle frontal gyrus (MNI coordinates: −38, 58, 20; $K = 40$, $z = 3.44$, $p < 0.001$ uncorrected) when compared to AACs females.

No group differences were observed for white matter and gray matter densities between BDs and AACs (see Supplementary Table 1).

Correlations

Pearson correlations within the BD group revealed positive associations between the left middle frontal gyrus GM densities and the self-control subscale of the BIS ($r = 0.45$, $p < 0.05$ – see **Figure 3**). No significant correlations between GM densities and the BIS sub-factor self-control were observed in the AAC group. Finally, no significant correlations between GM densities and alcohol-related measures were observed in the BD group (see Supplementary Table 2).

DISCUSSION

In this VBM study, we used a ROI-based analysis of brain regions involved in the inhibitory circuitry and self-regulatory processes in a group of 20 BDs and 16 AACs. Overall we found increased GM densities in the left middle frontal gyrus of BDs when compared with their AACs counterparts. Additionally, we explored the associations between GM densities in the left middle frontal gyrus and BIS total scale and subscales scores. We found positive correlations between GM densities in the left middle frontal gyrus and scores in the BIS subscale self-control only in the BD group, that were not observed in the AAC group. Furthermore, no associations between GM densities and alcohol-related measures were observed in the BD group.

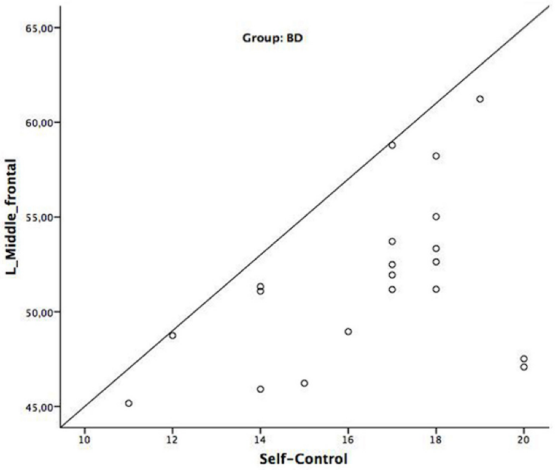

FIGURE 3 | Image shows the positive associations between brain data (GM densities) and BIS (self-control) scores in the BD group.

Increased GM densities in the middle frontal gyrus are consistent with previous studies (Squeglia et al., 2012; Doallo et al., 2014). In particular, thicker frontal areas were observed in female BDs (age range: 16–19 years old) in comparison with non-BDs females (Squeglia et al., 2012). Additionally, Doallo et al. (2014) found higher GM densities in the DLPFC of young BDs (age range: 20–24), with similar ages to our BD group (age range: 18–23), when compared to light consumers. These authors interpreted their findings as a consequence of high alcohol intake during important developmental periods such as adolescence and early adulthood. However, they also highlighted that these abnormalities could also be considered as a risk factor for heavy substance use (i.e., due to diminished efficiency in information processing and problem solving abilities, in addition to decreased ability in weighting risks vs. benefits), rather than a consequence of BD (Squeglia et al., 2012; Doallo et al., 2014).

Nevertheless, structural magnetic neuroimaging studies have produced inconsistent results regarding the effect of alcohol exposure in the volume and gray matter density of the frontal cortex, with studies showing no differences of decreased volumes or density in the alcohol consumers. In fact, Wilson et al. (2015) and Gropper et al. (2016) reported a deleterious effect of alcohol exposure in the ventral diencephalon, middle temporal gyrus and hippocampus, yet no significant effects on the frontal and parietal cortices. Other contradictory evidence was documented by a study using Orientation Dispersion Imaging, a method that assesses microstructural features directly related to neuronal morphology (Morris et al., 2017). In this study, the authors documented diminished dendritic complexity and organization in the DLPFC in a BD cohort (mean age: 22 years), despite no significant correlation between these measures and alcohol use severity was observed, suggesting that these neuronal abnormalities in BDs were not possibly modulated by the high alcohol intake. Longitudinal studies have also documented decreased volume and cortical thickness of the middle frontal gyrus (Wilson et al., 2015; Squeglia et al., 2017) in young adolescents (age range: 12–18) prior to alcohol use onset, which was further associated with alcohol initiation and BD. These results suggested that premorbid characteristics such as a delay of GM growth, which is a part of the typical normative neurodevelopmental process, could be associated with the BD onset (Squeglia et al., 2014, 2017; Wilson et al., 2015).

Such inconsistencies among studies are likely due to the use of different methods to perform the morphometric analysis of brain structure and volume or density (e.g., Luciana et al., 2013), as well as different age groups and participants with different patterns of consumption. While some of the studies analyzed cortical thickness (Luciana et al., 2013; Squeglia et al., 2017), others evaluated volumes or densities (Doallo et al., 2014), which limit the generalization of the findings, as these measures are not directly comparable. In fact, volume seems to be more closely related to surface area than to cortical thickness. Surface area and cortical thickness fluctuate along the course of brain development but not necessarily following the same direction or rate of variance than volume or densities (Winkler et al., 2009, 2010; Tamnes et al., 2017). Finally, different age ranges are associated with distinct neurodevelopment periods and can therefore represent an additional confounding factor. Overall, our findings showed increased GM densities in the left middle frontal gyrus in BD (age range: 18–23), which are in line with previous studies using participants with the same age interval (Doallo et al., 2014). Moreover, no differences in the total gray and white matter volumes between the BDs and the AAC group were observed, which excluded the impact of factors that could interfere with brain morphometry such as oedema or dehydration.

While our study cannot account for understanding these prefrontal brain abnormalities as a risk factor or as due to the neurotoxic effects of alcohol consumption, the morphologic changes in regions associated with self-regulatory processes that we observed in our BD group, could be related with two different hypotheses. The first hypothesis suggests that our result could be related with a delayed or an abnormal timing of the GM growth. In fact, and as it has been suggested by longitudinal studies, a reduction of gray matter was associated to a delay of gray matter growth in a prospective study of BDs before alcohol initiation (Squeglia et al., 2014, 2017; Wilson et al., 2015). Abnormalities in the middle frontal gyrus have been frequently associated to difficulties in regulating behavior when facing failure and undercontrol, and prospectively predicting substance use (age range: 9–12 years) (Heitzeg et al., 2014). In fact, a positive association between GM densities in the left middle frontal gyrus and scores in the self-control subscale of the BIS was also found in our BD group, which is consistent with others (Cho et al., 2013). A second hypothesis is that the abnormalities in the left middle frontal gyrus could be secondary to alcohol misuse, in accordance with other evidence (Crews and Boettiger, 2009; Bava and Tapert, 2010; Koob, 2011).

Nevertheless, from this study design, we cannot extrapolate about the causes and/or consequences of the BD behavior, as the cross sectional nature of the study is an important limitation. Other limitations include the need of bigger sample

as necessary in order to increase the statistical power. The method of analysis (VBM) is an additional constraint. VBM is a fully automated method, as manual segmentation methods are considered the gold standard for structural neuroimaging studies. Finally, we could have had an additional control group including light or regular drinkers, in order to compare them with BDs and with the AACs. Future studies should take the advantage of longitudinal designs with more than two follow up assessments and the combination of morphometric, genetics and behavioral measures in order to disentangle whether structural abnormalities reflect vulnerability factors or consequences of high alcohol consumption.

CONCLUSION

This study suggests frontal GM abnormalities in BDs college students, which is likely to impact self-regulatory processes. The pattern of increased regional GM density suggests that developmental factors may contribute to brain alterations in BDs.

AUTHOR CONTRIBUTIONS

SS wrote the manuscript, collected data, preprocessed the data, carried out the statistical analysis, and helped with subject's recruitment and assessment. AS coordinated data acquisition, preprocessing and statistical analysis and collaborated in manuscript writing. PM helped with data preprocessing. OG collaborated in manuscript writing and AC designed the study, coordinated subject's recruitment and assessment and data acquisition, and collaborated in manuscript writing. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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College Binge Drinking Associated with Decreased Frontal Activation to Negative Emotional Distractors during Inhibitory Control

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The transition to college is associated with an increase in heavy episodic alcohol use, or binge drinking, during a time when the prefrontal cortex and prefrontal-limbic circuitry continue to mature. Traits associated with this immaturity, including impulsivity in emotional contexts, may contribute to risky and heavy episodic alcohol consumption. The current study used blood oxygen level dependent (BOLD) multiband functional magnetic resonance imaging (fMRI) to assess brain activation during a task that required participants to ignore background images with positive, negative, or neutral emotional valence while performing an inhibitory control task (Go-NoGo). Subjects were 23 college freshmen (seven male, 18–20 years) who engaged in a range of drinking behavior (past 3 months' binge episodes range = 0–19, mean = 4.6, total drinks consumed range = 0–104, mean = 32.0). Brain activation on inhibitory trials (NoGo) was contrasted between negative and neutral conditions and between positive and neutral conditions using non-parametric testing (5000 permutations) and cluster-based thresholding ($z = 2.3$), $p \leq 0.05$ corrected. Results showed that a higher recent incidence of binge drinking was significantly associated with decreased activation of dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), and anterior cingulate cortex (ACC), brain regions strongly implicated in executive functioning, during negative relative to neutral inhibitory trials. No significant associations between binge drinking and brain activation were observed for positive relative to neutral images. While task performance was not significantly associated with binge drinking in this sample, subjects with heavier recent binge drinking showed decreased recruitment of executive control regions under negative versus neutral distractor conditions. These findings suggest that in young adults with heavier recent binge drinking, processing of negative emotional images interferes more with inhibitory control neurocircuitry than in young adults who do not binge drink often. This pattern of altered frontal lobe activation associated with binge drinking may serve as an early marker of risk for future self-regulation deficits that could lead to problematic alcohol use. These findings underscore the importance of understanding the impact of emotion on cognitive control and associated brain functioning in binge drinking behaviors among young adults.

Keywords: fMRI, negative emotion, binge drinking, college students, DLPFC, ACC

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INTRODUCTION

The transition to college is often associated with an escalation in alcohol drinking (Schulenberg and Maggs, 2002), with college students surpassing similarly aged non-students in overall alcohol use and incidence of binge drinking (O'Malley and Johnston, 2002; Carter et al., 2010). Negative consequences associated with binge drinking in college populations include accidental deaths, injuries, assaults, unsafe sex, academic difficulties, and alcohol-related health problems (Hingson et al., 2005, 2006, 2009). Heavy alcohol consumption also is associated with alcohol abuse and dependence (Grant et al., 2009), as is an earlier onset of alcohol use (Hingson et al., 2006, 2009). Binge drinking among college students, coupled with vulnerability of the still-developing brain to the effects of alcohol, may augment the high rate of alcohol use disorders observed within this age group (NSDUH, 2016). Impulsivity, a trait subserved in part by the prefrontal cortex and prefrontal-limbic circuitry, is associated with heavy episodic alcohol consumption and may contribute to the increased rates of binge drinking observed during the transition to college (Nigg et al., 2006; Littlefield et al., 2010; Henges and Marczinski, 2012).

Magnetic resonance imaging (MRI) techniques have demonstrated that brain development continues at a rapid pace through adolescence and into early adulthood, with the majority of alterations occurring in prefrontal cortex (PFC) and in circuits connecting PFC to other brain regions (Sowell et al., 2001; Gogtay et al., 2004; Giorgio et al., 2010). Structural brain changes in PFC have even been detected in as short as a 6-month interval during the first year of college (Bennett and Baird, 2006). PFC development in adolescence and early adulthood is associated with improvements in response inhibition and reduced impulsivity (Johnstone et al., 2005; Durston and Casey, 2006; Jonkman, 2006; Rubia et al., 2007; Stevens et al., 2007). Protracted maturation of PFC and related circuits may therefore render emerging adults, ranging in age from 18 to 24 years, more prone than older individuals to impulsive, risky behaviors, including alcohol consumption and binge drinking (Spear, 2000; Steinberg, 2005; Van Duijvenvoorde et al., 2016). Binge drinking in this age group could in turn, further negatively impact inhibitory control (Sher et al., 1997; Weissenborn and Duka, 2003), given that ongoing plasticity associated with continued development may render PFC and associated functions more vulnerable to the neurotoxic effects of alcohol in younger drinkers (Hermens et al., 2013).

Structural MRI studies have reported increased gray matter volumes in ventral striatum (Howell et al., 2013) and thinner anterior cingulate cortex (ACC; Mashhoon et al., 2014) among college-aged binge drinkers compared to light drinkers, suggesting roles for both reward-processing and regulatory brain regions in binge drinking among youth. Effects of early heavy or binge alcohol use on brain function have been examined longitudinally using fMRI during Go-NoGo tasks, in which inhibitory control is assessed by requiring the suppression of a prepotent response to an infrequent "NoGo" cue in a stream of frequent "Go" cues. In a sample of 16–19-year-olds, lower VMPFC/ACC activation during NoGo trials was found to predict increased substance use and dependence symptoms 18 months later (Mahmood et al., 2013). Similarly, adolescents who later transitioned to heavy drinking were found to show reduced activation in frontal, parietal, subcortical and cerebellar regions during NoGo versus Go trials, relative to adolescents who remained non-drinkers at follow-up (Wetherill et al., 2013). A preliminary prospective study of young adult binge drinkers found correlations between maximum drinks per occasion, activation of a fronto-parietal network during successful inhibition in a Go-NoGo task, and self-reported impulsivity/compulsivity (Worhunsky et al., 2016). While a variety of brain regions have been implicated in altered inhibitory control in alcohol and substance users, a comprehensive review of neuroimaging studies of early alcohol and substance use and abuse reported PFC to be the brain region most frequently impacted by alcohol in youth (Silveri et al., 2016).

Impulsivity, or a lack of inhibitory control, is a broad psychological construct that has multiple sub-components, some of which have been found to be more relevant to drinking frequency, drinking quantity, or negative alcohol-related outcomes in college populations (Cyders et al., 2009). Specifically, among college freshmen who completed the UPPS-P impulsivity scale (Urgency, Premeditation, Perseverance, Sensation Seeking - Positive Urgency; Lynam et al., 2006; Cyders and Smith, 2007, 2008), sensation-seeking was associated with drinking frequency, while positive urgency, or the tendency to act rashly during positive emotions, was related to quantity of drinks consumed per occasion and to negative alcohol-related outcomes (Cyders et al., 2009). Furthermore, negative urgency, or the tendency to act rashly during negative emotions, more than other impulsivity factors, has been found to elevate risk for alcohol abuse in adult populations (Fischer et al., 2004; Verdejo-Garcia et al., 2007; Dick et al., 2011), and also has been linked to poorer Go-NoGo task performance (Dick et al., 2011). Commission errors on the Go-NoGo task have also been linked to binge drinking behaviors among college students (Nigg et al., 2006; Henges and Marczinski, 2012). However, only moderate associations have been found between performance of inhibitory control tasks and self-reported impulsivity (Dick et al., 2011). Use of an emotional Go-NoGo protocol, in which impulsive errors must be avoided in the context of negative and positive emotionally valenced stimuli, may provide a unique, and potentially more sensitive behavioral measure of negative and positive urgency.

The current study used blood oxygen level dependent (BOLD) fMRI to assess brain activation in a sample of 18–19 year-old college freshmen performing an emotional Go-NoGo task, in which participants avoid impulsive errors while ignoring background images selected to elicit negative and positive emotions, as compared to emotionally neutral images. Prior research in healthy young adults has found associations between self-reported impulsivity and activation of dorsomedial PFC (DMPFC) and orbitofrontal cortex (OFC), and between risk taking and activation of OFC and ventromedial PFC (VMPFC) during performance of a Go-NoGo task with neutral or aversive image distractors (Brown et al., 2015). However, specific relationships between inhibitory control in emotional contexts and drinking behaviors in young adults have not yet been studied

using fMRI, nor have the neural correlates of the role of positive emotional distraction during inhibitory control been examined.

Whole brain analyses were performed in order to identify brain regions recruited in response to the presence of distracting emotional information during performance of an inhibitory control task. It was hypothesized that emotional relative to neutral distractors would recruit limbic brain areas; specifically, it was anticipated that amygdala would activate in response to negative distractors and ventral striatum would activate in response to positive distractors. Furthermore, inhibitory control efforts during emotional versus neutral background conditions were predicted to require additional executive control and thus elicit additional activation in PFC regulatory regions. A second analysis was conducted to determine whether recruitment of PFC and limbic brain areas during negative versus neutral and positive versus neutral contrasts varied as a function of binge drinking behavior. Given prior evidence of links between heavy drinking and impulsivity in emotional contexts, it was hypothesized that positive associations would be observed between activation of limbic regions during emotional versus neutral inhibitory trials and binge drinking. It also was predicted that a higher incidence of binge drinking would be associated with a failure to recruit executive regions in response to increased inhibitory demands on emotional versus neutral inhibitory trials.

MATERIALS AND METHODS

Participants

Participants included 23 healthy college freshmen (seven male, ages 18–20 years) currently enrolled in a 4-year college program. Alcohol consumption in the prior 3 months was assessed via a Timeline Follow Back interview. Binges were defined as 4+ (female) or 5+ (male) standard drinks in one drinking occasion. Demographic and alcohol consumption measures are summarized in **Table 1**. Subjects were screened and excluded for more than ten lifetime uses of marijuana, more than 25 lifetime uses of tobacco products or any period of regular use (weekly or more frequent use), and any use of illicit drugs other than marijuana. Participants completed urine screening prior to scanning to rule out current psychoactive substance use and pregnancy. Participants were free of neurological disorders, prior head trauma with loss of consciousness, and MRI contraindications such as metal in the body. Participants were required to be alcohol abstinent 48 h prior to scanning. IQ was assessed via the Weschler Abbreviated Scale of Intelligence (WASI, 2 subscale). In a brief family history epidemiology interview, five subjects endorsed a positive family history of alcohol or substance use disorder (father, $n = 2$, or grandparent, $n = 3$).

The Structured Clinical Interview for DSM-IV (SCID) was used to assess presence or absence of psychiatric disorders. Based on this interview, three participants met criteria for past major depressive disorder (>6 months prior to participation). One participant met criteria for past social phobia (public speaking). One participant met criteria for current social phobia, generalized anxiety disorder, and bulimia nervosa. Two participants met criteria for an alcohol use disorder, which is unsurprising given efforts to recruit heavy drinkers. All participants provided written informed consent prior to participation. This study was approved by the Partners Human Research Committee for McLean Hospital.

TABLE 1 | Demographic and alcohol use measures.

Measures	Range	Mean	Standard deviation
Age	18.05 – 20.02	18.8	0.4
IQ	93 – 133	115.3	10.3
Number of drinks (past 3 mo)	0 – 103.5	33.8	35.6
Number of binges (past 3 mo)	0 – 19	5.0	6.1
Days since last use[a]	3 – 66	17.7	17.8
Days since last binge[b]	5 – 68	21.0	20.0

Data represent the range, mean and standard deviation from the total sample ($n = 23$), except: [a]Estimates reflect data from individuals who reported a minimum of one drink within the past 90 days, $n = 19$; [b]Estimates reflect data from individuals who reported a minimum of one binge within the past 90 days, $n = 14$.

Clinical and Impulsivity Measures

General functioning, including depression and anxiety levels, were assessed via the Counseling Center Assessment of Psychological Symptoms (C-CAPS), a 62-item multi-dimensional mental health assessment tool designed for use in college populations, which includes the following subscales: Depression, Generalized Anxiety, Social Anxiety, Academic Distress, Eating Concerns, Family Distress, Hostility, and Alcohol and Substance Use (C-CAPS, 2011). Problematic alcohol use was assessed via the Alcohol Use Disorder Identification Test (AUDIT), a 10-item screening questionnaire that queries quantity and frequency of alcohol use, binge drinking, dependence symptoms, and alcohol-related problems (Saunders et al., 1993; Babor and Higgins-Biddle, 2000). Self-reported impulsivity was assessed using two survey measures. The Barrett Impulsiveness Scale (BIS-11) provides measures of Attention Impulsivity, Motor Impulsivity and Non-planning Impulsivity (Patton et al., 1995) and the UPPS-P assesses five personality pathways to impulsive behavior: Negative Urgency, (lack of) Premeditation, (lack of) Perseverance, Sensation Seeking, and Positive Urgency (Cyders and Smith, 2007). Survey measures are summarized in **Table 2**.

Go-NoGo Task

During fMRI, subjects performed a task that combines a Go-NoGo task with emotionally arousing background images. This task was adapted from the behavioral task described in Cohen-Gilbert and Thomas (2013) for use with fMRI. As in the prior study, 360 background images were selected from the normatively rated *International Affective Picture System (IAPS)* (Lang et al., 2008) based on valence ratings: 120 highly positive, 120 highly negative, and 120 neutral. Forty images from each of the three valence categories were used to create 120 scrambled images that then served as non-emotional backgrounds that had no discernible image content. Images were presented in blocks of 20 trials of the same background type (positive,

TABLE 2 | Clinical and impulsivity measures.

Measures		Range	Mean	Standard deviation
AUDIT		0 – 17	6.1	5.1
C-CAPS	Depression	0 – 27	10.1	7.3
	Social anxiety	1 – 18	10.9	5.0
	Generalized anxiety	1 – 15	6.0	4.4
	Substance/Alcohol use	0 – 18	6.1	5.0
BIS-11	Attention	12 – 24	16.0	3.1
	Motor	16 – 27	21.6	2.7
	Non-planning	19 – 35	24.1	4.4
	Total	47 – 78	61.7	7.5
UPPS-P	Negative urgency	16 – 45	29.1	7.0
	(Lack of) Premeditation	15 – 34	21.9	5.0
	(Lack of) Perseverance	13 – 31	20.7	4.7
	Sensation seeking	21 – 45	32.3	5.3
	Positive urgency	21 – 46	30.8	7.5

Data represent range, means and standard deviations from the total sample (n = 23).

TABLE 3 | Go-NoGo task performance.

Measures	Positive	Negative	Neutral	Scrambled
NoGo accuracy (%)	72.5 (17.6)	72.2 (18.9)	73.6 (15.9)	76.2 (16.3)
Go accuracy (%)	98.4 (2.5)	98.4 (2.2)	98.5 (2.6)	98.7 (2.4)
Go reaction time (ms)	362.9 (32.5)	366.8 (32.2)	358.3 (29.9)	358.9 (28.7)

Data represent the means and (standard deviations) from the total sample (n = 23).

negative, neutral or scrambled). Letter stimuli were presented sequentially in a small white box at the center of the background image. Subjects were instructed to respond (button press with thumb) as quickly as possible to every letter except for a target: 'X'. Xs appeared on 25% of the trials such that participants acquired a prepotent tendency to press and had to actively inhibit responding during NoGo trials. The task was presented via E-prime software synched to the MR scanner via RF pulse. The paradigm used a rapid event-related design, with each trial lasting 1500 ms, including 500 ms of fixation, followed by 350 ms of the background image presented alone, and then 650 ms in which the letter cue and background image were on the screen together. Task jitter was created via distribution of target (NoGo) trials within the stream of Go trials, which were treated as an implicit baseline and not separately modeled (Garavan et al., 2002). Trial order (Go versus NoGo) was optimized for fMRI design efficiency using the Optseq2 program[1]. The task consisted 480 total trials presented in three runs (160 trials/run). This rapid stimulus presentation was used to maintain high levels of inhibitory demand and prevent ceiling effects in this high functioning young adult sample. Task performance measures including accuracy on NoGo trials, accuracy on Go trials, and reaction time on correct Go trials (**Table 3**), were recorded using an MRI-compatible fiber optic response pad (fORP). NoGo trials were randomly distributed throughout each run with the constraint that each 20-trial block contained five NoGo trials.

[1]http://surfer.nmr.mgh.harvard.edu/optseq/

Acquisition and Preprocessing of MRI Data

Data were acquired on a Siemens TIM Trio 3 Tesla scanner (Erlangen, Germany) with a 32-channel head coil. High-resolution structural images were collected using a T1-weighted multiecho Multiplanar Rapidly Acquired Gradient-Echo (ME-MPRAGE) 3D sequence in 4 echoes (TE = 1.64/3.5/5.36/7.22 ms, TR = 2.1 s, TI = 1.1 s, FA = 12°, 176 slices, 1 × 1 × 1.3 mm voxel, acquisition time = 5 min) for registration of functional images to standard space. Whole-brain multiband gradient echo echo-planar imaging (EPI) with BOLD contrast was used to collect fMRI data in three runs (5:13 min/run) (Feinberg et al., 2010). Images were acquired in 54 interleaved, oblique slices (TR/TE/FA = 750 ms/30 ms/52°, FOV = 220, voxel size: 2.8 mm × 2.8 mm × 2.8 mm, multiband = 6, GRAPPA = 2). A fieldmap was acquired at the same resolution and slice locations to allow for offline correction of field inhomogeneities (TR = 1000, TE = 10/12.46 ms, FA = 90°, 2:44 min). Prior to statistical analyses, preprocessing was performed on raw functional images using the FMRIB Software Library (FSL) software v5.0.10 (Smith et al., 2004) including: motion correction, slice-timing correction, non-brain removal, spatial smoothing (FWHM 6mm Gaussian kernel), and grand-mean intensity normalization of the 4D dataset by a single multiplicative factor. Runs began with a 30 s rest block (40 volumes) before task onset, which was removed prior to the current analysis, thus no additional volumes were removed to allow for signal equilibration. ICA AROMA, an independent component analysis-based denoising tool, was then used to remove motion-related components and other components of no interest (e.g., respiration and artifacts) from the fMRI data[2] (Pruim et al., 2015). No subjects were removed from the analysis due to excessive motion in the scanner. Subject motion was minimal and did not exceed 3 mm (1 voxel) with the exception of a single movement spike slightly above this threshold. Denoised data were then temporally filtered using a Gaussian-weighted least-squares straight line fit with a highpass cutoff = 100 s and underwent fieldmap based distortion correction. fMRI data were registered to MNI152 standard space by first registering the data to the high-resolution structural image using boundary-based registration (BBR) and then transforming into MNI stereotaxic space using the first registration step combined with the registration information from registering the high-resolution structural image to MNI152 standard space, which was done using FNIRT.

Statistical Analyses

Analysis of Task Performance and Survey Data

Performance data were analyzed using repeated-measures analyses of variance (ANOVAs) and paired samples *t*-tests. Correlations were conducted to test for relationships between drinking measures, survey measures, and task performance using Pearson's correlations. These statistical analyses were carried out using SPSS (version 23.0).

[2]https://github.com/rhr-pruim/ICA-AROMA

Analysis of fMRI Data

FEAT v6.00 was used to conduct hierarchical voxel-wise general linear model (GLM) analyses. First-level modeling was conducted for each of the three runs for each participant. NoGo trials within the four background conditions (positive, negative, neutral, scrambled) were each modeled as separate regressors, convolved with a gamma function. Temporal derivatives were also included in the model. Go trials were treated as an implicit baseline of tonic, task-related activity and were not modeled separately. Contrasts of parameter estimates (COPE) were calculated between positive and neutral conditions and between negative and neutral conditions. The scrambled condition was not examined in the current analysis due to a lack of specific hypotheses regarding brain activation for this condition in relation to alcohol use. For each COPE, the three task runs were combined for each participant using a second-level fixed effects GLM to create averaged COPE maps.

In order to identify brain regions recruited in response to increased emotional distraction during inhibitory control, a third-level whole brain voxel-wise single-group GLM was conducted across all participants for each of the (second-level) contrasts of interest. Estimation and inference were done using FSL Randomise, with non-parametric permutation testing (5000 permutations) and cluster-based thresholding ($z = 2.3$). Results of the whole-brain analysis are shown for a significance level of $p \leq 0.05$, corrected for family wise error. Use of non-parametric permutation testing obviates any concerns related to inflated false-positive rates in fMRI inference for spatial extent that were described in a recent report (Eklund et al., 2016).

In order to test our hypotheses related to associations of prefrontal and limbic brain regions with recent binge drinking, a second group-level GLM was conducted for each contrast of interest in which the number of binges in the past 3 months was included as a predictor. A mask encompassing the brain regions hypothesized to be most impacted by binge drinking – PFC, amygdala, and nucleus accumbens – was applied for this analysis. The mask was constructed by combining the frontal cortex region, defined by MNI Structural Atlas, with the bilateral amygdala and bilateral nucleus accumbens regions from the Harvard-Oxford Subcortical Structure Atlas. Because binge drinking varied between males and females within this sample and because biological sex may influence the neurological impact of alcohol use, sex was included as a covariate of non-interest. Estimation and inference were performed using FSL Randomise (5000 permutations) with cluster-based thresholding ($z = 2.3$). Results are shown for a significance level of $p \leq 0.05$, corrected for family wise error.

RESULTS

Behavioral, Impulsivity and Clinical Results

Repeated-measures ANOVAs were used to examine the impact of background distractor images (positive, negative, neutral or scrambled) on task performance measures: accuracy on NoGo trials, accuracy on Go trials, and reaction time on correct Go trials. These analyses showed no significant effects of background on accuracy on either Go or NoGo trials. A significant main effect of background on reaction time was observed, $F(3,66) = 3.98$, $p = 0.011$. *Post hoc* paired samples *t*-tests revealed significantly longer reaction times on negative trials relative to neutral trials, $t(22) = 3.45$, $p = 0.002$, and scrambled trials, $t(22) = 2.85$, $p = 0.009$. Task performance measures were not significantly correlated with past 3 months' binges or number of drinks or with drinking outcome measures (AUDIT and CCAPS substance and alcohol use subscale). Likewise, task performance was not significantly associated with self-reported impulsivity (BIS-11 and UPPS-P) and no significant correlations were found between drinking measures and self-reported impulsivity. As would be expected, AUDIT scores were significantly positively related to past 3 months' binges, $r = 0.701$, $p < 0.001$, and past 3 months' drinks, $r = 0.757$, $p < 0.001$. Similarly, the alcohol and substance use problems score on the C-CAPS was significantly related to past 3 months' binges, $r = 0.643$, $p = 0.001$, and drinks, $r = 0.772$, $p < 0.001$.

fMRI Results

Emotion Related Activation during Inhibitory Control

In order to identify brain regions recruited in response to the addition of task-irrelevant emotional information during conditions demanding inhibitory control (NoGo trials), contrasts of negative versus neutral and positive versus neutral conditions were first examined in the full sample.

Negative versus neutral background conditions

A contrast of negative and neutral NoGo trials revealed a single spatially extended cluster comprised of multiple brain regions that showed greater activation during negative versus neutral background conditions. Regions within the cluster included bilateral OFC (**Figures 1A,B**) and amygdala (**Figure 1A**), as well as a large left-lateralized prefrontal area comprising left Inferior Frontal Gyrus (IFG), Middle Frontal Gyrus (MFG), precentral gyrus, and frontal pole (**Figure 1B**). In addition to PFC and limbic regions, activation was observed bilaterally in the temporal pole and inferior temporal gyrus, and in the right superior temporal gyrus. Activation also was observed in many visual processing regions, including temporal and occipital fusiform cortex, lateral occipital cortex and occipital pole, and in the cerebellum. A summary of the anatomical locations of local maxima for this cluster is provided in **Table 4**. No significant regions of activation were revealed in the neutral > negative contrast.

Positive versus neutral background conditions

The positive versus neutral contrast did not reveal any PFC regions that were significantly activated in positive relative to neutral distractor conditions. Furthermore, contrary to one of the study hypotheses, no activation was observed in the ventral striatum on this contrast. Activated regions (**Figure 2**) included: inferior temporal gyrus, temporal and occipital fusiform cortex, lateral occipital cortex, occipital pole, cuneus, precuneus, and

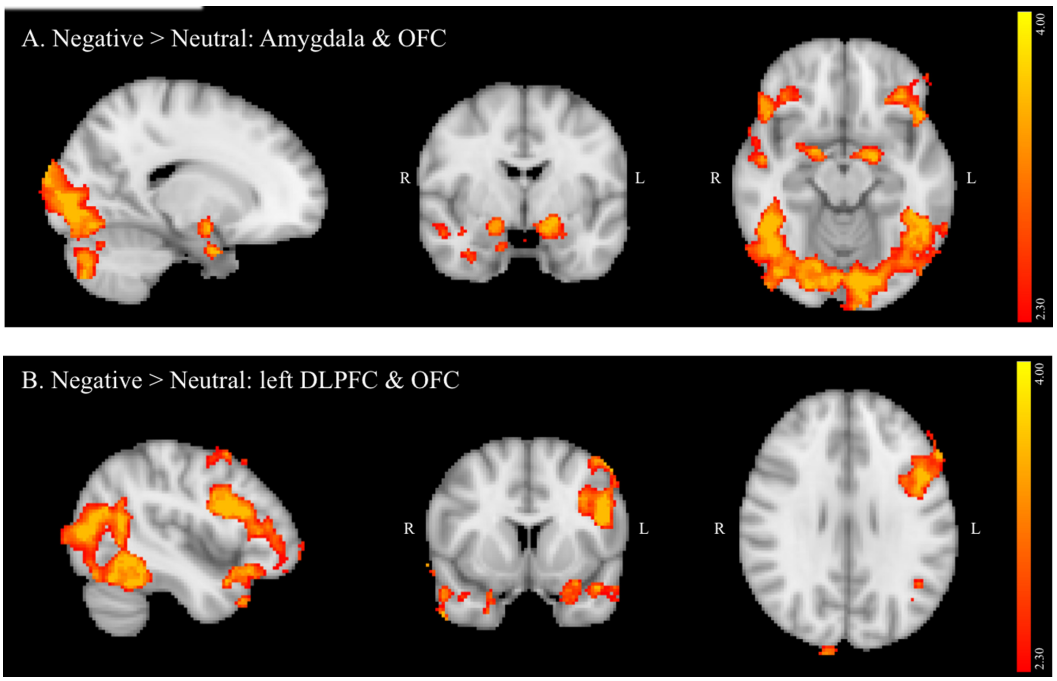


FIGURE 1 | (A,B) Region showing greater activation to negative versus neutral background conditions during NoGo trials. MNI co-ordinates: **(A)** $x = 17$, $y = -4$, $z = -15$; **(B)** $x = -45$, $y = 10$, $z = 28$.

TABLE 4 | Local maxima of activation for all participants: negative > neutral contrast.

Region	Side	Volume (mm^3)	z-max df = 22	MNI Coordinates		
				x	*y*	*z*
Extended region including:		49166				
Frontal pole	L		3.54	−54	44	−12
Frontal orbital cortex/Frontal pole	R		3.54	38	34	−22
Inferior frontal gyrus	L		3.54	−46	34	12
Temporal pole	R		3.54	44	26	−34
Temporal pole/Frontal orbital cortex	L		3.54	−28	18	−30
Temporal pole	R		3.54	54	10	−40
Parahippocampal gyrus/Amygdala	R		3.54	20	0	−30
Amygdala	R		3.54	20	−2	16
Temporal fusiform cortex	R		3.54	36	−6	−32
Cerebellum	R		3.54	36	−76	−52

cerebellum. A summary of the anatomical locations of local maxima for this cluster is provided in **Table 5**. No significant regions of activation were revealed in the neutral > positive contrast.

Binge Drinking Related Activation

For the negative > neutral contrast, a single large cluster of activation comprised of multiple brain regions was significantly negatively correlated with past 3 months' binges. Areas within the cluster included right dorsolateral PFC (DLPFC) and dorsomedial PFC (DMPFC, **Figure 3A**), including MFG and superior frontal gyrus (SFG) and a relatively small region of the juxtapositional lobule cortex (formerly pre-motor cortex). The cluster also included bilateral ACC (**Figure 3B**) and bilateral paracingulate cortex. **Figure 3C** depicts the negative linear relationship between strength of activation within this cluster and number of past 3 months' binges.

DISCUSSION

Drinking potentiates impulsive actions, particularly during emotion-laden circumstances, which may in turn lead to

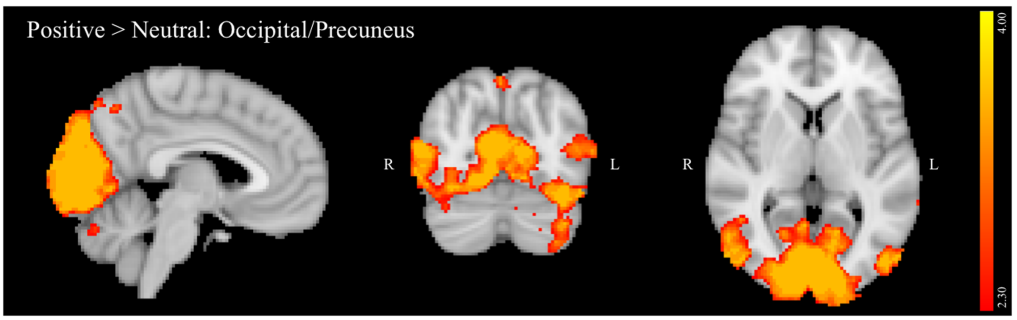


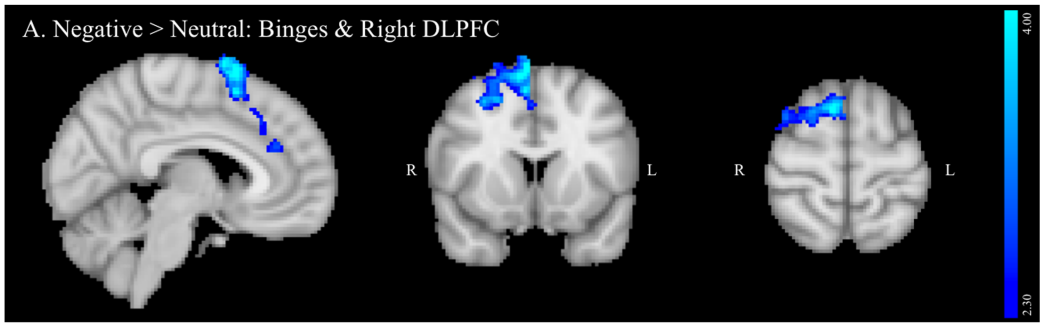
FIGURE 2 | Region showing greater activation to positive versus neutral background conditions during NoGo trials. MNI co-ordinates: $x = 5$, $y = -71$, $z = 5$.

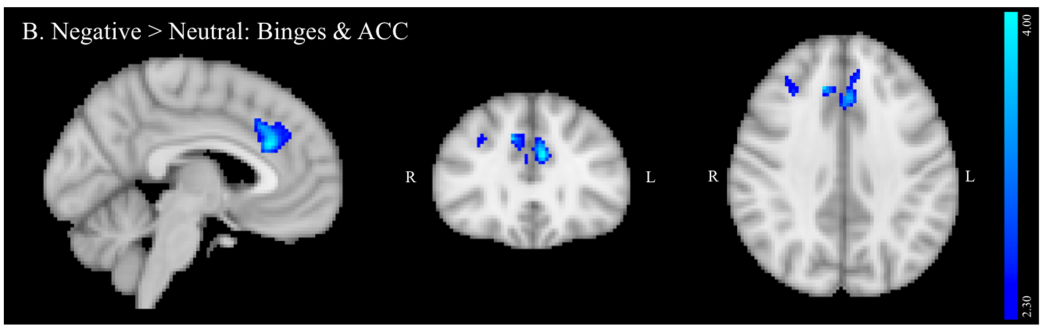
TABLE 5 | Local maxima for all participants: positive > neutral contrast.

Region	Side	Volume (mm^3)	z-max df = 22	MNI coordinates		
				x	*y*	*z*
Extended region including:		43086				
Inferior temporal gyrus/Temporal Occipital fusiform cortex/Cerebellum	R		3.54	48	−46	−30
Cerebellum	L		3.54	−38	−70	−40
Precuneous cortex	B		3.54	2	−74	54
Cerebellum	R		3.24	16	−78	−40
Lateral occipital cortex	L		3.54	−48	−86	2

continued drinking to binge levels. Such behaviors have significant and lasting deleterious effects on brain regions critical to cognitive and emotional regulation, particularly in youth. The current study sample consisted of college freshmen who represented a continuum of drinking that ranged from not yet initiated through meeting criteria for alcohol use disorder. In this group, activation of DLPFC, DMPFC and ACC during a response inhibition task with negative emotion-based distractors was found to decrease with greater recent heavy episodic alcohol use. This reduced activation may reflect a failure to bring regulatory brain regions online when negative emotional distractors elevate cognitive control demands. In other words, with increased binge drinking, task-irrelevant negatively valenced information increasingly damps down recruitment of brain regions implicated in executive control and error monitoring (Carter et al., 1998; Smith and Jonides, 1999; Van Veen and Carter, 2002; Ridderinkhof et al., 2004). Binge-related activation effects were specific only to the negatively valenced distractor condition, as no relationship to binge consumption was evident for activation during exposure to positively valenced distractors.

In the full sample, though not specifically related to binge drinking, negative relative to neutral distractor conditions also significantly recruited amygdala, OFC, and left DLPFC (IFG and MFG) during NoGo trials. Given that the amygdala has been reliably associated with threat monitoring and processing of negative emotion (LeDoux, 2003), activation in this region suggests that negatively valenced background images effectively elicited negative emotion in the context of concurrent inhibitory control despite instructions to ignore image content. Increased activation of DLPFC and OFC on negative versus neutral NoGo trials supports the hypothesis that impulse control becomes more challenging in the context of these negative distractors, requiring increased recruitment of regions implicated in successful response inhibition (Spinella, 2004). Furthermore, lateralization of the observed DLPFC activation aligns with studies suggesting that left PFC is particularly crucial in top-down regulation of negative emotion (Bruder et al., 2017). Current findings also are congruent with a meta-analysis of tasks probing the interaction of emotion and cognitive control, which found that task irrelevant emotion consistently recruited clusters in SFG, MFG and IFG, and amygdala, though this analysis did not differentiate between valence or modality of emotional distractors (Cromheeke and Mueller, 2014). Recruitment of visual processing areas by the current task, including occipital pole, lateral occipital, and fusiform cortices in both negative versus neutral and positive versus neutral contrasts in the current study likely reflects increased visual processing of the emotional images due to their higher salience relative to neutral background images. In contrast to negative distractors, positive distractors failed to elicit significant recruitment of predicted limbic and PFC regions. The absence of ventral striatum activation may reflect that positively valenced images in the current study were not rewarding *per se,* since this region is most reliably implicated in the processing of reward (Knutson et al., 2001). Examining the impact of these stimuli during the context of a challenging and potentially frustrating task – and during inhibitory trials in particular – may have





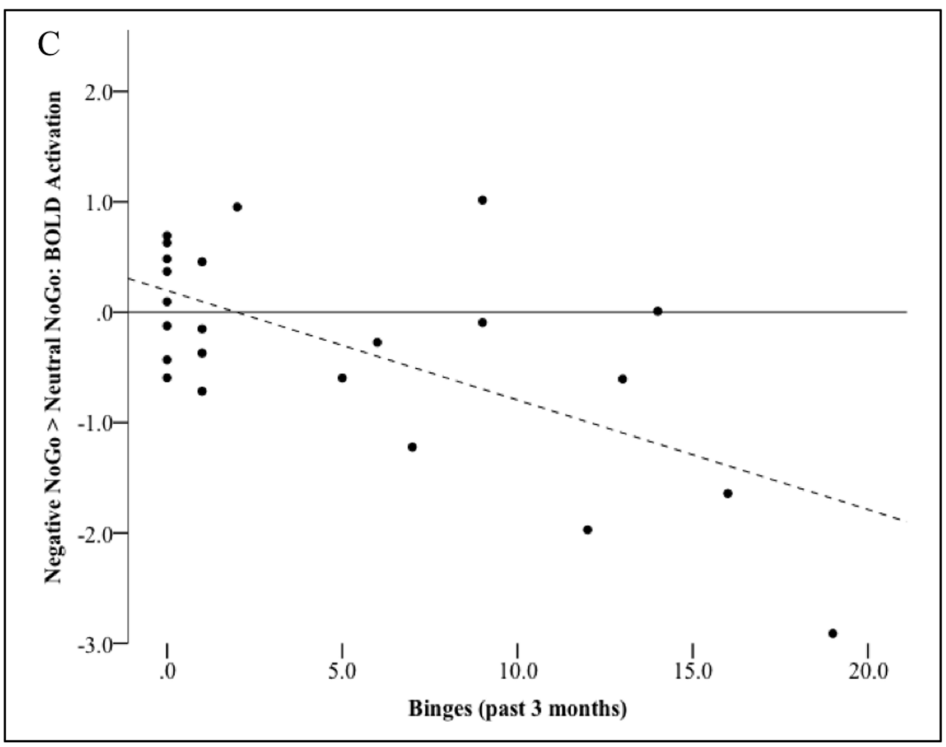


FIGURE 3 | (A–C) Region negatively associated with number of binges (past 3 months) in the negative NoGo versus neutral NoGo contrast. MNI co-ordinates: **(A)** $x = 6$, $y = 12$, $z = 63$; **(B)** $x = -5$, $y = 30$, $z = 36$; **(C)** Scatterplot of activation within this region (negative NoGo versus neutral NoGo contrast) versus number of binges (past 3 months).

further reduced activation of ventral striatum. Absence of PFC activation further suggests that positive images may have been less effective distractors, given the lack of an impact on inhibitory control demands. This may, in turn, inform why binge drinking did not predict activation on the positive versus neutral contrast.

With regard to overall task performance, as in Cohen-Gilbert and Thomas (2013), neither positive nor negative

emotional images impacted accuracy on Go or NoGo trials in this task, however, slower response times were observed on negative relative to neutral trials. This slowed responding suggests that negative images were more salient than non-emotional distractors, pulling attention away from the assigned inhibitory control task. Recruitment of PFC regions in response to negative versus neutral, but not positive versus neutral distractors, further supports the possibility that negative image distractors in this task pose a greater challenge to cognitive control. Finally, brain activation differences associated with binge drinking on the negative versus neutral contrast were observed in the absence of effects on task performance, as drinking measures were not significantly associated with accuracy or reaction time measures. The reduced impact of positive distractors on performance may also contribute to the absence of the hypothesized impact of binge drinking on frontal and limbic brain activation during positive NoGo trials.

Elevated impulsivity has been tied to increased alcohol use and heavy episodic alcohol consumption among college students (Cyders et al., 2009) and the tendency toward rash action is further increased by alcohol consumption. However, despite prior research suggesting relationships between impulsivity and binge drinking (Nigg et al., 2006; Henges and Marczinski, 2012), no significant relationships between self-report or behavioral measures of impulsivity and drinking behavior were observed in the current study. Several factors may contribute to this. First, response inhibition has been found to serve as an incremental predictor of alcohol and substance use, but accounts for only a small amount of variance in outcomes (Nigg et al., 2006). Studies reporting relationships between survey or strictly behavioral measures of impulsivity and drinking behavior typically feature considerably larger sample sizes and thus have the power to detect more modest effects. Furthermore, a meta-analysis of commission errors on Go-NoGo tasks in substance users found evidence of deficits in alcohol dependent individuals, but not in heavy drinkers who did not meet criteria for dependence, suggesting the impact of alcohol on inhibitory control may be dose-dependent (Smith et al., 2014). There also is evidence that relationships between alcohol abuse and impulsivity are at least partly driven by common comorbid psychopathological symptoms (Whiteside and Lynam, 2003).

In previous work, relative to age-matched light drinkers, healthy college aged binge drinkers demonstrated no significant differences on clinical measures of depression, anxiety, impulsivity or emotional intelligence, or across multiple cognitive domains, with the exception of modestly lower verbal learning scores in binge drinkers (Sneider et al., 2013). In contrast, significant binge-related structural and neurochemical differences were observed, with the binge group exhibiting a thinner cortex (Mashhoon et al., 2014) and lower brain GABA metabolite levels (Silveri et al., 2014), both of which were specific to the frontal lobe. These multimodal results suggest that while the frontal cortex is differentially sensitive to binge versus light alcohol consumption, observed neurobiological alterations associated with binge drinking may not necessarily manifest as clinical symptoms or cognitive impairments. Results of the current study extend the current literature to include functional differences on an executive functioning task requiring PFC activation in the presence of negatively valenced stimuli, which was negatively linearly associated with increasing numbers of binges. Among a number of possible interpretations, altered neuroimaging measures may reflect acute neurotoxic effects of binge drinking, which could increase risk for future adverse outcomes (or resolve with age-related declines in problematic use, i.e., "maturing out"). Alternatively, given a clinically and cognitively healthy status, a neurobiological signature of binge drinking could reflect protective adaptations to chronic, intermittent alcohol exposure. A third possibility is a combination of these interpretations: that neurobiological adaptations protect the young brain from immediate functional impairment, while simultaneously increasing risk for future adverse outcomes. Similarly in this sample, the college freshmen participants were healthy, high-functioning individuals, many of whom did not begin heavy drinking until the transition to college. Thus, similar task performance despite the presence of brain activation differences may reflect successful compensatory mechanisms or brain differences in this type of cohort that may still be too subtle to manifest as a significant behavioral difference.

There are some minor limitations, besides a modest sample size, that should be considered when interpreting results. The task design, while minimally altering the behavioral task as presented outside the scanner, does not allow for separate modeling of Go trial activation, which prevents the direct comparison of inhibitory to non-inhibitory trials within each background condition. However, this trade-off allowed us to maintain high levels of inhibitory demand and prevent ceiling effects in this high functioning young adult sample, and equally important, allowed us to test our main hypotheses related to the impact of emotionally valenced stimuli on inhibitory processing. Drinking patterns varied between males and females in the study sample, with included males tending to be the light drinkers, due in part to heavier drinking males being excluded due to co-marijuana use. With a low number of males in the overall sample, the influence of sex differences could not be investigated. Sex likely plays a significant role in specifying relationships between emotion, response inhibition, binge drinking and neurobiology (Townshend and Duka, 2005; Nederkoorn et al., 2009) and will be important to study in future work.

CONCLUSION

The current study provides evidence that recent binge drinking is associated with decreased activation of key executive regions in the presence of negative, but not positive, emotional distractors during performance of an inhibitory control task. This reduced activation may indicate a failure to engage cognitive control regions to regulate emotion processing and

may serve as an early marker of risk for future self-regulation deficits associated with problematic alcohol use. These findings underscore the importance of understanding the impact of emotion on cognitive control and associated brain functioning in binge drinking behaviors among emerging adults. Brain activation patterns in this sample of college freshmen are being examined as potential predictors of subsequent alcohol consumption patterns throughout college, as follow-up assessments are being conducted yearly after the baseline imaging assessment. Longitudinal data will help elucidate whether activation differences are direct consequences of recent alcohol use or of a combination of related environmental and neurobiological factors. These data will also inform whether this neurobiological signature is predictive of longer-term problematic use.

ETHICS STATEMENT

The procedures reported in this study were approved by the Research Ethics Boards relevant to McLean Hospital, and were carried out in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

JC-G and MS conceptualized the study. EO and AS contributed to study recruitment, coordination and data collection. MR implemented the fMRI scanning sequence. JC-G, LN, JS, EO, and AS conducted data processing and analyses. JC-G, LN, and MS drafted the manuscript. All co-authors made contributions, edited and approved the final manuscript.

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