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Binge drinking in the adolescent and young brain, volume II

Edited by
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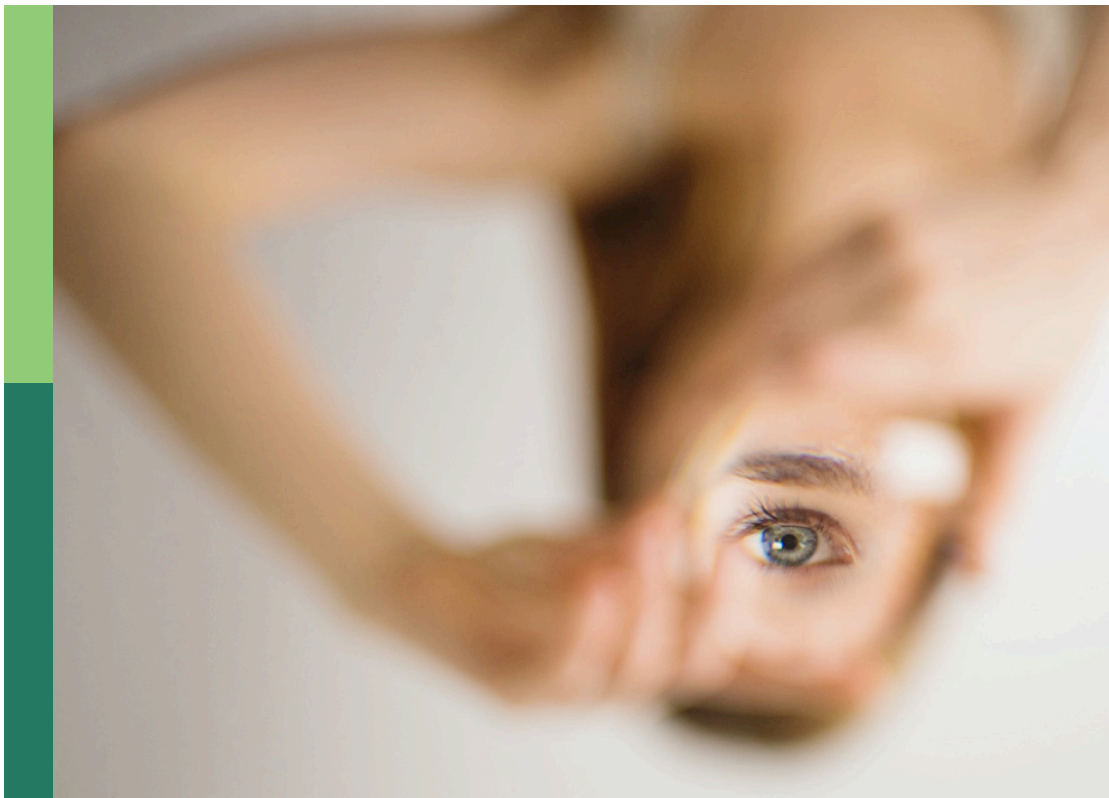

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Binge drinking in the adolescent and young brain, volume II

Topic editors

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Editorial: Binge drinking in the adolescent and young brain, volume II

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Editorial on the Research Topic
Binge drinking in the adolescent and young brain, volume II

Alcohol is by far the most widely used and consumed psychoactive agent in the world. According to current estimates, there are more than 2.4 million active consumers worldwide (about one third of the world's population; Griswold et al., 2018). Almost all societies that consume alcohol show, in turn, related physical, social, and psychological problems (Babor et al., 2022). In this sense, alcohol misuse is recognized as being responsible for 3 million fatalities every year-around 4% of all deaths globally (World Health Organization, 2018). This percentage markedly increases in the American and European youth, where alcohol is associated with nearly three in 10 deaths in people aged 15–29 years (World Health Organization, 2011).

Adolescence and young adulthood are periods of vulnerability in which many psychiatric disorders such as anxiety, depression or substance abuse manifest for the first time (Paus et al., 2008; Hawkins, 2009). In addition, significant maturational changes take place on the brain during this crucial developmental period, which is considered to last up to 24 years of age (Sawyer et al., 2018). The ongoing neuromaturation seems to involve greater vulnerability–in comparison to adulthood- to disruptive events in the brain such as binge drinking (BD; Spear, 2016; Chung et al., 2018). This pattern of consumption is commonly defined as the consumption of five or more standard drinks (four or more for females) in about 2 h on at least 1 day in the past month (National Institute of Alcohol Abuse and Alcoholism, 2020; Substance Abuse and Mental Health Services Administration, 2022). It constitutes a special concern for this population, as it has been associated with structural and functional impairments in still-maturing regions (e.g., the prefrontal cortex; Cservenka and Brumback, 2017; Lees et al., 2019; Pérez-García et al., 2022) and neuropsychological and neurofunctional deficits in executive functions (e.g., inhibitory control; Carbia et al., 2018; Almeida-Antunes et al., 2021; Seabra et al., 2023), together with a high risk of developing future alcohol addiction (Crews et al., 2016; Ventura-Cots et al., 2017; Tavolacci et al., 2019).

Collectively, the high prevalence of BD at this age along with its serious health problems has led to a significant increase in the number of investigations of this phenomenon, reaching a 7-fold increase between 2000 and 2018, with a slight decrease in the last few years (see Figure 1). Due to the growing interest concerning this pattern of heavy alcohol drinking, in 2019 we published the first volume of the Research Topic "*Binge drinking in the adolescent and young brain*" (López-Caneda et al., 2019). As showed in this issue, the evidence gathered from more than 20 published papers points to brain anomalies associated with BD at different levels: cellular (e.g., Nickell et al., 2017), structural (e.g., Sousa et al., 2017), functional (e.g., Folgueira-Ares et al., 2017), and cognitive (e.g., Gil-Hernández et al., 2017). In this second volume, we aim to update the latest research related to BD in order to bring the most recent findings that shed new light on this complex and challenging problem in alcohol research and society as a whole.

Firstly, with regard to preclinical studies, three articles included in this Research Topic employed animal models to explore the potential neurotoxic effects of BD. Specifically, the study by Sauton et al. longitudinally assessed decision-making capacities, memory and anxiety-like behavior as well as striatal dopaminergic signaling in male and female rats with a history of BD exposure. Voluntary BD intake was associated with weak decision-making abilities in males, impaired dopamine transmission in the core of the nucleus accumbens (NAcc) in females and increased motor impulsivity in both sexes, suggesting that chronic voluntary BD exposure may lead to a vicious cycle resulting in BD perpetuation and contributing to alcohol dependence vulnerability. In the same line, Jeanblanc et al. assessed the effect of different Baclofen (a GABAB receptor agonist used to treat alcohol use disorder) compounds on daily BD behavior and on dopamine release in the core of the NAcc in rats. Findings showed that both RS(±)-Baclofen and R(+)-Baclofen enantiomers were effective in reducing alcohol intake in animals with a BD-type pattern of alcohol self-administration, particularly in male rats, and that both forms of Baclofen decreased dopamine release in the NAcc in control animals-potentially reducing the rewarding properties of alcohol-, an effect that was lost in the BD group. The third preclinical study, conducted by Jimenez Chavez et al., concluded that BD history in adult and adolescent mice induces relatively few signs of alcohol withdrawal-related negative affect, although several design constraints were raised by the authors as potential causes of this unexpected outcome (e.g., space employed for behavioral testing, locations of the colony rooms in which mice consumed alcohol, small sample size for the replication study). Despite these limitations, authors observed that a 2-week BD history was sufficient to induce some signs of mild cognitive impairment -namely, impaired working and spatial memory-, particularly in adolescent-onset binge drinkers (BDs), which persist after 1 month following the cessation of drinking.

Several human studies encompassed in this Research Topic have also reported abnormal memory functioning associated with a BD pattern. Accordingly, Vinader-Caerols and Monleón described impair faces memory -assessed by the Wechsler Memory Scale (WMS-III; Wechsler, 2004) in male adolescent BDs in comparison with aged-matched abstainers and BDs with cannabis consumption. After receiving a risk dose of alcohol, female BDs performed better than abstainers in the scene memory test of the WMS-III, indicating a possible cognitive tolerance to acute alcohol intake in woman. Similarly, findings from Kang and Kim's study revealed that college students who engage in BD display difficulties with verbal and non-verbal memory-showing lower performance in the free recall condition of the California Verbal Learning Test and in the delayed recall condition of the Rey-Osterrieth Complex Figure Test-as well as deficits in cognitive control-as indicated by the lower number of categories completed in the Wisconsin Card Sorting Test. In another study assessing memory, Johnstone et al. investigated the negative emotional memory bias in the context of BD and problematic alcohol use and its potential association with coping motivations and depressive symptoms. Results support that engaging in BD as a coping mechanism for negative affect or experiencing elevated depression was indirectly related to more negative (self-referent) memory biases, particularly in females. In a related vein, in the study by Cortés-Tomás et al., coping with depressive moods also emerged as a significant factor in explaining risk to engage in BD in young females. In addition, positive expectancies toward alcohol and social and enhancement motives were also important determinants of the BD behavior.

In addition, two electrophysiological studies reported abnormal neural activity linked to memory processes in young with a BD pattern. Rodríguez Holguín et al. analyzed verbal memory during a verbal paired associates learning task using electroencephalography (EEG) and findings revealed that the old/new effect -i.e., larger amplitudes in event-related potentials for old (i.e., previously studied) items in comparison with new items- was absent in the BD relatively to the control group, indicating anomalous brain activity during the recognition of previously learned words in young BDs. In addition, BDs also displayed poorer recall of previously studied words in a version of the California Verbal Learning Test, which is consistent with a verbal memory impairment in this population. These results are congruent with the EEG study conducted by Huang et al., which found an absence of the subsequent memory effect in BDs as compared to aged-matched light drinkers. Indeed, BDs showed attenuated (instead of increased) event-related theta activity and lack of theta phase-locking (an index of neural synchrony) between frontal and posterior/temporal regions during encoding of images that were prospectively retained over 6 months in remote memory, suggesting BD-induced disturbances in brain areas critical for memory formation. In a 2-year longitudinal study, Antón-Toro et al. recorded the brain electrophysiological activity of BDs and their control peers during an inhibitory control (Go/No-Go) task by magnetoencephalography (MEG) in two stages: the first one prior to the onset of alcohol consumption and, subsequently, 2 years later when some of them had started a BD-type pattern. Results showed that, before alcohol use initiation, increased functional connectivity (in the beta band) in prefrontal and temporal regions was associated with augmented risk of developing BD 2 years later. Furthermore, adolescents who transitioned into BD displayed a marked decline of functional synchronization in the prefrontal, temporal and parietal cortices along the follow-up period which, according to the authors, was suggestive of a disruption in the typical neurodevelopmental trajectory for this age. The study protocol by Almeida-Antunes et al. also proposed to analyze the functional connectivity patterns linked

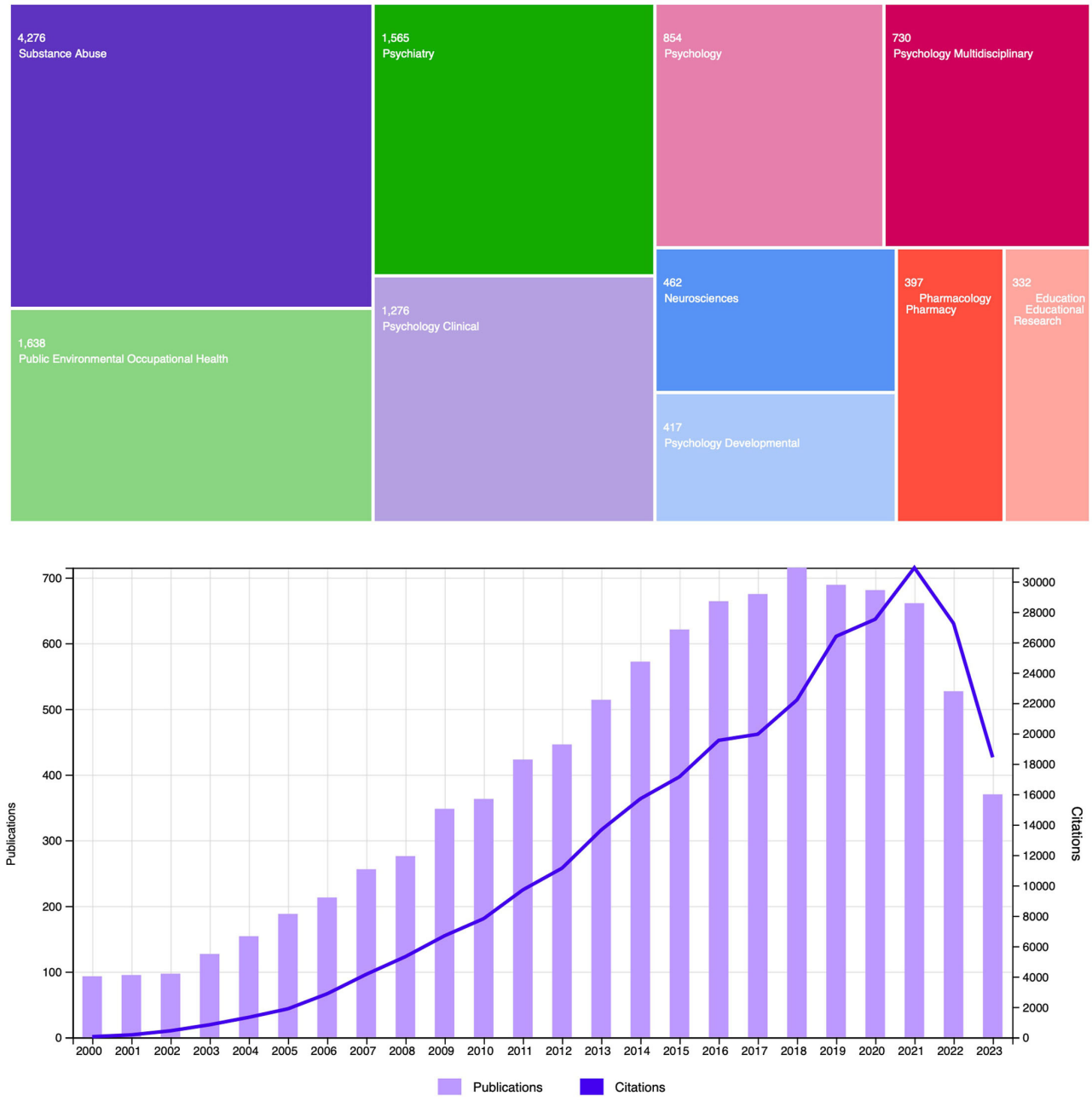

FIGURE 1
Number of articles related to binge drinking during adolescence and youth for the period January 2000–November 2023, per research area **(above)** and per year-including the number of articles citing research in this topic **(below)**. The search strategy was conducted in Web of Science with 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")).

to inhibitory control processes, but in this case they intended to explore the memory inhibition/suppression abilities in BDs and non-/light-drinkers in two occasions, before and after several sessions of memory inhibition training (involving cognitive and electrical stimulation). With this aim, authors expect to be able to determine by the first time potential neurofunctional anomalies in the memory inhibition processes linked to BD habits and, subsequently, improve the abilities to suppress alcohol-related memories, which might have a significant impact in alcohol use and craving.

The only longitudinal study examining brain structural changes associated with BD was conducted by Pérez-García et al. Findings revealed that a continued BD pattern in emerging adults is linked to gray matter anomalies in regions related to reward processing (reduced volume in the right NAcc in male BDs), emotional regulation (larger surface area in the left insula in both male and

female BDs) and executive functions (thinner cortices in the right rostral middle frontal gyrus in male BDs). Similarly, a critical review conducted by Tetteh-Quarshie and Risher emphasizes the factors that lead to BD-induced brain abnormalities, highlighting the role of the maturational changes occurring during adolescence as a key factor when explaining the neurocognitive and neurostructural effects of BD. Also focusing on the still-maturing brain, the opinion article by Angioletti and Balconi introduces the relationship between BD and problem gambling in adolescents, indicating a connection between the two behaviors. The article underscores the maturational imbalance between the fully mature, over activated reward system and the still-maturing executive system as a potential vehicle toward risky behaviors-including BD and problem gambling- and also underlines the need for tailored preventive and treatment interventions for adolescents with BD and risky gambling, focusing on cognitive factors, especially executive functions and decision-making.

Finally, an objective and homogeneous definition/characterization of BD seems crucial to enable comparisons of findings across different studies. To this end, André et al. developed a new tool to identify and classify BD patterns, applicable to both genders. Authors introduced a 5-item model-based on the Alcohol Use Disorders Identification Test (Saunders et al., 1993) and the Alcohol Use Questionnaire (Townshend and Duka, 2002)-combining multiple key factors of BD, such as quantity/frequency of consumption (6-drink frequency), behavior (speed of consumption), and physiology (frequency of drunkenness and hangover), resulting in a comprehensive and valuable measure for assessing BD severity and categorizing drinking patterns across diverse populations.

In summary, the collection of articles included in this second volume covers a range of important topics related to BD during adolescence and young adulthood, including the behavioral, emotional, cognitive and neurobiological impact of this heavy pattern of alcohol use. However, further research is still needed in order to better characterize the effects of BD on this population. Particularly, conducting longitudinal studies initiating before the transition from non-/low-drinking into BD will allow for a more accurate assessment of the neurodevelopmental impact and potential causal relationships between BD and brain impairments (Gilpin et al., 2012; Antón-Toro et al., 2021). Likewise, examining the spectrum of alcohol consumption, from light to high-intensity drinkers and individuals with alcohol abuse, would provide a more thorough understanding of how varying levels and patterns of alcohol intake may contribute to different behavioral, emotional, and neurocognitive anomalies (Patrick and Azar, 2018; Maurage et al., 2020). Also, future studies should include a more diverse cross-section of the general population (beyond college students) to increase the applicability and generalization of research outcomes. Additionally, research involving participants with comorbidities frequently associated with heavy alcohol drinking, such as anxiety, depression, or other substance abuse, despite its intrinsic limitations, might shed light on the possible interactions/aggravations of these conditions. In summary, bridging the gaps in the existing literature and integrating it with the existing knowledge can contribute to develop more effective prevention and intervention strategies. Ultimately, this will hopefully help to mitigate some of the detrimental effects of BD on the adolescent and young brain.

Author contributions

EL-C: Conceptualization, Data curation, Funding acquisition, Writing – original draft. SL: Supervision, Writing – review & editing. SC: Supervision, Writing – review & editing. CC: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Binge Drinking, Alone or With Cannabis, During Adolescence Triggers Different Effects on Immediate Visual Memory in Men and Women

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Background: This study examines the interaction between a history of binge drinking (BD), alone or with cannabis consumption, and the effects of acute alcohol exposure on immediate visual memory (IVM) (faces memory task, scenes memory task and IVM-IQ) in adolescents of both sexes.

Method: Two hundred and ninety adolescents, grouped into refrainers, binge drinkers and subjects with a history of simultaneous BD/Cannabis co-use, received a risk dose of alcohol or a control drink.

Results: Consumption Pattern (refrainers *vs.* binge drinkers *vs.* BD/Cannabis consumers) was not significant, while Treatment (acute alcohol *vs.* control drink) was significant in both sexes. Also, male binge drinkers' performance in the faces memory task was poorer than that of refrainers and BD/Cannabis consumers who consumed the control drink. BD/Cannabis consumers performed this task as capably as refrainers. In women, binge drinkers performed better than refrainers in scene memory and IVM-IQ tests when given alcohol, and binge drinkers performed worse than refrainers after consuming the control drink.

Conclusions: Acute alcohol consumption worsens IVM. Cannabis exerts a buffering effect in men. A cognitive tolerance effect is observed in women. Exposure during adolescence to alcohol, alone or with cannabis, can trigger different cognitive effects in men and women that could endure into adulthood.

Keywords: binge drinking, cannabis, immediate visual memory, adolescents, sex

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INTRODUCTION

We have previously observed differential effects of alcohol on memory performance in adolescent binge drinkers, with immediate visual memory (IVM) proving to be particularly sensitive to impairment by alcohol (1, 2). The prevalent pattern of alcohol use among adolescents and young adults in Western countries is binge drinking (BD), which has been defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as a pattern of drinking that raises a person's blood alcohol concentration (BAC) to 0.8 g/L or above (3). This pattern is characterized by intermittent consumption of large quantities of alcohol in short periods at intervals of between 1 week and 1 month and alternation between intoxication and withdrawal (4–6).

Researchers have investigated the effects of BD on different kinds of memory. Among them, word fragment completion, free recall, and IVM appear to be the most sensitive in adolescents and young adults, as they are affected by moderate doses of alcohol (BAC = 0.3 −0.38 g/L) [e.g., (2, 7)]. Higher doses of alcohol (BAC levels of BD, i.e., around 0.8 g/L) are necessary for this significant impairment to be observed with other types of memory, such as working memory [e.g., (1)] and short-term memory [e.g., (8)]. A plausible explanation for the lack of effects reported with BACs under 0.8 g/L [e.g., (8–10)] is that the brain of binge drinkers employs compensatory mechanisms in additional brain areas in order to perform tasks adequately, and that these resources are undermined by higher BACs [e.g., (11)].

On the other hand, according to a report from the Spanish Observatory of Drugs and Addictions (12), 13.4% of the Spanish adolescents who consumed alcohol during the last year also used cannabis, while 91.7 % of those who used cannabis also claimed to drink alcohol. This indicates that almost all cannabis users are co-users of alcohol.

The effects of alcohol and cannabis co-use on cognitive functions have been the subject of less research, and are more ambiguous than those of these substances when consumed alone. Some authors (13–15) consider that cannabis tempers the deteriorating effect of alcohol on cognitive functions, while others (16, 17) argue for a synergistic effect of cannabis on the deteriorating effect of alcohol on memory. In addition, there are no studies that have evaluated the phenomenon of cognitive tolerance in alcohol and cannabis co-users, a phenomenon observed in female alcohol users (2).

Experimental results of research performed with subjects of a single sex are sometimes extrapolated to both sexes. Sex should be considered as an important biological variable in basic and preclinical research, and results should not be automatically applied to both men and women (18). Sex differences in the effects of alcohol have been reported, supporting the view that the brains of male and female adolescents are differentially affected by alcohol use (19). There is evidence suggesting that female adolescents are more vulnerable to the neurotoxic effects of alcohol on cognition (19, 20), since the cognitive tolerance effect of alcohol on IVM develops in BD women but not in BD men (2). Several studies have demonstrated the differential associations of alcohol and cannabis co-use with the neurocognitive functioning of males and females, showing a different pattern of neurocognitive impairment in men and women [e.g., (21)]. In the light of these data, we deem it crucial to include both sexes in this study.

Taking into account the scarcity of studies evaluating the cognitive effects of alcohol and cannabis co-use in healthy adolescents, and considering the potential vulnerability of females to the neurotoxic effects of alcohol, the main objective of this research was to study experimentally the interaction between a history of BD, alone or simultaneously with cannabis use, and the effects of acute alcohol exposure on IVM (faces memory, scenes memory and IVM-IQ) in adolescents of both sexes. IVM was assessed by the Wechsler Memory Scale 3rd Edition (22), as it is a standard clinical instrument commonly used for evaluating this type of memory. Based on previous works, we already know that some long-term effects of repeated alcohol exposure in adolescents (such as alcohol tolerance or damaged cognitive abilities) are manifested more readily following ingestion of an acute dose of alcohol. Our hypotheses are: (1) A history of consumption and/or acute alcohol consumption would produce an impairment of IVM with sex-differential effects, being more evident in women than in men; (2) A synergistic effect could be observed vs. a buffering effect of cannabis on the detrimental effect of alcohol, which may also be sex-dependent.

METHODS

Subjects

Two hundred and ninety 18–19 years old adolescent students (one hundred and eighteen males and one hundred and seventy-two females) from the University of Valencia, Spain, filled in a self-report questionnaire about physical and psychological health, frequency and level of consumption of alcohol, cannabis, alcohol with cannabis, or other drugs, and hours and quality of sleep. The participants were recruited for the study based on strict exclusion and inclusion criteria. 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 or having a history of substance use (including those studied herein); and having first-degree relatives with drug misuse problems. The following inclusion criteria were used: age 18–19 years old; a healthy body mass index (mean in men: 22.61 ± 0.24, mean in women: 21.55 ± 0.2); good health (without major medical problems); and being refrainers, occasional consumers of alcohol, binge drinkers or BD and cannabis co-users. The participants were classified as refrainers if they had never consumed alcoholic drinks or had drunk very sporadically. They were classified as alcohol consumers with a BD pattern in accordance with the NIAAA criteria for Spain [see (23)], i.e., if they had drunk six or more standard drink units (SDU = 10 g of alcohol) of distilled spirits (alcohol content ≥ 40 vol. %) in a short of period of time in the case of men, and five or more SDU in the case of women, at a minimum frequency of three occasions per month, throughout the previous 12 months (6). Finally, the participants were classified as co-users if they reported a pattern of BD along with cannabis use (i.e., they usually smoked a joint while they have an episode of BD). In fact, alcohol consumption is widespread among adolescents who use cannabis (in Spain, 91.7% who smoke cannabis also drink alcohol) (12).

The participants were told to follow their normal sleep pattern and meal routine, and to eat 1 h before the experimental session.

A telephone interview of approximately 15 min was conducted with each subject in order to confirm the information previously provided in the self-report and to fix a date and time for the test session. The participant's data were verified again on the test day. The data concerning the menstrual cycles of the female groups were registered in the self-report and during the telephone interview, and cycle phase was considered in the test in order to counterbalance this variable in each group.

Test and Apparatus

The Alcohol Use Disorders Identification Test (AUDIT) (24) was employed to determine a problematic use of alcohol among the subjects. AUDIT is considered an appropriate screening instrument to classify BD and non-BD university students (25). The AUDIT consists of 10 questions that evaluate the quantity and frequency of alcohol intake, as well as alcohol-related behaviors and their consequences.

The Cannabis Abuse Screening Test (CAST) (26) is a six-item self-report that we employed to detect a problematic use of cannabis among the subjects during the previous 12 months.

A digital automatic blood pressure monitor (M10-IT, OMRON, Spain) was employed to register systolic and diastolic blood pressure and heart rate in all the subjects.

An alcoholmeter (Alcoquant® 6020, Envitec, Germany) was employed to evaluate BAC before and after (20 and 50 min) drink intake.

A drug test (DrugTest® 5000, Dräger, Spain) was employed to analyze the presence of drugs in a saliva sample collected from each participant before drink intake.

IVM was assessed using the Wechsler Memory Scale 3rd Edition (WMS–III; version adapted for the Spanish population) (22). The IVM subscales require the respondent to recognize faces (faces memory) and remember scenes (scenes memory). Specifically, in the faces memory task, the participants are shown 24 target faces, one at a time for 2 s. Then participants are shown 48 faces (24 targets and 24 distractors) and are asked to identify the target faces by responding either "yes" or "no" to each face. In the scenes memory task, the participants view four different scenes of four family members engaged in a common activity (such as buying clothing). After viewing all four scenes, the participants are shown a card divided into four quadrants, given the name of the scene, and asked to recall it, indicating where each family member was located in the original picture and what that family member was doing. Subjects' scores on the IVM scales (0–20 scalar scores were used both in face and scene memory tests) were transformed into centiles according to the subject's age to obtain the IQ of IVM.

Procedure

The experimental procedure was approved by the Research Ethics Committee of the University of Valencia (Certification number: H1485172642673; approved on July 7th, 2017), and was in accordance with the Helsinki Agreement. All the subjects provided written informed consent to participate in the study. According to their Consumption Pattern (Refrainers, Binge Drinkers and BD/Cannabis consumers) and the Treatment received (Control drink and Alcohol), the participants were assigned to one of six experimental conditions for each sex: Refrainers-Control drink (R-Co); Refrainers-Alcohol (R-A); Binge Drinkers-Control drink (BD-Co); Binge Drinkers-Alcohol (BD-A); BD/Cannabis-Control drink (BD/C-Co) and BD/Cannabis-Alcohol (BD/C-A).

The participants were instructed to abstain from any intake of alcohol, caffeinated beverages, drugs or medication and strenuous exercise for 24 h before the experimental session, and to refrain from eating and smoking at least 1 h prior to the session. At the beginning of the experimental session BAC was measured in BD and co-user subjects using the alcoholmeter to ensure that they had not consumed alcohol. A saliva sample of the co-users was also analyzed by the drug test to make sure that they had not used other drugs.

In addition, a problematic use of alcohol or cannabis among the BD subjects and co-users was assessed using the AUDIT and CAST test, respectively. None of the subjects was found to be alcohol or cannabis-dependent (mean AUDIT: 8.35 $\pm$ 0.39 in men; 7.3 $\pm$ 0.28 in women; mean CAST: 2.83 $\pm$ 0.38 in men; 2.57 $\pm$ 0.28 in women). Next, each subject received a flavored refreshment (lime, orange or cola, without caffeine) contained in cans of 330 ml, alone or mixed (according to the experimental group) with distilled drinks of alcohol content = 40% vol. (vodka or gin) at a risk dose of 120 ml (equivalent to 38.4 g of alcohol). The subjects were instructed to consume their drink within a period of 20 min. The participants ate a light snack (the same for all the participants) and the beverages were always consumed in the presence of a research assistant. After finishing the drink, all the subjects rinsed their mouths with water, and BAC was repeatedly measured every 5 min throughout the waiting period, until it peaked ($\sim$20 min after consuming the drink). The subjects performed the IVM tests, faces memory test and scenes memory test, in a counterbalanced manner, while BAC was descending. The BAC of each experimental subject was measured again at end of the experiment.

BAC was 0.00 g/L for men and women before the alcoholic drink, and was 0.36 $\pm$ 0.008 g/L for men and 0.53 $\pm$ 0.01 g/L for women afterwards. It is important to point out that, although all the subjects consumed the same amount of alcohol, the statistical differences in BAC between men and women did not allow a direct comparison between the sexes. On the other hand, it was possible to study the effects of alcohol on each sex.

Statistical Analyses

Data from men and women were analyzed separately, as BAC was found to be statistically different between the two sexes. The data were submitted to parametric analysis after checking that they met the criteria for normality and homogeneity of variances. Each analysis (faces memory, scenes memory and IVM-IQ) contained the between-subject factors Consumption Pattern (Refrainers, Binge Drinkers and BD/Cannabis consumers) and Treatment (Control drink and Alcohol). When their interaction was statistically significant, pairwise comparisons were carried out. All analyses were performed using the "SPSS" Statistics software package, version 26.0 for Windows (27).

RESULTS

IVM in Men (BAC: 0.36 ± 0.008 g/L)

Table 1 shows a summary of descriptive statistics and significant differences observed among men with respect to Consumption Pattern and Treatment in the faces memory task, scenes memory task and IVM-IQ.

TABLE 1 | Descriptive statistics for consumption pattern and treatment factors and significant differences observed in faces memory, scenes memory and IVM-IQ in men and women.

	Consumption pattern				Treatment		
Men	**Refrainers (*n* = 38)**	**Binge Drinkers (*n* = 50)**	**BD/Cannabis consumers (*n* = 30)**	**Statistical Power[a] / Eta[2]**	**Control drink (*n* = 65)**	**Alcohol (*n* = 53)**	**Statistical Power[a] / Eta[2]**
Faces memory	8.44 ± 0.37	7.44 ± 0.34	8.6 ± 0.57	0.352 / 0.03	8.75 ± 0.33	7.2 ± 0.32***	0.96 / 0.111
Scenes memory	9.39 ± 0.61	9.7 ± 0.51	8.76 ± 0.72	0.142 / 0.01	9.93 ± 0.42	8.66 ± 0.55	0.362 / 0.023
IVM-IQ	95.00 ± 2.35	92.780 ± 2.01	93.33 ± 3.11	0.096 / 0.005	97.36 ± 1.68	89.05 ± 2.12**	0.861 / 0.078
	Consumption pattern				**Treatment**		
Women	**Refrainers (*n* = 56)**	**Binge Drinkers (*n* = 80)**	**BD/Cannabis consumers (*n* = 36)**	**Statistical Power[a] / Eta[2]**	**Control drink (*n* = 100)**	**Alcohol (*n* = 72)**	**Statistical Power[a] / Eta[2]**
Faces memory	8.83 ± 0.39	8.61 ± 0.35	9.91 ± 0.47	0.182 / 0.009	9.91 ± 0.27	7.63 ± 0.35***	0.992 / 0.104
Scenes memory	9.33 ± 0.42	8.77 ± 0.38	9.02 ± 0.55	0.08 / 0.002	9.69 ± 0.3	8.06 ± 0.41*	0.761 / 0.042
IVM-IQ	95.94 ± 1.96	93.62 ± 1.58	98.16 ± 2.35	0.168 / 0.008	100.04 ± 1.28	88.79 ± 1.68***	0.995 / 0.111

Results are expressed as mean ± SEM.
[a]*Statistical Power was calculated using alpha = 0.05.*
*$p < 0.05$; **$p < 0.005$; ***$p < 0.001$ vs. Control drink.*

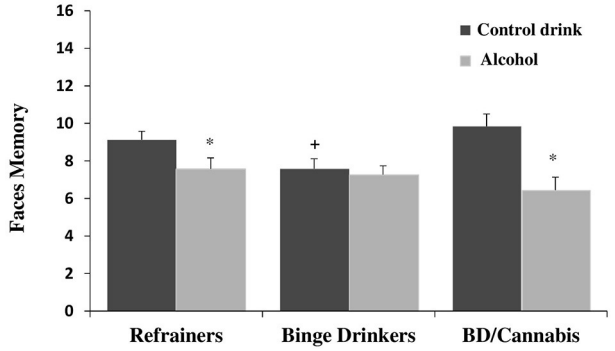

FIGURE 1 | Performance in faces memory task (mean + SEM) in men. *$p < 0.05$ *vs.* Control drink. +$p < 0.05$ *vs.* Refrainers-Control drink (R-Co) and BD/Cannabis-Control drink (BD/C-Co).

Faces Memory

There was no significant main effect of Consumption Pattern on performance [$F_{(2, 112)} = 1.705$, ns]. The factor Treatment was statistically significant [$F_{(1, 112)} = 14.007$, $p < 0.001$], with subjects given alcohol showing lower scores than those given the control drink (see **Table 1**). The interaction Consumption Pattern X Treatment was also statistically significant [$F_{(2, 112)} = 3.523$, $p < 0.05$]. *Post hoc* comparisons showed that the R-A and BD/C-A groups performed worse than the R-Co and BD/C-Co groups, respectively ($ps < 0.05$); and that the BD-Co group performed worse than the R-Co and BD/C-Co groups ($ps < 0.05$), while no differences were detected between the last two groups (see **Figure 1**).

Scenes Memory

The factors Consumption Pattern [$F_{(2, 112)} = 0.567$, ns] and Treatment [$F_{(1, 112)} = 2.622$, ns] were not statistically significant, and neither was their interaction [$F_{(2, 112)} = 0.812$, ns].

IVM-IQ

There was no significant main effect of Consumption Pattern on performance [$F_{(2, 112)} = 0.294$, ns]. The factor Treatment was statistically significant [$F_{(1, 112)} = 9.431$, $p < 0.005$], with subjects given alcohol showing lower IVM-IQ than those given the control drink (see **Table 1**). The interaction Consumption Pattern X Treatment was not statistically significant [$F_{(2, 112)} = 0.105$, ns].

IVM in Women (BAC: 0.53 ± 0.01 g/L)

Table 1 shows a summary of descriptive statistics and significant differences observed among women in terms of the factors Consumption Pattern and Treatment in the faces memory task, scenes memory task and IVM-IQ.

Faces Memory

There was no significant main effect of Consumption Pattern on performance [$F_{(2, 166)} = 0.785$, ns]. The factor Treatment was statistically significant [$F_{(1, 166)} = 19.302$, $p < 0.001$], with subjects given alcohol scoring lower than those given the control drink (see **Table 1**). The interaction Consumption Pattern X Treatment was not statistically significant [$F_{(2, 166)} = 0.341$, ns].

Scenes Memory

There was no significant main effect of Consumption Pattern on performance [$F_{(2, 166)} = 0.182$, ns]. The factor Treatment was statistically significant [$F_{(1, 166)} = 7.203$, $p < 0.01$], with subjects given alcohol obtaining lower scores than those given the control drink (see **Table 1**). The interaction Consumption Pattern X Treatment was also statistically significant [$F_{(2, 166)} = 8.167$, $p < 0.001$]; the R-A group performed worse than the R-Co group, and BD-Co and BD/C-Co participants performed worse than the R-Co subjects, while the BD-A group performed better than the R-A group ($ps < 0.05$) (see **Figure 2**).

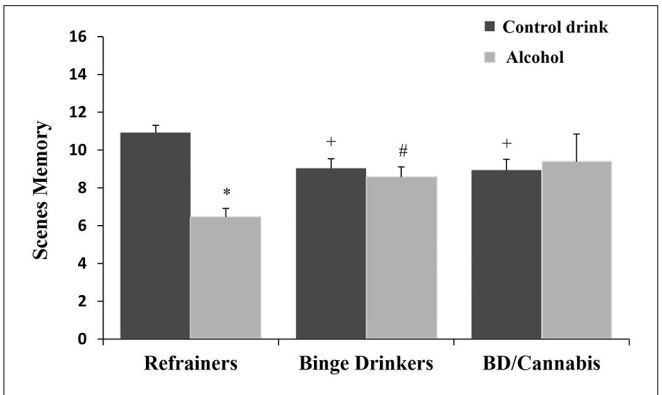

FIGURE 2 | Performance in scenes memory task (mean + SEM) in women. *$p < 0.05$ *vs.* Control drink. $^{+}p < 0.05$ *vs.* Refrainers-Control drink (R-Co). $^{\#}p < 0.05$ *vs.* Refrainers-Alcohol (R-A).

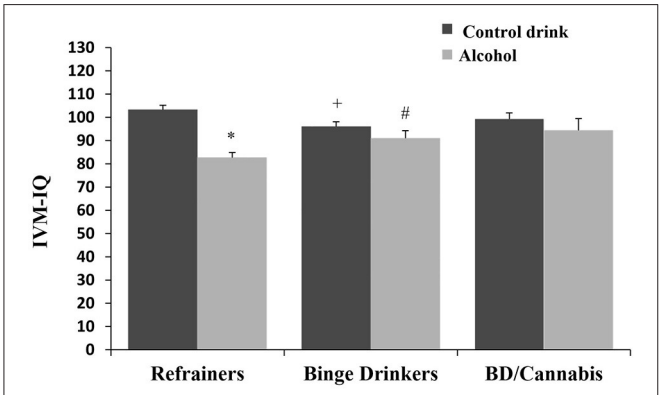

FIGURE 3 | Immediate Visual Memory-IQ (mean + SEM) in women. *$p < 0.05$ *vs.* Control drink. $^{+}p < 0.05$ *vs.* Refrainers-Control drink (R-Co). $^{\#}p < 0.05$ *vs.* Refrainers-Alcohol (R-A).

IVM-IQ

There was no significant main effect of Consumption Pattern on performance [$F_{(2, 166)} = 0.707$, ns]. The factor Treatment was statistically significant [$F_{(1, 166)} = 20.733$, $p < 0.001$], with subjects receiving alcohol displaying lower IVM-IQ than those given the control drink (see **Table 1**). The interaction Consumption Pattern X Treatment was also statistically significant [$F_{(2, 166)} = 5.051$, $p < 0.01$], with the R-A group performing worse than the R-Co group, the BD-Co group performing worse than R-Co subjects, and the BD-A group outperforming the R-A group ($ps < 0.05$) (see **Figure 3**).

DISCUSSION

A distinctive contribution of this study is to evaluate experimentally, together, the impact of an acute alcohol consumption episode and a BD history of consumption on IVM (faces memory, scenes memory and IVM-IQ) in adolescent men and women. We could not directly examine sex differences in IVM functioning among our adolescent population, but our study provides interesting data for each sex.

We have observed that a moderate acute dose of alcohol (BAC = 0.36 g/L in men and 0.53 g/L in women) is enough to impair faces memory and IVM-IQ in men, and faces and scenes memory and IVM-IQ in women, and corroborate that IVM is sensitive to the neurotoxic effects of acute alcohol consumption (2, 7). However, the maintenance of a BD pattern for 1 year did not affect IVM in any sex.

The literature suggests that this BD pattern and its maintenance over time have differential effects on memory (28). In the longitudinal study of Carbia et al. (28) executive difficulties disappeared after maintaining a BD pattern of alcohol consumption for 2 years (which was interpreted as an improvement), and the authors proposed than an alcohol-related delay in neuro-maturation, principally affecting prefrontal regions, resulted in BD subjects gaining executive efficiency later than age-matched non-BD individuals.

The pattern of alcohol and cannabis co-use did not affect the IVM in our study. Simultaneous alcohol and cannabis use in young drinkers (18–25 years old) has been associated with an increase of negative consequences (29). The existing literature on the effects of simultaneous alcohol and cannabis consumption on memory is scarce and contradictory. On the one hand, a synergistic deteriorating effect of alcohol and cannabis on cognitive processes has been reported (16, 17), with co-users being more likely to experience more severe cognitive consequences than users of alcohol alone (30). On the other hand, a buffering effect of cannabis against the deteriorating effects of alcohol on memory has been demonstrated by other researchers (13, 14). Cannabidiol (CBD) is a component of the cannabis plant with anti-inflammatory properties whose ability to improve cognitive impairment has been explored to an extent, but not conclusively. Nevertheless, authors such as Osborne et al. (31) have shown that CBD improves cognition in multiple preclinical models of cognitive impairment, including those of neuropsychiatric (schizophrenia), neurodegenerative (Alzheimer's disease), neuro-inflammatory (meningitis, sepsis and cerebral malaria) and neurological (hepatic encephalopathy and brain ischemia) disorders.

In line with the aforementioned evidence, we have observed, after a previous year of simultaneous consumption, a dampening effect of cannabis on the deteriorating effects of alcohol in the faces memory test when performed by men. After receiving the control drink, co-users performed this task as well as refrainers, while participants with a BD history performed worse than refrainers and co-users. It is plausible that the neuro-inflammatory effects of alcohol, responsible for cognitive decline, were counteracted by the anti-inflammatory efficacy of cannabis. Nevertheless, as other authors (14) have pointed out, long-term use of these substances can negatively increase vulnerability to the development of addictions. Furthermore, it must be taken into account the timeframe of consumption of these substances, as it is associated with the cognitive impairment (32).

In women, the interaction Consumption Pattern X Treatment was statistically significant with respect to scenes memory and IVM-IQ, and alcohol generated an effect of cognitive tolerance.

This suggests that our binge drinkers developed tolerance in such a way that the deteriorating effect of alcohol on their scenes memory and IVM-IQ after drinking alcohol was weaker than that seen in refrainers. Thus, binge drinkers performed better than refrainers when given alcohol (displaying the abovementioned development of alcohol tolerance) and binge drinkers performed worse than refrainers after consuming a control drink (as their memory would have been damaged). The existence of this cognitive tolerance is endorsed by the fact that the scenes memory and IVM-IQ of female binge drinkers receiving the alcoholic drink did not differ from those of binge drinkers given the control drink. This phenomenon of cognitive tolerance was not so obvious in co-users, since there were differences in scenes memory between refrainers and co-users who received the control drink, but there were no differences in scenes memory or in IVM-IQ between refrainers and co-users who received alcohol. On the other hand, the phenomenon of women beginning to drink earlier and progressing more rapidly than men from the first exposure to the addiction phase, known as the "telescoping effect" (33–35), could explain why adolescent women develop cognitive tolerance earlier than men.

The alcohol acutely consumed by the participants in our study (38.4 g of alcohol) was close to the so called "risky alcohol consumption" for men and women (>5 SDU for men, and >4 SDU for women; 50 and 40 g of alcohol, respectively) (36). Some of the different effects observed in men and women in our study could be explained by the differences in BAC between the sexes in our population. It is possible that cognitive tolerance to alcohol would also be observed in male subjects with a higher BAC. This brings us to a limitation of our study, as the statistical differences in BAC between men and women did not allow a direct comparison between sexes. In this context, identifying gender-specific effects of alcohol and cannabis on male and female adolescents separately may help to explain differential proneness to substance use in adolescents (21). Acute alcohol consumption *vs.* a history of BD pattern leads to differential effects on cognition that depend on the type of memory in question. In conclusion, exposure during adolescence to alcohol, alone or with cannabis, can trigger different cognitive effects in men and women, which contribute to enduring cognitive deficits in adulthood. Moreover, our findings are consistent with the greater vulnerability of adolescent women to the neurotoxic effects of alcohol. Further research is needed–particularly, longitudinal studies including women and exploring the timeframe of consumption of these substances–in order to confirm the aforementioned findings and consolidate our conclusions. This will allow us to better understand the mechanisms underlying the effects on memory of alcohol, consumed alone or simultaneously with cannabis, and to develop optimal treatment methods for cannabis /alcohol dependence in men and women.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of the University of Valencia (Certification number: H1485172642673; approved on July 7th, 2017). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Consequences, Motives, and Expectancies of Consumption as Predictors of Binge Drinking in University Women

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The increasing presence of women, especially university women, in risky alcohol consumption such as Binge Drinking (BD), which is associated with gender-specific biopsychosocial problems, makes it necessary to analyze the variables underlying BD in order to adjust possible interventions more in line with their reality. The motives and expectancies of this pattern of consumption, as well as the consequences derived from it, are some of the variables that are shown to have the greatest weight in the prediction of BD. In the present study we analyze, on the one hand, the performance of these variables among college women with alcohol use, and on the other hand, which of these variables allow us to classify BD. A total of 501 female university consumers of alcohol (mean age 19.02 years) were assessed. Specifically, they completed a self-report of alcohol consumption (77.1% engage in BD), the Expectancy Questionnaire (EQ), the Drinking Motives Questionnaire (DMQ-R) and the Alcohol Consumption Consequences Evaluation (ACCE). BD female students scored significantly higher on these instruments, except for compliance motives. The logistic regression analysis carried out to estimate the probability of performing BD using the social and conformity motives, the ACCE and positive expectancies correctly estimated ($\chi^2_8 = 9.149$, $p < 0.33$) 88.6% of the cases and explained 26.2% of the BD. Thus, young women with a level of consequences classified as high risk (>25 in ACCE) have a 3.55-fold increase in the probability of having BD, compared to women classified as low risk by the ACCE. On the other hand, women classified as moderate risk by the ACCE have a 4.77-fold increase in the probability of having BD. In the case of social motives and positive expectancies, their increase multiplies by 1.165 and 1.024, respectively, the probability of having BD. The results of this study highlight the importance of adapting preventive measures to the consequences experienced by BD university students, especially in relation to the social motives and positive expectancies that modulate decision-making when engaging in this pattern of consumption.

Keywords: risky consumption, binge drinking, motives, expectancies, consequences, university women

INTRODUCTION

Binge drinking (BD) constitutes one of the most frequent patterns of risky consumption among young people (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2004; Observatorio Español de las Drogas y las Adicciones, 2021), with a special prevalence among university students (Grant et al., 2015; Johnston et al., 2015; Amare and Getinet, 2019; Crawford et al., 2019; Haardörfer et al., 2021).

Even though men as a whole continue to outnumber women in terms of the number of BD consumers and the amount of alcohol consumed (White et al., 2015), the number of women engaging in this pattern of consumption in the recent years is increasing and sometimes even surpassing that of men (White et al., 2015; Grant et al., 2017; Iwamoto et al., 2018; Wilsnack et al., 2018; Kang et al., 2020; Alves et al., 2021; Aston et al., 2021; Observatorio Español de las Drogas y las Adicciones, 2021). In the case of adolescent girls aged 18 in Spain who consume alcohol, 61.6% admit to having been intoxicated in the past year, compared to 59.2% of partners of the same age (Observatorio Español de las Drogas y las Adicciones (OEDA), and Delegación del Gobierno para el Plan Nacional sobre Drogas, 2020). Moreover, in college women from different Spanish universities (Cortés et al., 2017) the percentage of them who engage in BD reaches 60.4%, compared to 39.6% of their male counterparts.

This new reality places women at a higher risk of suffering harmful consequences due to their physiological characteristics (weight, body composition, etc.) and their body's rate of absorption and metabolism of alcohol (Ashley et al., 1977; Erol and Karpyak, 2015). Several effects of alcohol have been documented in university women (Patrick et al., 2020), such as menstrual cycle alterations and infertility (Van Heertum and Rossi, 2017), memory loss (Baildon et al., 2021), feelings of sadness and depression (Barnett et al., 2014; Patrick et al., 2020), increased risk of sexually transmitted infections (Hutton et al., 2008), violence from their partners (Stanesby et al., 2018), as well as increased susceptibility to infectious, cardiac, and liver diseases (Hashimoto and Wiren, 2008; Kirpich et al., 2017).

This greater presence of women who engage in BD in combination with the consequences derived from this pattern of consumption justify the need to conduct more detailed analyses of the factors that predict this risky consumption (LaBrie et al., 2009; Brady et al., 2016; Iwamoto et al., 2018).

On the one hand, social learning theories suggest that cognitions -motives and expectancies- influence behavior (Bandura and McClelland, 1977; Maisto et al., 1999) and on the other hand, research with university students has shown that the consequences experienced when consuming alcohol affect the way in which young people evaluate the experiences of their consumption, as well as the subsequent consumption behavior, so it becomes another source of cognition to consider (Mallett et al., 2008; Patrick and Maggs, 2011; Yurasek et al., 2011; Merrill et al., 2013; Barnett et al., 2015).

Research regarding the role of consumption expectancies as a determining factor in university women's BD behavior (Lyons and Willott, 2008; Watts et al., 2015; Jacobs and Jacobs, 2016; Kim, 2018) concludes that positive expectancies related to social aspects are strong predictors of BD. Lyons and Willott (2008), Young et al. (2015), and Iwamoto et al. (2016) allude to the fact that consuming alcohol produces feelings of power, a trait that they believe will help them fit in with their peer group and gain social attention. Furthermore, Iwamoto et al. (2018) show that positive expectancies related to improving sexual experiences and reducing tension are related to BD.

Findings regarding negative expectancies have been less consistent, given that an inversely proportional relationship can be seen between these and alcohol consumption, regardless of gender (Nicolai et al., 2010; Ramirez et al., 2020), although when risky consumption is evaluated, this relationship becomes positive (Zamboanga et al., 2010; Pabst et al., 2014; Patrick et al., 2016; Alves et al., 2021). Different authors (Zamboanga and Ham, 2008; Bacio, 2021) explain this positive association between negative expectancies and risky consumption, such as BD, by indicating that university students might find the effects that researchers label as negative to be attractive.

The motives behind alcohol consumption are considered to be closer to carrying out the activity rather than to expectancies, which tend to have a more distant influence on it (Cooper, 1994). In this regard, it is possible for a person to expect alcohol consumption to relieve stress, but to not consume it when he/she feels stressed. However, a person is much more likely to be motivated to consume alcohol after experiencing how drinking alcohol helped them cope with stress. As Capron and Schmidt (2012) conclude, motives mainly feed on the real experiences (consequences) that people experience with alcohol consumption, and not only on the beliefs or expectations about what will happen after its use.

To date, several studies with general university population (both males and females) report that coping motives stand out for their greater weight in explaining both BD (Herschl et al., 2012; Patrick et al., 2017; Terry-McElrath et al., 2017), as well as problems derived from this consumption behavior (Cooper et al., 2016; Bacio, 2021; Bresin and Mekawi, 2021; Richards et al., 2021). Enhancement and social motives also share an important weight in the prediction of BD (Patrick et al., 2021; Richards et al., 2021). However, when dealing with larger consumption amounts both tend to lose explanatory weight, especially social motives (Tragesser et al., 2007; Cooper et al., 2008; Kuntsche and Cooper, 2010), even though people who mainly drink for social motives are more vulnerable to social norms regarding alcohol consumption. For this reason, they show a higher risk of developing excessive consumption patterns and experiencing associated problems when they are integrated into a subculture of heavy alcohol consumption, such as university (Watts et al., 2015; Jacobs and Jacobs, 2016; Kim, 2018; Bainter and Ackerman, 2021).

On the other hand, when reviewing the research related to conformity motives, there are some inconsistencies in university population (Cooper et al., 2016; Bresin and Mekawi, 2021). Several studies have observed a negative and weak relationship of this motives with alcohol consumption (Grant V. V. et al., 2009; Richards et al., 2021), and others have found it to have a positive and weak relationship with problems derived from consumption

(Vernig and Orsillo, 2015; Wahesh and Lewis, 2015; Bacio, 2021; Richards et al., 2021).

Studies carried out exclusively with women at university show similar results, highlighting coping motives for their greater predictive weight, both in terms of patterns of risky alcohol consumption, and of the consequences derived from them (LaBrie et al., 2007; O'Brien et al., 2008; Kenney et al., 2015; Hussman, 2018; Kim, 2018). It is followed by enhancement motives (LaBrie et al., 2007; O'Brien et al., 2008; Loxton et al., 2015), and lastly, social motives (LaBrie et al., 2007; O'Brien et al., 2008). Only the work of Hussman (2018), in which she includes specific norms related to the female gender, shows that conformity motives obtain a relevant weight when explaining BD behavior and its consequences.

Until now, research has focused mainly on what young people hope to achieve with alcohol consumption -outcome expectancies-, on the reasons they have for drinking -consumption motives- and on the positive association of both aspects with BD and its consequences (Neighbors et al., 2003; Read et al., 2004). However, there is still a lack of research in university students in terms of the evaluation of the influence of consequences on BD (Lee et al., 2011). Corbin et al. (2008) have shown that the consequences of alcohol use represent a unique variation in predicting this drinking pattern after controlling for drinking expectancies, suggesting that consequences may differ from expectations and justify a separate evaluation (Lee et al., 2011). Likewise, Capron and Schmidt (2012) conclude that consumption consequences regarded as positive by university students predict a higher percentage of BD variance above the social and enhancement motives for consumption. Longitudinal studies have also observed that experiencing positive consequences derived from consumption predicts the likelihood of university students engaging in BD (Patrick and Maggs, 2011; Park et al., 2013; Patrick et al., 2016).

In this study, after evaluating the type of consequences, motives, and expectancies that define BD in female university students, we analyzed which of these variables help classify women in this consumption pattern. All this will allow specifying the best type of intervention that can be applied in this group. To develop this general objective, the variables considered for carrying out said classification will be described first, then the contrast will be continued based on the manifestation of the BD/non-BD behavior, and finally, an estimation will be made of the probability of occurrence of the behavior from these variables.

MATERIALS AND METHODS

Participants

The sample of this study consists of 501 alcohol-consuming female university students between 18 and 20 years old –18 years old (25.9%, $n = 130$), 19 years old (33.5%, $n = 168$), and 20 years old (40.5%, $n = 203$) with a mean age of 19.15 years (SD = 0.80). The age of onset for alcohol consumption is 15 (SD = 1.46) and 87.4% ($n = 438$) have engaged in BD and 12.6% ($n = 63$) no BD. The entire sample consisted of 898 participants, however, 397 cases were excluded because missing values and only the sample for which complete information was available was used.

Participants were recruited using the "snowball" method. The researchers visited classes of three Degrees of the University of Valencia with the highest female ratio–(Psychology, Language Therapy and Social Work). In all cases, they asked for student's voluntary collaboration. Students who agreed to participate were summoned another day to fill out the questionnaire. Prior to the completion of the tests, all young people signed an informed consent, where the research objectives were clearly reflected, and the anonymity of the data was guaranteed. The instrument was filled out in the presence of one of the interviewers.

Variables

Sociodemographic: Sex, chronological age, and age of onset of alcohol consumption have been included.

Pattern of Consumption/BD: A self-report form of the last 6 months was used. This time interval makes it possible to account for the intermittent consumption (with periods of non-consumption that can exceed 30 days) carried out by young people (Townshend and Duka, 2005; Courtney and Polich, 2009).

This self-report form is an adaptation of the Timeline Followback (TLFB) by Sobell and Sobell (1996). For each day, the start and end time of each episode of consumption is recorded as well as the number of consumed SDUs (Standard Drinking Units). To help calculate the SDUs, participants were presented with a figure containing the equivalences between alcoholic beverages, their volume, and the number of respective SDUs. From the information offered by the participants in this self-report, the following variables were generated:

Maximum SDUs consumed: the consumption episode with the highest amount of SDUs ingested was selected.

Engagement or not in BD: the participants were classified as BD or non-BD based on the SDUs consumed in the episode of maximum consumption and the number of hours in which the consumption took place. The proposal of the National Institute on Alcohol Abuse and Alcoholism [NIAAA] (2004) was used as criterion to define the BD in this study, but in this case the grams of alcohol proposed by the original definition were adjusted to the Spanish SDU (1 SDU = 10 grams). Thus, women who consumed six or more SDUs in an interval of 2–3 h were classified as BD.

Expectancy Questionnaire (EQ, Leigh and Stacy, 1993; Spanish adaptation from Camacho et al., 2010). The scale consists of 34 items in a 6-point Likert format (0 = Never a 5 = Always) measuring positive and negative expectancies about alcohol consumption. Items take the form of short phrases prefaced by When I drink alcohol. . . Respondents were instructed to indicate the likelihood that the indicated effects or consequences would happen to them when they drink. The eight scales included in the questionnaire (grouped into two factors) are listed in **Table 1** together with their reliability coefficients for the present sample. The original questionnaire presented adequate reliability coefficient, ranging from 0.73 for the tension-reduction scale to 0.91 for the sex scale; as well as 0.94 for positive expectancies and 0.88 for negative expectancies. The adaptation to Spanish obtained similar results, both in the first order factors (0.75–0.93)

TABLE 1 | Reliability coefficients of the evaluated sample.

	Second-order factors	First-order factors	Alpha coefficient
Expectancy questionnaire (EQ)	Positive expectancies 0.93	Positive social	0.89
		Fun	0.89
		Sex	0.89
		Tension reduction	0.78
	Negative expectancies 0.87	Negative social	0.73
		Emotions	0.80
		Physical effects	0.77
		Cognitive effects	0.76
Drinking motives questionnaire–revised (DMQ-R)		Social	0.74
		Enhancement	0.86
		Conformity	0.87
		Coping with anxiety	0.65
		Coping with depression	0.91
ACCE			0.93

and in the second order factors (0.95 for positive expectancies and 0.91 for negative expectancies).

Drinking Motives Questionnaire–Revised (M-DMQ-R) (Grant et al., 2007; Spanish adaptation from Mezquita et al., 2011). It consists of 28 items, each contributing to one of five subscales. Using a five-point scale (from 1 -almost never/never- to 5 -almost always/always-) participants were asked to decide how frequently their own drinking is motivated by each of the reasons listed. Mezquita et al. (2011) obtained internal consistency values between $\alpha = 0.88$ of coping with depression and $\alpha = 0.63$ of coping with anxiety. **Table 1** shows the reliability coefficients obtained in this sample.

Alcohol Consumption Consequences Evaluation–(ACCE) (Sancerni-Beitia et al., 2020). It is a one-dimensional questionnaire with 43 dichotomous items (Yes/No) that comprise a wide range of consequences derived from their alcohol consumption during the last year, ordered according to two parameters: severity (identifies which consequences warn of problems of special relevance to be considered in terms of prevention/intervention) and discrimination (indicating that small differences in the trait are associated with a large difference in the probability of accepting the item). In its development it showed adequate psychometric properties: $\alpha = 0.93$. This instrument allows individuals to be classified into three risk groups (low, moderate, and high risk): low risk (coded with 1) when scores are under 20 points, moderate (coded with 2) between 21 and 24 points, and high (coded 3) when scores are over 25 points.

Procedure

For data collection, eight people received training in administering the instrument, so correct completion of it was guaranteed. All of them had two guided practices under the tutelage of the signatories of this study.

The study was conducted in compliance with Spanish legislation (Organic Law 3/2018, of December 5) and the code of ethics for research involving human subjects, as outlined by the University of Valencia Human Research Ethics Committee. The survey used in this study is completely anonymous. In addition, the survey itself includes an introduction that specifies the objectives to be achieved and the benefits it can bring, as well as an explicit reference to compliance with the current Data Protection Law. The last part of the introduction includes a paragraph in which the person indicates that they agree to participate voluntarily in the study.

Data Analysis

Using the statistical package IBM SPSS Statistics 26, descriptive analyses of the following variables were carried out according to the first specific objective: age of onset of alcohol consumption, expectancies, consumption motives, and consequences experienced after consumption. *T*-tests were performed to contrast the means of the mentioned variables in the groups of young people who did or did not engage in BD according the second specific objective.

Next, a binary logistic regression was conducted to obtain an estimate of the probability of BD from three independent quantitative variables -expectancies, ACCE, and motives- according to the third objective. With this regression it was possible to estimate the probability of performing BD based on the set of independent variables, quantifying the importance of the relationship, and classifying the young women into the different established categories.

As stated in the introduction, expectancies, motives, and consequences can influence BD, to a greater or lesser extent. In this study, the relationships of these variables with the dependent variable BD is analyzed in combination, with the value 1 being assigned to the people of the group of interest, that is, to the group that consumes intensively (consume 60 grams or more) and 0 to the rest.

Given that ACCE classifies risk into three groups, two dummy variables were constructed. The reference category in both cases was the group of low-risk women, the ACCE1 dummy variable included high-risk young women, and the ACCE2 dummy variable those of moderate risk.

RESULTS

Table 2 shows the means and standard deviations of expectancies, motives, and consequences for the full sample and differentiating between BD and non-BD, as well as the differences between their means.

The logistic regression analysis includes all the independent variables: ACCE, positive and negative expectancies, and the five groups of motives -social, enhancement, conformity, coping with anxiety, and coping with depression. This model makes it possible to make a correct estimate ($\chi^2_8 = 8.33$, $p < 0.402$) of 88.8% of the cases and accounts 27.3% of the BD variable (R Nagelkerke), although not all the independent variables are useful. Specifically, enhancement (Wald = 0.084, $p = 0.772$),

TABLE 2 | Mean scores on each bing drinking subscale and between-group comparison.

		Full sample mean (SD) $n = 501$	Non-BD mean (SD) $n = 63$	BD mean (SD) $n = 438$	t	d
ACCE		21.45 (10.23)	11.25 (9.12)	22.56 (9.50)	8.87**	1.19
Expectancies	Positive	47.90 (20.21)	30.87 (18.22)	47.18 (18.93)	6.42**	0.86
	Negative	20.39 (12.63)	15.03 (13.45)	19.88 (12.01)	2.95**	0.39
Motives	Social	14.00 (4.26)	11.16 (3.72)	14.40 (4.20)	5.81**	0.78
	Enhancement	11.48 (4.90)	8.65 (3.94)	11.86 (4.89)	5.84**	0.67
	Conformity	6.27 (2.74)	6.48 (3.39)	6.24 (2.64)	0.64	0.09
	Coping-with-anxiety	5.80 (2.44)	5.05 (2.05)	5.89 (2.45)	2.95**	0.35
	Coping-with-depression	13.00 (5.92)	11.00 (3.63)	13.25 (6.08)	4.01**	0.38

$^{**}p < 0.01$.

coping with anxiety (Wald = 0.017, $p = 0.895$), and depression motives (Wald = 0.132, $p = 0.717$), as well as negative expectancies (Wald = 3.748, $p = 0.053$) were not significant. By including only social and conformity motives, ACCE, and positive expectancies as predictors, a model is obtained that allows a correct estimate to be made ($\chi^2_8 = 9.149$, $p < 0.33$) of 88.6% of the cases and an explained variance percentage of 26.2%, **Table 3**.

Logistic regression revealed that the ACCE variables, positive expectancies and social and conformity motives had a statistically significant effect on the probability of developing risky drinking behavior. **Table 4** summarizes the results of the logistic regression.

The probability of engaging in heavy alcohol consumption is 3.55 times higher in the high-risk group (ACCE1) than in the low-risk group. In the case of the moderate risk group (ACCE2) this probability is 4.77 times higher.

On the other hand, an increase in the score for social motives multiplies the probability of engaging in BD by 1.165, and an increase in the score for positive expectancies multiplies this probability by 1.024. However, conformity motives seem to work inversely, given that low scores on this variable increase (OR = 0.838) the probability of BD.

DISCUSSION

The aim of this study was not only to gain a greater knowledge of the cognitive factors that underlie the pattern of alcohol consumption carried out by university women, but also to go one step further, and evaluate which variables (expectancies, motives, and consequences experienced by subjects after consuming alcohol) are that make it more likely to engage in BD.

When assessing the determinants of drinking–expectancies, motives and experienced consequences–comparing women who engage in BD with those who consume alcohol at a lower level, the first ones score higher on all determinants, as in previous literature (Iwamoto et al., 2018; McCaul et al., 2019). Specifically, among women who consume alcohol and engaged in BD, it is the positive expectancies that show greater relevance, compared to the negative ones (Watts et al., 2015; Young et al., 2015; Jacobs and Jacobs, 2016; Iwamoto et al., 2018; Kim, 2018). On the other hand, among the reasons for consumption, BD female university students allude to social motives, followed by coping with depression, and enhancement motives. The importance they give to social and enhancement motives for consumption supports the results of other studies in which most university students report that they drink for social and fun reasons (Patrick et al., 2021; Richards et al., 2021).

In the case of coping motives, most research carried out to date (Cooper et al., 2016; Hussman, 2018; Bacio, 2021; Richards et al., 2021) does not allow differentiating the type of emotion that is coped with through consumption (anxiety and/or depression) as it is assessed jointly. In this work, by using an assessment instrument that differentiates these two factors -those of anxiety and those of depression-, it has been possible to determine that it is the coping motives of depressive moods (for example, *to forget my worries; to stop thinking negatively about myself; to stop feeling pessimistic about the future.*) that contribute to explaining different risky consumption patterns. The relevance of anxiety-related coping motives (e.g., *to relax; because it makes me feel more self-confident; because it helps me when I am nervous*), which also show the lowest reliability coefficient in all samples tested, will have to be further explored in future research (Grant et al., 2007; Mezquita et al., 2011).

To achieve the second objective, logistic regression models allow us to know the strength of the association through the OR of the risk factors with the effect studied independently and to know the predictive value of each of them. As a descriptive method, it allows us to study the occurrence of a given event in a group of individuals. Once the model is fixed, the probability of performing BD can be estimated based on a series of variables, being very useful in prevention. This work therefore adds that possibility in the field of risky alcohol consumption.

TABLE 3 | Classification table.

		Predicted bring drinking		Correct percentage
		No	Yes	
Observed	No	8	55	12.7
Binge drinking	Yes	2	437	99.5
Global percentage				88.6

TABLE 4 | Logistics regression on binge drinking (BD) according to ACCE, positive expectancies, and social and conformity motives.

							95% C.I. for Exp (B)	
	B	S.E.	Wald	df	p	Exp (B)	Lower	Higher
ACCE			11.917	2	0.003			
ACCE (1)	1.267	0.470	7.255	1	0.007	3.551	1.412	8.927
ACCE (2)	1.563	0.623	6.304	1	0.012	4.773	1.409	16.172
Social motives	0.152	0.048	10.082	1	0.001	1.165	1.060	1.127
Conformity motives	−0.177	0.054	10.928	1	0.001	0.838	0.754	0.930
Positive expectancies	0.023	0.010	6.059	1	0.014	1.024	1.005	1.043
Constant	−0.262	0.505	0.270	1	0.603	0.769		

From the set of all the variables that have been included in the model, only social and conformity motives, ACCE, and positive expectancies are useful in classification BD in approximately 90% of the cases. It is worth noting that the enhancement and coping with depression motives that had a relevant weight among female consumers, especially among those who engage in BD, are relegated to second place when they enter our regression analysis.

The results obtained confirm, as stated by other researchers (for example Corbin et al., 2008; Capron and Schmidt, 2012), the adequacy of including the consequences that have been experienced with alcohol consumption over the last year among the possible independent variables, given that they provide a unique variation when assessing the probability of engaging in BD, beyond the contribution of consumption expectancies and motives. In addition, it is the variable that shows the highest coefficient of all those that have been evaluated in this study.

On the other hand, these results reinforce the findings of previous research in which it has been proven that social motives for consumption are closely linked to frequency and amount of alcohol ingested (Weybright et al., 2016; Richards et al., 2021), as well as the BD pattern (Patrick et al., 2020; Valencia-Martín et al., 2020; Richards et al., 2021). Despite this, research has focused more on extracting predictive models of the influence of coping and enhancement motives, indicating that they are more stable over time and that they are associated with a greater presence of negative consequences. Motives of a more external nature such as social is left out (Cooper et al., 2016) despite being the most present among university students (Patrick et al., 2021; Richards et al., 2021). The present study reinforces the importance of contemplating social motives, given that the higher the score in this type of motives, the greater the probability of BD, unlike the more internal reasons (coping and enhancement) in which this relationship is not so evident.

Regarding the results on conformity motives, despite the inconsistency shown by this construct (Cooper et al., 2016), our results coincide with those of previous research in which a negative relationship with alcohol consumption (Grant B. F. et al., 2009; Richards et al., 2021) and especially with risky alcohol consumption has been shown (Cooper, 1994; Kuntsche et al., 2008; Bainter and Ackerman, 2021). It is striking that Hussman (2018) finds conformity motives relevant for female university students engaged in BD. However, this result can be explained by her multidimensional assessment of this construct, using different scales that address both traditional norms of femininity (desire to be thin, investment in appearance, maintenance of social relationships) and other internalized ideologies that are relevant in emerging adulthood (objectification of the body, inauthenticity of relationships) (Hussman, 2018; Iwamoto et al., 2018).

It is worth noting that the group of female university students who acknowledged having experienced more than 25 of the consequences included in the ACCE, those with the highest risk, presented a lower probability of engaging in BD than the group of consumers rated as moderate risk with this same instrument. However, this is easily understandable if the heterogeneity of consumers included under the BD category is taken into account. Limiting the BD to a number of grams consumed in a time interval implies that this group includes consumers of the minimum amount required, but also those who double or even triple this amount. Many of the female university students who double or triple this amount already meet the criteria for an alcohol use disorder, far exceeding occasional consumption in the form of BD. It should also be added that as the years of BD consumption increase, other lesser amounts of consumption are added, which make it easier for young people to progress within the addictive process. It would be convenient in future studies to include a registry of alcohol consumption that is not limited to BD, but that would allow for classifications to be more adjusted to the real consumption pattern those young women are carrying out, also contemplating possible weekly and even daily risk consumption in those cases that are more advanced in the addictive process.

The information extracted from this study allows us to identify the potential points to work on to reduce the probability of BD. Mainly, it highlights the adequacy of applying intervention measures focused on the consequences that are experienced when consuming alcohol, paying special attention to how these can deteriorate one's daily life. In addition, the percentage explained over the BD obtained by motives and expectancies warns of the need to work on these consequences, relating them especially to social motives and to the positive expectancies that modulate decision-making when engaging in this pattern of consumption. It would be important to reflect on the extent to which the motives and expectancies that are linked to BD contradict the actually experienced consequences and whether these are permanent or not.

Furthermore, despite the low and negative weight of the conformity motives, it is important to increase the level of awareness that these young women have regarding the influence that social pressure may be having on deciding to engage in BD. It requires self-exploration and reflection on the false freedom they believe they have when they make the decision to engage in BD.

This section can be concluded by highlighting that with only four variables -consequences, positive expectancies, social motives, and conformity motives- it is possible to classify 26.3% of BD in university women, surpassing the results of previous investigations in which 9.5% (Motos-Sellés et al., 2015) and 18% of the variance of weekly risky consumption was explained (IbáñezI, Moya et al., 2010), based on age of onset of alcohol consumption and personality variables.

LIMITATIONS AND FUTURE DIRECTIONS

The limitations of this study include having used self-report measures to evaluate the different variables, thus assuming possible biases in the responses issued, including social desirability (Kaya et al., 2016). This could be the reason why a small group of women evaluated, despite being classified within the high-risk group in the ACCE, have not registered a pattern of consumption adjusted to this reality.

Although the sample with which the study was carried out is large, it was obtained without random selection or stratified sampling, so our results can only be generalized to groups of university women within a certain age range. With stratified sampling, a sample with more balanced BD/non-BD group sizes could be achieved. In addition, it would be very useful to establish categories within the BD group, given that consuming the minimum to enter this category (60 grams) is not the same as consuming other amounts in this sample (for example, 130 grams). At the moment, regardless of consumption, a person is included in the BD group if the 60-gram barrier is exceeded.

One last aspect to consider would be improving the evaluation of one of the most controversial constructs to date, conformity motives. Following the proposal of Hussman (2018) and Iwamoto et al. (2018), using instruments for women samples that include female normative aspects that better explain their need for adjustment could be considered.

Moreover, to improve the understanding of this behavior, it's recommended to carry out longitudinal studies in which the usefulness of this study for predictive purposes can be tested, as well as the inclusion of more variables that can account for the pattern of behavior.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This 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 patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

M-DS-B performed the analysis. M-TC-T, J-AG-C, and PM-S wrote the first draft of the manuscript. All authors contributed to the study conception and design, material preparation and data collection, commented on previous versions of the manuscript, read, and approved the final manuscript.

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Neuropsychological Profile of College Students Who Engage in Binge Drinking

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This study investigated the neuropsychological profile of college students who engage in binge drinking (BD) using comprehensive neuropsychological tests evaluating verbal/non-verbal memory, executive functions, and attention. Groups were determined based on scores on the Korean version of the Alcohol Use Disorder Identification Test (AUDIT-K) and Alcohol Use Questionnaire (AUQ). There were 79 and 81 participants in the BD and non-BD groups, respectively. We administered the Korean version of the California Verbal Learning Test (K-CVLT) and Rey-Osterrieth Complex Figure Test (RCFT) to evaluate verbal and non-verbal memory, respectively, and measured executive functions using the Wisconsin Card Sorting Test (WCST), Trail-Making Test, Controlled Oral Word Association Test and Stroop Color-Word Test. We administered the d2 test to evaluate attention. Neuropsychological performance was analyzed by multivariate analysis of variance. The BD group showed significantly poorer performance in the long-term free recall condition of the K-CVLT and delayed recall condition of the RCFT and completed significantly fewer categories on the WCST than the non-BD group. In addition, there were significant negative associations among the AUDIT-K total score, AUQ binge score, and long-term free recall score of the K-CVLT. There were significant negative associations between the total AUDIT-K score and delayed recall RCFT score, and between the total AUDIT-K total score and numbers of completed categories on the WCST. These results indicate that college students who participate in BD have difficulties with verbal/non-verbal memory and executive functions, and further suggest that excessive alcohol use could have detrimental effects on the hippocampal-prefrontal circuit even with a relatively short period of alcohol use.

Keywords: binge drinking, California Verbal Learning Test, executive function, non-verbal memory, Rey-Osterrieth Complex Figure Test, verbal memory, Wisconsin Card Sorting Test

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INTRODUCTION

It has long been accepted that chronic alcohol use has deleterious effects on the brain, leading to alcohol-related brain damage (Harper, 2009; Fritz et al., 2019). Individuals with alcohol-related brain damage display significant impairments in memory (Race and Verfaellie, 2012) and executive function (Maharasingam et al., 2013), in which dysfunctional hippocampal-prefrontal circuitry is implicated (Nunes et al., 2019).

Neuroimaging studies have shown that excessive alcohol consumption during adolescence or early adulthood, when the prefrontal cortex and parietal and temporal regions are still developing, is more detrimental to the brain than alcohol consumption at later times (Arnett, 2005; Spear, 2013). Binge drinking (BD), a pattern of drinking a large amount of alcohol within a short period followed by a period of abstinence (Wechsler and Nelson, 2001; Maurage et al., 2013), has attracted growing interest because BD is most prevalent among young adults, especially college students (Chun et al., 2003; Stephens and Duka, 2008). Although some recent studies have attempted to conceptualize and redefine BD (Maurage et al., 2020; Lannoy et al., 2021), BD is usually defined based on the quantity, speed, and frequency of alcohol consumption, as follows: 5 and 4 units of alcohol in males and females, respectively, more than once during the past 2 weeks; or 5 and 4 units of alcohol over a 2-h period, in males and females, respectively, leading to a blood alcohol concentration of 0.08 g/dL (Wechsler and Nelson, 2001; National Institute of Alcohol Abuse and Alcoholism [NIAAA], 2004).

Studies using structural neuroimaging techniques have reported structural abnormalities of cortical and subcortical areas in adolescents and young adults with BD. Reduced gray matter volumes, and thinner cortical tissues in frontal and temporal areas were observed in adolescents with BD compared to a non-BD group. In the former group, there was also a negative correlation between the number of binging episodes and frontal/parietal cortical thickness (Pfefferbaum et al., 2016). Subcortical areas, including the hippocampus (Medina et al., 2007; Meda et al., 2018) and cerebellum (Lisdahl et al., 2013), also exhibited decreased volumes in adolescents and young adults with BD compared to those without BD.

Functional alterations of brain systems involved in several cognitive domains, including working memory, inhibition and learning/memory, were also found in adolescents and young adults who engaged in BD. For example, young adults with BD exhibited greater activity in the dorsomedial prefrontal cortex during a working memory task (Campanella et al., 2013), and adolescents with BD showed decreased activity in frontal regions during a spatial working memory task compared to those without BD (Squeglia et al., 2011). In addition, young adults with BD exhibited greater activity in the frontal cortex, anterior cingulate cortex and insular during the Go/NoGo task, which measures inhibition ability, than those without BD (Ames et al., 2014). During a verbal paired associates task, adolescents with BD exhibited decreased activity in the inferior frontal region, but increased activity in the dorsal frontal and parietal regions, compared to those without BD (Schweinsburg et al., 2011).

In line with neuroimaging results, adolescents and young adults with BD exhibit impairments in a variety of cognitive domains. Particularly, neuropsychological studies of BD have focused on executive functions and memory/learning, which are mainly controlled by the prefrontal cortex and medial temporal cortex, respectively. Among the executive functions, inhibition, decision-making, and working memory have been studied most extensively (Carbia et al., 2018). Young adults with BD showed poorer performance on inhibition tasks, which measure the ability to inhibit pre-potent responses or mental representations, than those without BD (Czapla et al., 2015), although other studies did not observe significant differences between them (Moreno et al., 2012; Salas-Gomez et al., 2016). In addition, young adults with BD showed impaired decision-making abilities, which were measured by the Iowa Gambling Task (Xiao et al., 2009; Yoo and Kim, 2016). Regarding working memory, particularly spatial working memory, young female adults with BD exhibited poor performance (Townshend and Duka, 2005; Scaife and Duka, 2009), although other studies did not find significant differences between BD and non-BD female groups (Hartley et al., 2004). Adolescents and young adults with BD also showed verbal memory dysfunction (Carbia et al., 2017; Meda et al., 2018), although other studies did not observe significant differences in performance on verbal memory tasks between young adult BD and non-BD groups (Salas-Gomez et al., 2016).

The contradictory findings of neuropsychological and functional neuroimaging studies seem to be related to the use of different paradigms, tasks and definitions of BD. For example, the Go/NoGo task (Ames et al., 2014), Stop Signal task (Fernie et al., 2010) and Stroop Color-Word task (Salas-Gomez et al., 2016) have all been used to evaluate inhibition ability. Also, although most studies agreed regarding the definition of BD, they used different criteria in terms of the frequency of binge episodes (Severine et al., 2019).

Given that BD in college increases the likelihood of future development of alcohol use disorder (AUD) (O'Neill et al., 2001; Jennison, 2004), and the fact that college students with BD have difficulties with academic and social adjustment (Cha, 2005; Haller et al., 2010), the present study investigated the neuropsychological profile of college students who engage in BD using comprehensive neuropsychological tests. Neuropsychological assessments in various cognitive domains would promote understanding of the nature and degree of cognitive impairment, as well as its functional implications for individuals with BD. A neuropsychological profile also provides valuable insight regarding the most appropriate prevention and intervention strategies for individuals who engage in BD.

MATERIALS AND METHODS

Participants

The participant-selection procedures used herein have been described in previous studies by our research group (Yoo and Kim. 2016). We administered the Korean version of the Alcohol Use Disorder Identification Test (AUDIT-K, Barbor et al., 1992; Lee et al., 2000) and Alcohol Use Questionnaire (AUQ, Mehrabian and Russell, 1978), and a questionnaire containing items about the frequency of BD episodes in the previous 2 weeks and age of onset of alcohol consumption, to 1,030 college students.

Participants with total scores of 12–25 on the AUDIT-K (Kim et al., 1999; Lee et al., 2000) who drank five (male) or four (female) glasses more than once during the last 2 weeks (Wechsler and Nelson, 2001), and more than three (male) or two (female) glasses

per hour (National Institute of Alcohol Abuse and Alcoholism [NIAAA], 2004), were included in the BD group. A score ≥26 on the AUDIT-K indicates the possibility of alcohol dependence (Kim et al., 1999). Those with total scores less than 8 on the AUDIT-K who drank less than five (male) or four (female) glasses during the last 2 weeks, and less than two (male) or one (female) glasses per hour, were included in the non-BD group. One glass contains approximately 12 g ethanol. Thus, in this study, BD was defined based on the quantity, frequency and speed of alcohol consumption.

The Korean version of the Children of Alcoholics Screening Test (CAST-K, Jones, 1983; Kim et al., 1995) was administered as parents' alcohol use can affect their offspring's alcohol use (Ary et al., 1993). A score ≥6 on the CAST-K indicates the possibility of participants' parents had a history of AUD (Kim et al., 1995), therefore, participants who scored ≥6 score were excluded from this study. In addition, the Korean Wechsler Intelligence Scale (KWIS, Yum et al., 1992), Self-Rating Depression Scale (SDS, Zung et al., 1965), and State-Trait Anxiety Inventory (STAI, Spielberger et al., 1970) were administered to control for levels of intelligence, depression, and anxiety, respectively, since intelligence and emotion can affect performance of the neuropsychological tests (Lezak, 2012). To ensure that participants did not have neurological disorders, psychiatric disorders, or drug/alcohol abuse, the Structured Clinical Interview for DSM-IV-Non Patient (SCID-NP, First et al., 1996) was administered.

Following application of the inclusion and exclusion criteria, and the exclusion of those who refused to participate, 79 (males, $n = 22$; females, $n = 57$; age range, 18 ∼ 27 years) and 81 (males, $n = 17$; females, $n = 64$; age range, 18 ∼ 27 years) participants were classified into the BD and non-BD groups, respectively. This study was approved by Sungshin Women's University Institutional Bioethics Review Board (SSWUIRB, 2019-020). All participants provided written informed consent after receiving a complete description of the study and received remuneration for their participation.

Neuropsychological Measurements

For the evaluation of verbal and visuospatial memory, the Korean version of California Verbal Learning Test (K-CVLT) and Rey-Osterrieth Complex Figure Test (RCFT) were administered, respectively. The K-CVLT (Delis et al., 1987; Kim and Kang, 1999) consists of five free-recall trials of list A, followed by a free-recall trial of list B and short-term free and cued recalls of list A. After a 20-min delay, long-term free/cued recalls of list A and recognition tests were administered. The total numbers of responses to free recall trials 1–5, free recall of list B, and the short- and long-term free-recalls of list A, were recorded. The RCFT, which was administered to evaluate visuospatial memory (Lezak, 2012), involves three conditions: copying, immediate recall (3 min after copying), and 30-min delayed recall, and a recognition trial. Accuracy and response times were calculated for each condition based on the system developed by Meyers and Meyers (1995).

Executive functions were evaluated by the Wisconsin Card Sorting Test (WCST), Trail-Making Test (TMT), Controlled Oral Word Association Test (COWA), and Stroop Color Word Test. The WCST, which requires sorting cards based on color, number, and shape, measures problem-solving, abstract thinking, and mental-set shifting (Lezak, 2012). The numbers of total errors, perseverative errors, and categories completed were determined based on the scoring system developed by Heaton et al. (1993). The TMT consists of two parts, A and part B, which involve connecting digits with a line, and alternately connecting digits and letters, respectively. The TMT is sensitive for evaluating the ability to shift mental sets and control attention (Lezak, 2012). The total numbers of errors and response times were scored. The COWA, which is widely used to evaluate frontal lobe functions including controlled attention (Stuss and Benson, 1986), requires participants to respond to many words beginning with a particular letter and belonging to a particular category. The total numbers of responses were recorded by letter and category. The Stroop Color-Word Test is widely used for measuring interference control (Rapport et al., 2001), and the numbers of words read correctly during 45 s were counted (Golden, 1978). The interference control was calculated as follows; score of color-word condition–[(score of word condition × score of color condition) / (score of word condition + score of color condition)] (Golden, 1978; van Mourik et al., 2005).

The d2 test (Brickenkamp and Zillmer, 1998), which measures selective attention, requires participants to detect a target as quickly and accurately as possible. The total number of errors was determined, and concentration index was measured by subtracting number of commission errors from the total number of correct responses. Neuropsychological tests were administered during a single session that lasted about 2 h.

Statistical Analysis

The demographic characteristics of the BD and non-BD groups were analyzed using independent *t*-tests. Neuropsychological performance was analyzed by multivariate analysis of variance (MANOVA). All *p*-values were Bonferroni-corrected, and $p < 0.05$ was considered to be statistically significant. Associations between performance on the neuropsychological tests and BD severity were analyzed using the Pearson product-moment correlation coefficient. All statistical analyses were carried out using SPSS software (version 26.0; IBM Corp., Armonk, NY, United States). The Kolmogorov-Smirnov test and the Q-Q plot were used to ascertain whether data was normally distributed (Vetter, 2017).

RESULTS

Demographic Characteristics

The demographic characteristics of the BD and non-BD groups are described in **Table 1**. The two groups did not differ in age [$t(158) = -0.30$, $p = 0.77$], educational level [$t(158) = -0.52$, $p = 0.60$], SDS score [$t(158) = 0.64$, $p = 0.52$], STAI state anxiety score [$t(158) = 0.64$, $p = 0.52$], STAI trait anxiety score [$t(158) = 1.63$, $p = 0.10$], or total IQ score on the KWIS [$t(158) = -0.76$, $p = 0.45$]. However, the groups differed significantly in terms of the total AUDIT-K score [$t(158) = 33.59$,

TABLE 1 | Demographic characteristics of the binge drinking and non-binge drinking groups.

	Non-binge drinking group (n = 81)		Binge drinking group (n = 79)		t
	Mean (SD)		Mean (SD)		
Age (years)	21.72	(2.40)	21.61	(2.18)	−0.30
Education (years)	14.94	(1.25)	14.82	(1.54)	−0.52
SDS	40.96	(7.46)	41.68	(6.72)	0.64
STAI state	40.25	(10.70)	41.28	(9.63)	0.64
STAI trait	41.35	(9.74)	43.81	(9.33)	1.63
KWIS total IQ	114.37	(9.90)	113.28	(8.08)	−0.76
AUDIT-K	1.67	(1.90)	17.52	(3.79)	33.59***
Drinking speed (drinks/hour)	0.75	(0.56)	4.23	(1.38)	21.00***
Frequency of drunkenness within the last 6 months	0.12	(0.43)	7.14	(8.63)	7.31***
Percentage of drinking occasions resulting in drunkenness (%)	11.27	(25.19)	46.23	(30.91)	7.85***
AUQ binge drinking score	5.40	(5.65)	33.33	(14.27)	16.35***

***$p < 0.001$.

SDS, self-rating depression scale; STAI, Spielberger's state-trait anxiety inventory; KWIS, the Korean Wechsler intelligence scale; AUDIT-K, the Korean version of alcohol use disorder identification test; AUQ, alcohol use questionnaire.

$p < 0.001$], drinking speed [$t(158) = 21.00$, $p < 0.001$], frequency of drunkenness within the last 6 months [$t(158) = 7.31$, $p < 0.001$], percentage of drinking occasions resulting in drunkenness [$t(158) = 7.85$, $p < 0.001$], and AUQ binge score [$t(158) = 16.35$, $p < 0.001$].

Neuropsychological Measures

The MANOVA revealed significant differences in performances on the K-CVLT, RCFT, and WCST between the BD and non-BD groups. In terms of the K-CVLT, the BD group showed significantly poorer long-term free recall performance for list A than the non-BD group [$F_{(1,158)} = 6.33$, $p = 0.013$, $\eta^2_p = 0.039$]. Individuals with BD also exhibited lower scores in the delayed recall condition of the RCFT [$F_{(1,158)} = 4.03$, $p = 0.046$, $\eta^2_p = 0.025$] and completed fewer categories on the WCST [$F_{(1,158)} = 3.97$, $p = 0.048$, $\eta^2_p = 0.024$] compared to those without BD. The performances of the BD and non-BD groups on the neuropsychological measures are presented in **Table 2**. **Figure 1** presents the performances of the BD and non-BD groups on the long-term free recall of the K-CVLT and delayed recall condition of the RCFT.

Correlations Between Binge Drinking and Performance on the Neuropsychological Tasks

There were significant negative correlations between the AUDIT-K total score and long-term free recall score for list A of the K-CVLT [$r = -0.190$, $p < 0.01$], and between the AUQ binge score and long-term free recall score for list A of the K-CVLT [$r = -0.198$, $p < 0.01$]. In addition, there were significant negative associations between the AUDIT-K total score and delayed-recall RCFT score [$r = -0.161$, $p < 0.05$], and between the AUDIT-K total score and numbers of completed categories of the WCST [$r = -0.173$, $p < 0.05$]. These correlations were observed in individuals with BD, but not in those without BD.

DISCUSSION

Since cognitive impairment affects the functional outcomes of patients with AUD (Heirene et al., 2016), and cognitive difficulties observed in patients with AUD are also found in individuals with BD (Mota et al., 2013), the present study investigated the neuropsychological profile of college students who engage in BD. The BD and non-BD groups exhibited significant differences in performance on the measures evaluating verbal/non-verbal memory and cognitive flexibility.

College students with BD performed worse in terms of long-term free recall of list A of the K-CVLT than those without BD. In addition, there were significant negative correlations of the AUDIT-K total score and AUQ binge score with the long-term free recall score for list A of the K-CVLT. In other words, individuals with BD have difficulties with verbal memory, where additional alcohol consumption correlated with poorer performance on a scale measuring long-term verbal memory.

Previous studies have also reported that young adults with BD have verbal memory difficulties. For example, Parada et al. (2011), Mota et al. (2013), and Carbia et al. (2017) found that college students with BD performed worse in the immediate and delayed recall conditions of the logical memory subtest of the Wechsler Memory Scale-III than those without BD. Sneider et al. (2013) also observed that young adults with BD recalled significantly fewer words on trials 1∼5 of the CVLT than those without BD. In addition, Meda et al. (2018) investigated the effect of alcohol consumption on the hippocampus and parahippocampus in college students over 2 years, and found that a higher alcohol use index, i.e., greater alcohol consumption, was associated with an accelerated decline of gray matter in the hippocampus/parahippocampus, and a larger reduction of hippocampal volume was in turn associated with poor memory performance, as measured by the CVLT. Therefore, the present results indicate that college students who participate in BD have difficulties in verbal memory, and these difficulties seem

TABLE 2 | Neuropsychological performance of the binge drinking and non-binge drinking groups.

	Non-binge drinking group (*n* = 81)		Binge drinking group (*n* = 79)		*p*
	Mean (SD)		Mean (SD)		
RCFT					
Response time (ms)					
Copy	147.90	(41.56)	143.58	(52.82)	0.566
Immediate recall	176.48	(89.95)	159.03	(64.03)	0.160
Delayed recall	118.75	(49.72)	117.24	(48.34)	0.846
Accuracy					
Copy	33.05	(1.96)	32.31	(2.82)	0.056
Immediate recall	21.80	(5.40)	20.47	(5.46)	0.124
Delayed recall	21.89	(5.45)	20.19	(5.25)	0.046*
Recognition	19.99	(2.52)	20.35	(1.99)	0.309
K-CVLT					
List A trials 1–5	66.26	(7.91)	64.46	(8.11)	0.156
List B trial	9.09	(2.24)	8.85	(2.40)	0.517
List A short-term free recall	14.46	(1.57)	13.99	(2.10)	0.111
List A long-term free recall	15.10	(1.26)	14.53	(1.58)	0.013*
WCST					
Total number of errors	14.52	(9.46)	16.86	(14.04)	0.217
Perseverative errors	7.77	(5.07)	8.13	(6.69)	0.701
Categories completed	5.91	(0.50)	5.65	(1.10)	0.048*
TMT					
Response time (ms)					
Part A	27.93	(9.31)	26.52	(8.28)	0.314
Part B	57.80	(19.96)	55.54	(15.72)	0.428
Error					
Part A	0.01	(0.11)	0.00	(0.00)	0.325
Part B	0.21	(0.49)	0.22	(0.50)	0.946
COWA					
Letter	44.32	(11.10)	42.67	(8.52)	0.294
Category	39.33	(8.53)	38.71	(15.72)	0.642
Stroop					
Accuracy					
Word	84.90	(10.44)	85.50	(13.83)	0.758
Color	73.99	(10.11)	74.01	(11.21)	0.988
Word/Color	54.49	(11.76)	55.50	(9.82)	0.560
Interference Control	15.11	(10.61)	16.00	(7.43)	0.547
d2 Test					
Total number of errors	16.25	(15.16)	15.75	(12.93)	0.823
Concentration performances	227.06	(39.33)	228.00	(37.36)	0.877

*$p < 0.05$.

RCFT, rey-osterieth complex figure test; K-CVLT, the Korean version of the California verbal learning test; WCST, Wisconsin card sorting test; TMT, trail-making test; COWA, controlled oral word association test; Stroop, stroop color-word test.

to be related to structural alterations of medial temporal regions including the hippocampus which are involved in verbal memory function.

Individuals with BD also showed poorer performance in the delayed recall condition of the RCFT compared to those without BD, and there was a significant negative association between the total AUDIT-K score and score in the delayed recall condition of the RCFT. These results are consistent with those of previous studies reporting poorer performance in the delayed recall condition of the RCFT in adolescents and young adults with BD compared to those without BD (Hartley et al., 2004; Squeglia et al., 2009; Winward et al., 2014; Kim et al., 2020).

Although the mechanisms underlying the visual memory difficulties observed in individuals with BD are not yet fully understood, alterations in functional connectivity of the brain seem to be related to visual memory impairments. For example, Kim et al. (2020) observed significantly lower delayed recall RCFT score in college students with BD compared to those without BD, and a significant positive association between left prefrontal-parietal occipital midline functional connectivity and

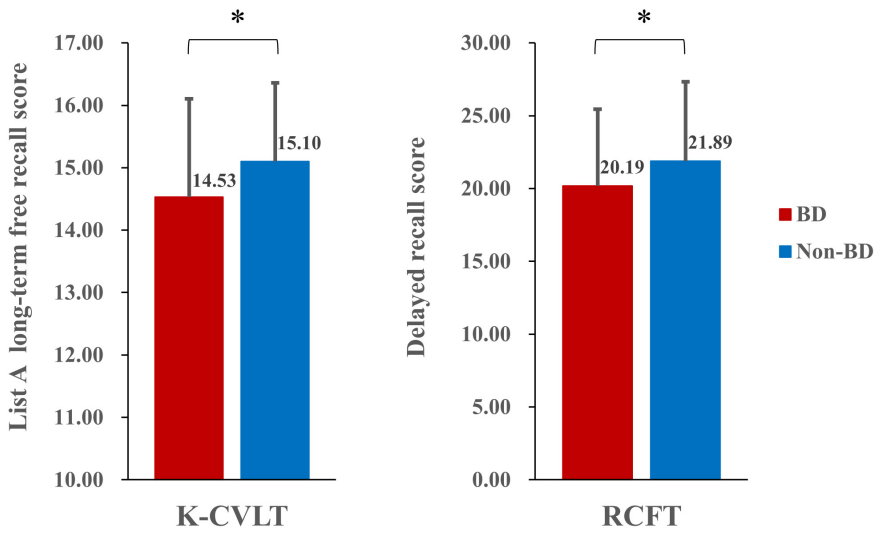

FIGURE 1 | Performance of the Korean version of the California Verbal Learning Test (K-CVLT) and Rey-Osterrieth Complex Figure Test (RCFT) in the binge and non-binge drinking groups. *$p < 0.05$.

performance in the delayed recall condition of the RCFT only in the BD group.

The RCFT is also known to be sensitive for assessment of executive functions, including organization and planning. For example, previous studies found that organizational strategies, evaluated *via* qualitative analysis of RCFT data, mediated visual memory deficits in patients with obsessive-compulsive disorder (Savage et al., 1999; Shin et al., 2004) and schizophrenia (Kim et al., 2008). Although studies about associations between executive functions and non-verbal memory using the RCFT in individuals with BD have not yet been reported, the difficulties with non-verbal memory observed in the present study could reflect difficulties of executive functions, such as organization and planning, in college students with BD.

The WCST, which is sensitive to prefrontal dysfunction (Demakis, 2003), has been widely used to evaluate executive functions (Rabin et al., 2005). Successful performance of the WCST requires strategic planning, the ability to use environmental feedback to shift cognitive set, goal-directed behavior, and the ability to inhibit impulsive responding (Stuss et al., 2006). Stephan et al. (2017) reported that the WCST is one of the most sensitive neuropsychological tests to detect changes resulting from alcohol abuse. In this study, individuals with BD completed fewer categories on the WCST compared to those without BD, and there was a significant association between the AUDIT-K total score and number of categories completed.

The number of categories completed refers to the number of sequences of 10 consecutive correct matches to the criterion sorting category and is the most common index used to assess cognitive control on the WCST along with perseverative errors (Stuss et al., 2006). Therefore, the present results indicate that individuals with BD have difficulties in cognitive control and these difficulties seem to be related to prefrontal dysfunction.

We administered TMT, COWA and Stroop Color-Word Test to evaluate components of executive functions, such as controlled attention and interference control, in addition to the WCST. We did not observe any significant differences between the BD and non-BD groups on the measures except the WCST. One possible explanation for the present results is that the deleterious effect of BD on the executive functions could be observed in a measure which is complicated and requires high-order cognitive functions such as the WCST (Faustino et al., 2021).

In addition, it is known that cognitive or behavioral changes emerge after alterations of the brain structure and function (Rubia et al., 2001). In other words, the emergence of behavioral deficits in the neuropsychological tasks require a somewhat long period of BD. For example, Lopez-Caneda et al. (2013) observed that young adults with BD and non-BD exhibited different EEG pattern, and the difference was more pronounced after 2 years of maintenance of BD. Furthermore, Gil-Hernandez and Garcia-Moreno (2016) observed better performance on some of the neuropsychological tests including the Stroop test in adolescents with BD than those without BD. The authors suggested that neurotoxic effects of BD on prefrontal cortex can be less evident in adolescence, but if BD persists the executive function would be exacerbated. As participants in the present study had a relatively short period of BD (the mean number of years of alcohol consumption in the BD group was 2.52), significant structural/functional alterations of brain and the resultant cognitive dysfunctions such as controlled attention or interference control could not be found.

The present study had several limitations that should be addressed in future studies. First, although the gender ratio between the BD and non-BD groups did not differ ($\chi^2 = 0.874$), we could not include equal numbers of male and female participants in each group. As significant differences in brain activation (Squeglia et al., 2011) and neuropsychological

performance (Hartley et al., 2004; Townshend and Duka, 2005) between male and female binge drinkers have been observed, studies examining gender differences would provide insight into the nuanced effects of alcohol consumption on brain functions and cognition in male and female binge drinkers. Second, the important question of whether cognitive difficulties are present prior to BD and predict its onset, or whether BD induces the cognitive difficulties, has been posed recently. However, because of the cross-sectional and exploratory nature of this study, the direction of cognitive difficulties and BD onset cannot be ascertained. Future prospective longitudinal studies could provide answers to this question. Finally, college students who engage in BD are more likely to use other substances, including cigarettes and marijuana (Jones et al., 2001), so these substances should be controlled for in future studies.

In conclusion, college students with BD exhibited significantly poorer performance in the long-term free-recall condition of the K-CVLT and delayed recall condition of the RCFT, and completed fewer categories on the WCST than those without BD. In addition, there were significant negative associations of the AUDIT-K total score and AUQ binge score with the score in the long-term free-recall condition of the K-CVLT, between the scores for the ADUIT-K and delayed recall condition of the RCFT, and between the AUDIT-K score and number of completed categories on the WCST. These results indicate that college students with BD have difficulties with verbal/non-verbal memory and executive functions, which are controlled mainly by the hippocampus and prefrontal cortex, respectively. The present results also provide valuable information about the deleterious effects of BD on memory and executive function, even when the duration of BD is relatively short. Therefore, efforts reducing excessive alcohol consumption among college students should be done *via* individual interventions such as mobile technology-based interventions (Fowler et al., 2016) or structural interventions including college policies restricting places for alcohol consumption (Toomey et al., 2007).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study involving human participants was reviewed and approved by Sungshin Women's University Institutional Review Board (SSWUIRB, 2019-020). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

M-SK helped in conceptualization, funding acquisition, writing of the manuscript, and supervised the overall aspects of the manuscript. J-GK contributed to recruit participants, administer, and score neuropsychological tests and interpretation of the results, and writing of the manuscript. Both authors contributed to the article and approved the submitted version.

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OPINION
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Binge Drinking and Problem Gambling Association in Adolescents and Young Adults

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Keywords: adolescence, binge drinking, gambling, executive functions, decision-making

INTRODUCING THE LINK BETWEEN BINGE DRINKING (BD) AND PROBLEM GAMBLING

While the association between alcohol use disorders and problem gambling has been object of discussion in previous research literature, less is known about the link between Binge Drinking (BD) and risk gambling in adolescents.

Starting from a definition of those two phenomena, shared definitions and criteria for BD (Maurage et al., 2020) and for problem gambling (Neal et al., 2005) have been proposed. Nonetheless, such a topic is still a matter of debate. In the literature concerning BD, one of the most recognized definition of the phenomenon is the one of the National Institute on Alcohol Abuse and Alcoholism (NIAAA, USA), which describes it as the consumption of >56 g (women) or >70 g (men) of ethanol in <2 hours, bringing blood alcohol concentration to at least 0.08%. As for the relatively recent proposal of an integrated definition of BD, see Maurage et al. (2020). At-risk/problem gambling can, instead, be described as a behavior characterized by "difficulties in limiting money and/or time spent on gambling, which leads to adverse consequences for the gambler, his/her relatives, or the community" (pp. 1) and tends to encompass gamblers who have experienced problem gambling without meeting the diagnostic criteria of gambling disorder (Neal et al., 2005).

Interestingly, in terms of prevalence, evidence has shown that both BD (Kraus and Nociar, 2016; Substance Abuse Mental Health Services Administration, 2018) and gambling (Shaffer and Hall, 2001; Calado and Griffiths, 2016; Calado et al., 2017) show higher prevalence rates in adolescents and young adults than adults. Despite gambling on lottery products (e.g., scratch tickets), private card games (e.g., poker), putting bets on games of skill, and sports betting are the most regularly reported behaviors for gambling in teenagers in most North American, European, and Australasian studies (Delfabbro et al., 2016), the increased prevalence rates of gambling in this age group may be explained by the augmented availability of gambling opportunities via the internet, mobile phone and interactive television and by the normalization of this behavior in society (Calado et al., 2017).

Previous research suggested the association between BD and problem gambling. For instance, college students who matched the criterion for BD were more likely to engage in sports betting, video and regular poker, the web, office pools, and other skill games than those who did not satisfy the criteria (Bhullar et al., 2012). In US college athletes, problem gambling showed the strongest association with at-least-weekly heavy episodic drinking, followed by marijuana and cigarette use (Huang et al., 2011). Sundqvist et al. (2015) examined the association between BD and at-risk gambling in the general Swedish population and found they are linked behaviors. However, age and smoking had the greatest impact on the association, suggesting the relevance of demographic

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variables for this population. Even socio-demographic factors, such as the housing conditions (e.g., not living with both parents in the same household and not having a university-educated parent) were associated with both heavy episodic drinking and risk gambling (Kaltenegger et al., 2019). The association between BD and problem gambling in adolescents has been confirmed also by a cross-sectional study involving thirty-three European countries (Gori et al., 2015; Molinaro et al., 2018).

Although socio-demographic factors seem to mediate the relationship between BD and problem gambling, it is necessary to underline that even factors related to cerebral and cognitive development are involved in the development of this co-occurrence of risky behaviors.

This contribution follows a specific structure. We will start by describing the neurodevelopmental reasons why adolescents are at risk for BD and gambling behavior. Then, we will focus on how cognitive factors also contribute to this association and we will discuss decision-making dysfunction in adolescents with BD as the common ground with problem gambling. With the aim of providing not only an overview of the impaired brain functions that come into play in this comorbidity (i.e., the *pars destruens*), the fourth section focuses on the *pars construens*, that is the description of potential clinical interventions at the intersection between BD and problem gambling.

In conclusion, the need for tailor-made prevention and treatment for adolescence with BD and problem gambling so to address these multiple risk domains will be stressed.

WHY TEENAGERS ARE AT RISK FOR BD AND GAMBLING

Firstly, what are the neurodevelopmental reasons why teenagers are at risk for BD and gambling behaviors? To date, the investigation of the cognitive and neurological basis of adolescents' conduct has yielded substantial advancements in the neurodevelopmental field (Ernst et al., 2006, 2009; Steinberg, 2010; Casey et al., 2011). Notably, the typical development of pubertal age includes the development of brain structures that support the consequent cognitive development, encompassing the ability to process rewards and punishments but also self-awareness and self-regulation processes, which allow managing the propensity to novelty-seeking and risk-taking that is typical of adolescent behavior. And therefore, where does the aspect of vulnerability to risk behaviors typical of this age fit in?

Previous neurobiological models described how subcortical neural circuitries develop faster than cortical regions (*i.e.,* prefrontal cortex) in adolescents (Casey et al., 2011). The misalignment relative to the maturation of neural areas that support the increase in motivation and satisfaction of needs and structures that deal with motivation regulation makes the adolescent's necessary adjustment to societal norms and individual ambitions complex. A peculiarity of typical adolescent development concerns the importance of the short-term rewards that derive from one's choices and conducts, which tends to be greater than the capacity for self-regulation. This aspect exposes them to situations that can be risky for their health, but also to new necessary challenges for the typical human development (Windle et al., 2008).

Four different theoretical models in cognitive neuroscience described adolescence neurocognitive mechanisms related to the development of regulated behavior. According to the model of the "dual system" (Steinberg, 2010) and the theory of "maturational imbalance" (Casey et al., 2011), higher risk-taking throughout adolescence leads to a mix of augmented sensitivity to gains and primal impulse control. Also, the "triadic model" stated that adolescence is marked by variations in the interplay between approach behavior, avoidance tendencies, and regulatory systems (Ernst et al., 2006, 2009). Indeed, the approach system typically appears hypersensitive, whereas the avoidance system is somewhat hyposensitive. Also, the development of the regulation system of Executive Functions (EFs) may not yet be sufficiently mature to control and adaptively modulate the other two systems. Finally, a neuroeconomic approach to teenage decision-making (van Duijvenvoorde and Crone, 2013) try to account for the association between risky choice, sensitivity to gains and losses, and social perspective-taking typically characterizing the adolescence developmental phase. Specifically, the immaturity of cortical areas supporting the "hot" executive system (*i.e.,* the system including functions activated under motivationally significant and affective conditions, such as the ability to delay gratification and affective decision-making; Zelazo and Carlson, 2012) may explain the reason why the explicit knowledge about the risks and outcomes of the conduct, which depends on a developed cognitive control, seems to be in place, while the affective control of the choice is not (Steinberg, 2005), thus leading to poor decision-making processes.

With reference to these cognitive and executive factors in the context of addiction in adolescents, Noël (2014) focused specifically on the individual differences in cognition and neural functions accounting for the onset of alcohol use disorder and gambling in adolescence. It addressed the vulnerable points and discussed the role of dysfunctional EF and decision-making in this population. However, the impairment of those abilities has been detected even in association with BD in adolescents and this is what will be discussed in the next section. From a lifespan-oriented perspective, it is essential to conduct neurodevelopment studies exploring the neurocognitive vulnerability to risky behaviors in adolescents. In fact, adolescence and youth are periods characterized by significant structural and functional changes in the brain. Implementing such dysfunctional behaviors (BD and gambling) during that critical period of growth becomes potentially predictive of future brain, cognitive, behavioral, and psychological alterations, which can manifest themselves through functional consequences over time.

EXECUTIVE AND DECISION-MAKING DYSFUNCTION IN ADOLESCENTS WITH BD: COMMON GROUND WITH PROBLEM GAMBLING

Both neural and behavioral impairments related to EF have been noted in adolescents with alcohol use disorder and gambling

(Noël, 2014), but also in young binge drinkers (Lannoy et al., 2019). Indeed, adolescents and young patients with BD display an alteration of cognitive functioning supported by the cortico-frontal regions and hippocampus (Squeglia et al., 2012). More specifically, adolescents and young adults showing BD and heavy-drinking have a thinner and lower volumes of gray matter in prefrontal cortex and cerebellar regions, as well as attenuated white matter development. When presented with working memory, language learning, and inhibitory control tasks, they also demonstrate increased brain activity in fronto-parietal areas. Binge and heavy drinkers demonstrate enhanced brain response to alcohol signals in mesocorticolimbic areas such as the striatum, anterior cingulate cortex, hippocampus, and amygdala, compared to controls or light drinkers (Cservenka and Brumback, 2017).

Also, besides EF impairments, several studies showed that binge drinkers had poorer decision-making abilities measured with the Iowa Gambling Task (Goudriaan et al., 2007, 2011; Xiao et al., 2009, 2013; Moreno et al., 2012).

At the neural level, different neurocognitive findings have been described depending on the decision-making process assessed through the decision-making task (Cservenka and Brumback, 2017). In BD individuals, riskier decision-making behavior was linked to dorsal striatum hypoactivation (Jones et al., 2016). Binge drinkers, on the other hand, showed increased activity in the prefrontal, orbitofrontal, and upper parietal dorsolateral cortex in association with hazardous choices in a risk-taking task (Worbe et al., 2014). Xiao et al. (2013) findings at the Iowa Gambling Task showed that, compared to never drinkers, binge drinkers display an augmented bilateral activation of the insula and left amygdala, two affective neural hubs linked, respectively to the translation of inner body information into feelings and the elaboration of reward and emotions. Taken all together, these findings suggest poor decision-making ability in BD both at the behavioral and neural level, with a potential social implication for the individual, that is the higher vulnerability of adolescents to other risky behaviors such as alcohol use disorder or problem gambling (Xiao et al., 2013).

Of interest for this contribution, here we intend to discuss and propose how this decision-making dysfunction could be one of the main common grounds between BD and problem gambling. This assumption is supported by the findings focusing on decision-making in adolescents with gambling (*e.g.,* Ciccarelli et al., 2016; Cosenza et al., 2017) and adolescents with BD. For example, Goudriaan et al. (2007) found that poor binge drinkers' decision-making abilities at the Iowa Gambling Task were unrelated to their impulsivity score. Again, Moreno et al. (2012) found decision-making deficits in the absence of inhibitory control impairments. Also, Na et al. (2019) assessed, by means of Event-Related Potentials, the ability to use feedback for decision-making in female college students binge drinkers and found a deficit in the early evaluation of positive vs. negative feedback, concluding that this deficit may impact on dysfunctional behavioral decision-making.

These findings support Verdejo-Garcia's (2017) hypothesis that, while decision-making abilities and executive processes may be linked, individuals can also have a dissociated pattern characterized by decision-making impairments but preserved EF (as in the case of Moreno et al., 2012), or functional decision-making but EFs impairment (Balconi and Angioletti, 2021; Balconi and Campanella, 2021) highlighting the process independent contribution (Verdejo-Garcia, 2017). For example, in our recent work on internet use vulnerability in healthy young adults (a different population than the one discussed in this opinion article), we have highlighted how high scores in the internet addiction test seem to correspond to an attentional bias for internet addiction-related cues (pictures representing online gambling), while decision-making abilities appeared preserved (Balconi and Angioletti, 2021). This example is consistent because it refers to a different population, potentially preclinical and in which decision-making is preserved. It has been reported here in order to further underline the possible dissociation between impaired executive functioning and decision-making.

At the level of theoretical understanding, this possible dissociation has yet to be deepened and systematized in relation to adolescents with BD and problem gambling. This reflection could be a useful starting point to deepen this aspect also in the entire field of "new" behavioral addictions. Additionally, it proves useful to identify a dissociation between effectively impaired functions in this population to develop tailored preventive or rehabilitative approaches. This knowledge may have clinical implications ranging from the combination of multiple training approaches to precision medicine. For instance, multiple training approaches could combine psychosocial interventions with specific cognitive training on decision-making dedicated to adolescents with BD and problem gambling.

With the aim of providing applications and highlighting the first practical implications of this contribution, the next section aims to focus on the clinical interventions at the intersection between BD and problem gambling, with reference to adolescents and young age groups where possible.

CLINICAL INTERVENTIONS AT THE INTERSECTION BETWEEN BD AND PROBLEM GAMBLING

As discussed up to this point, the adolescent phase consists of a stage of life in which the individual is particularly exposed to transgressions and risky impulses, such as alcohol consumption, substance use (Charrier et al., 2020), and gambling behavior (Noël, 2014). The proof related to the co-occurrence of risky behaviors in adolescents may have consequences for designing approaches and planning preventive and treatment clinical interventions: the most promising intervention programs to reduce risk behaviors seems to be those that target multiple risk domains (Spring et al., 2012).

With reference to the available clinical interventions at the intersection between BD and problem gambling in adolescents, Martin et al. (2020) reviewed the effectiveness of therapeutic interventions for adolescents using alcohol and/or other drugs in the Australian context and found a paucity of quality research on this topic. Such, a critical issue seems primarily due to the

fact that the studies that are accessible do not account for all the treatment strategies actually adopted in the field. While some of these interventions have a solid evidence base, others (such as encounter groups and journaling) require further in-depth research before being used with teenagers (Martin et al., 2020). In general, psychosocial, rather than pharmacological, interventions are recommended as first-line treatment for adults with BD (Rolland and Naassila, 2017). However, well-defined protocols and tested clinical recommendations would be necessary to work both in terms of prevention and clinical intervention with these vulnerable samples.

Despite the paucity of systematic reviews on this topic, this contribution wants to underline the need for clinical interventions dedicated to cognitive factors, such as the neurocognitive aspects of EFs, in adolescents with BD and problem gambling. To date, there is a lack of neurocognitive interventions specifically dedicated to EF and decision-making for this population. Specific training and tools to prevent and rehabilitate the EF processes impaired in BD, particularly inhibitory control (Lannoy et al., 2019), have been addressed before. Also, neuromodulation techniques (specifically, transcranial Direct Current Stimulation over the left dorsolateral prefrontal cortex; Den Uyl et al., 2015) have been recognized as interesting avenues for targeting inhibitory control in this population.

Nonetheless, when there is a co-occurrence of problem gambling in adolescents, the clinical interventions might benefit from the integration of specific training on working memory, self-regulation (Noël, 2014), and decision-making. Given the shortage of research exploring intervention on combined BD and problem gambling, one possibility is to refer to the interventions available to date for the treatment of neurocognitive aspects related to problem gambling in adolescence. Frisone et al. (2020) underlined that the data referred to the treatment of gambling in adolescence appeared as limited as the studies proposing preventive approaches. Typically, psychological treatment approaches adopted with adults with gambling disorder–such as motivational interviewing, cognitive behavioral therapy, and brief mindfulness interventions (Menchon et al., 2018)–are also proposed for adolescents with problem gambling. These interventions may have an impact on decision-making capabilities with problem gambling (*i.e.,* cognitive behavioral treatment; Oldershaw et al., 2012). Also, cognitive training (Luquiens et al., 2019) and neuromodulation could be new avenues for enhancing EF in gambling. For instance, neuromodulation applied over the dorsolateral prefrontal cortex has been associated to enhanced decision making and cognitive flexibility in a sample of male adults with gambling disorder (Soyata et al., 2019).

Although there is some evidence that psychological intervention programs can improve EF and decision-making in teenagers with BD and problem gambling, novel neurocognitive approaches are required to specifically target the impaired decision-making abilities and immature self-regulation system in this population. In addition, even though research and clinical practice are still in an embryonic stage for these approaches, other types of intervention (such as non-invasive neurofeedback) could be warranted to investigate if neuromodulation interventions are promising even at this stage of life and for this behavioral co-occurrence.

CONCLUDING REMARKS

To summarize, little is known about the link between BD and problem gambling in adolescence. However, while socio-demographic factors appear to influence this relationship, even factors related to adolescent cerebral and cognitive development should be taken into consideration, since they constitute a factor that makes teenagers vulnerable to the development of this risky behavior pattern. A first consideration is that more studies in this area are needed to better understand the co-occurrence or possible causality between BD and gambling in adolescents and young adults. These future studies will have to take into account that there are aspects related to the age of prevalent manifestation of problem gambling (14–15 years) compared to BD (20–21 or 18–25 years; Barnes et al., 2009; Substance Abuse Mental Health Services Administration, 2018), as well as to personality traits related to these two risky behaviors that could constitute barriers to conducting studies in this field and that must be taken into account to obtain a complete picture of this co-occurrence.

The impairment of EF and decision-making in adolescents could be considered a critical common feature of both BD and problem gambling and this aspect could deserve further attention in this field. Despite several studies assessing potential cognitive impairment in young BD and (to a lesser extent) problem gamblers, no studies have explored the cognitive performance of individuals with these two risk behaviors. This constitutes a gap in the literature that could be filled in the next few years and before developing adequate neurocognitive interventions for this population. Indeed, one of the more practical goals of this discussion is to solicit the development of tailor-made preventive and treatment interventions for adolescence with BD and problem gambling, in order to address these multiple risk domains, as well as EFs (especially decision-making) efficiency.

Therefore, the additional value of this contribution consists of (i) the specific focus on the EFs and decision-making in adolescents showing the comorbidity between BD and problem gambling; (ii) the distinction between a possible impairment in decision-making while EFs are preserved in this population, (iii) highlighting the lack of neurocognitive interventions specifically dedicated to EFs and decision-making for this population with BD and problem gambling. Despite its novel characteristics, one of potential shortcomings of this work is that it is an opinion article only providing comments on the interpretation of recent data in the research area of BD and problem gambling in teenagers, rather than a thorough assessment of the literature.

Future research directions should address these limitations and conduct studies that delve deeper into the link between these two behaviors, as well as into the potential neuro-functional and cognitive alterations associated with them, with particular attention to executive functions and decision-making. These studies could then consequently form the

basis for the research and development of new preventive and rehabilitative neurocognitive treatments, including for example cognitive training and neuromodulation techniques, specifically dedicated to EF and decision-making in this population.

AUTHOR CONTRIBUTIONS

LA and MB wrote the first draft and each section of the manuscript and contributed to the manuscript final writing and revision, read, and approved the submitted version.

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Effects of Persistent Binge Drinking on Brain Structure in Emerging Adults: A Longitudinal Study

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Previous cross-sectional research has largely associated binge drinking (BD) with changes in volume and thickness during adolescence and early adulthood. Nevertheless, the long-term alcohol-related effects on gray matter features in youths who had maintained a BD pattern over time have not yet been sufficiently explored. The present study aimed to assess group differences both cross-sectionally and longitudinally [using symmetric percent change (SPC)] on several structural measures (i.e., thickness, surface area, volume). For this purpose, magnetic resonance imaging was recorded twice within a 2-year interval; at baseline (18–19 years) and a follow-up (20–21 years). The sample included 44 university students who were classified as 16 stable binge drinkers (8 females) and 28 stable controls (13 females). Whole-brain analysis showed larger insular surface area in binge drinkers relative to controls at follow-up (cluster-wise $p = 0.045$). On the other hand, region of interest (ROI) analyses on thickness also revealed a group by sex interaction at follow-up ($p = 0.005$), indicating that BD males had smaller right rostral middle frontal gyrus thickness than both control males ($p = 0.011$) and BD females ($p = 0.029$). Similarly, ROI-based analysis on longitudinal data showed a group by sex interaction in the right nucleus accumbens ($p = 0.009$) which revealed a decreased volume across time in BD males than in control males ($p = 0.007$). Overall, continued BD pattern during emerging adulthood appears to lead to gray matter abnormalities in regions intimately involved in reward processing, emotional regulation and executive functions. Notably, some anomalies varied significantly depending on sex, suggesting a sex-specific impact of BD on typical neurodevelopment processes.

Keywords: binge drinking, brain structure, longitudinal, sex differences, surface-based morphometry, emerging adulthood

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INTRODUCTION

Alcohol is the most widely available and commonly used drug during adolescence and youth, as informed by epidemiological surveys (1, 2). Among the various alcohol consumption patterns, binge drinking (BD) is the most prevalent among young adults. It has been associated with several neuropsychological, structural, and functional anomalies (3–5), as well as with an increased risk of

developing alcohol use disorder (6–8). This type of drinking is characterized by the intake of large amounts of alcohol in a brief time followed by intervals of abstinence, and it is generally defined as the consumption of 5 or more drinks (4 or more for females) on one occasion within a 2-h time period (which leads to a blood alcohol concentration of at least 0.08 g/dL) (9). Notably, peak BD rates are reached between ages 18 and 25 (2), a life-changing period in which brain maturation is still under development and may be particularly vulnerable to the neurotoxic effects of alcohol (10–13).

When interpreting the results of studies that have assessed how alcohol intake affects the adolescent brain, we must also consider the differences and overlap between BD and other types of consumption. Although the definition of BD has long been debated, in the present work, we consider the combination of rapid and intermittent intoxication episodes with periods of abstinence as a key feature to characterize this pattern, as proposed by Maurage et al. (14). On this basis, the confusion around BD pattern conceptualization is reduced, allowing us to distinguish the effects of BD from those of other drinking patterns, for instance heavy drinking, which refers to consumption of alcohol more frequently (14, 15).

Neuroanatomical differences in both binge drinkers (BDs) and young people with heavy drinking relative to controls have been extensively reported by magnetic resonance imaging (MRI) studies, suggesting that the two drinking behaviors are associated with distinct gray matter changes (5, 16–18). As our interest is focused on exploring specific effects of BD, we set for our sample strict inclusion and exclusion criteria to better isolate the effects of BD on the developing brain.

Previous cross-sectional studies that have used specific BD criteria to characterize the impact of alcohol consumption during adolescence and young adulthood have consistently shown that this pattern can lead to common gray matter abnormalities (in volume and/or thickness) in prefrontal regions (i.e., middle frontal gyrus and anterior cingulate) and subcortical limbic areas (i.e., ventral striatum/accumbens) intimately involved in the control and regulation of impulsive or risky behaviors, as well as in processing rewarding stimuli (19–24). Likewise, sex differences in the effect of BD on brain structure, including but not limited to prefrontal regions, have also been identified in other studies which reported both reduced volume and lower thickness in frontal, striatal, middle temporal, and parietal regions in male BDs than their control peers, while female BDs showed the opposite pattern (25, 26). It is worth noting that the significance of the directionality of the anomalies is not clear yet. It has been hypothesized that either the increase or decrease in gray matter features (observed in BDs relative to controls in these studies) may represent an alteration in typical neurodevelopment, probably caused by the neurotoxic effects of alcohol (27, 28).

Longitudinal investigations that have attempted to shed light on the consequences of excessive alcohol consumption on the brain have revealed altered developmental trajectories in young heavy drinkers relative to controls (27, 29–34). Specifically, studies that have examined neural structure both before and after the onset of heavy drinking reported recurrent accelerated gray matter declines, particularly in frontal (27, 29, 33, 34) and temporal regions (32, 33). On the other hand, in line with some of the longitudinal studies stated above, two works exploring the effects of continuous heavy drinking among emerging adults, who were heavy drinkers at baseline, also informed of gray matter loss in frontal and temporal (30) as well as subcortical regions (31). Remarkably, similar frontal findings were revealed in a study that performed a single MRI scan after a 10-year history of heavy alcohol consumption (35). However, most of these studies recruited young people with a history of heavy drinking. Therefore, a study whose participants have a specific BD pattern as the main consumption behavior is necessary.

Taking into account these considerations, we aimed to assess whether the possible anomalies related to a BD pattern are maintained or increased over a 2-year follow-up period. Thus, we compared brain trajectories of university students who maintained a stable BD pattern vs. their control peers in three gray matter cortical features, including thickness, volume, and surface area, as well as subcortical volumes, through surface-based morphometry (SBM) method. Interestingly, recent studies have suggested that thickness and surface area are heritable but genetically and phenotypically independent (36, 37) and regulated by different processes (37, 38). To carry out the longitudinal analysis, we applied a robust measure [i.e., symmetric percent change (SPC)] that has not been used before in BD research to explore cortical and subcortical development changes over time. In addition, another important goal of this study was to examine potential sex-related differences on the effects of the maintenance of the BD pattern.

Accordingly, we tested three hypotheses. First, based on the aforementioned cross-sectional findings, we predicted that young BDs would exhibit alterations in gray matter morphology indices compared to controls at baseline, specifically in brain regions that showed anomalies in at least two independent studies, such as anterior cingulate, middle frontal gyrus, and ventral striatum/accumbens. Second, we expected that these potential abnormalities would be more pronounced at follow-up and that other initially unobserved anomalies may emerge due to maintaining the pattern of consumption. Third, we hypothesized that differences in SPC rate would be found between BDs and controls. No specific directional hypotheses were advanced regarding the examined structural metrics, given the inconsistent findings from previous research.

MATERIALS AND METHODS

Participants

The final sample comprised 44 participants who were enrolled in a longitudinal neuroimaging study within the framework of a broader research project on consequences of BD among university students (39–41). All subjects completed MRI assessments at two different times; at baseline and a follow-up when they were aged 18–19 and 20–21 years, respectively.

Initially, 2,998 first-year students from the University of Santiago de Compostela (USC, Spain) were selected based on their responses to a classroom questionnaire assessing

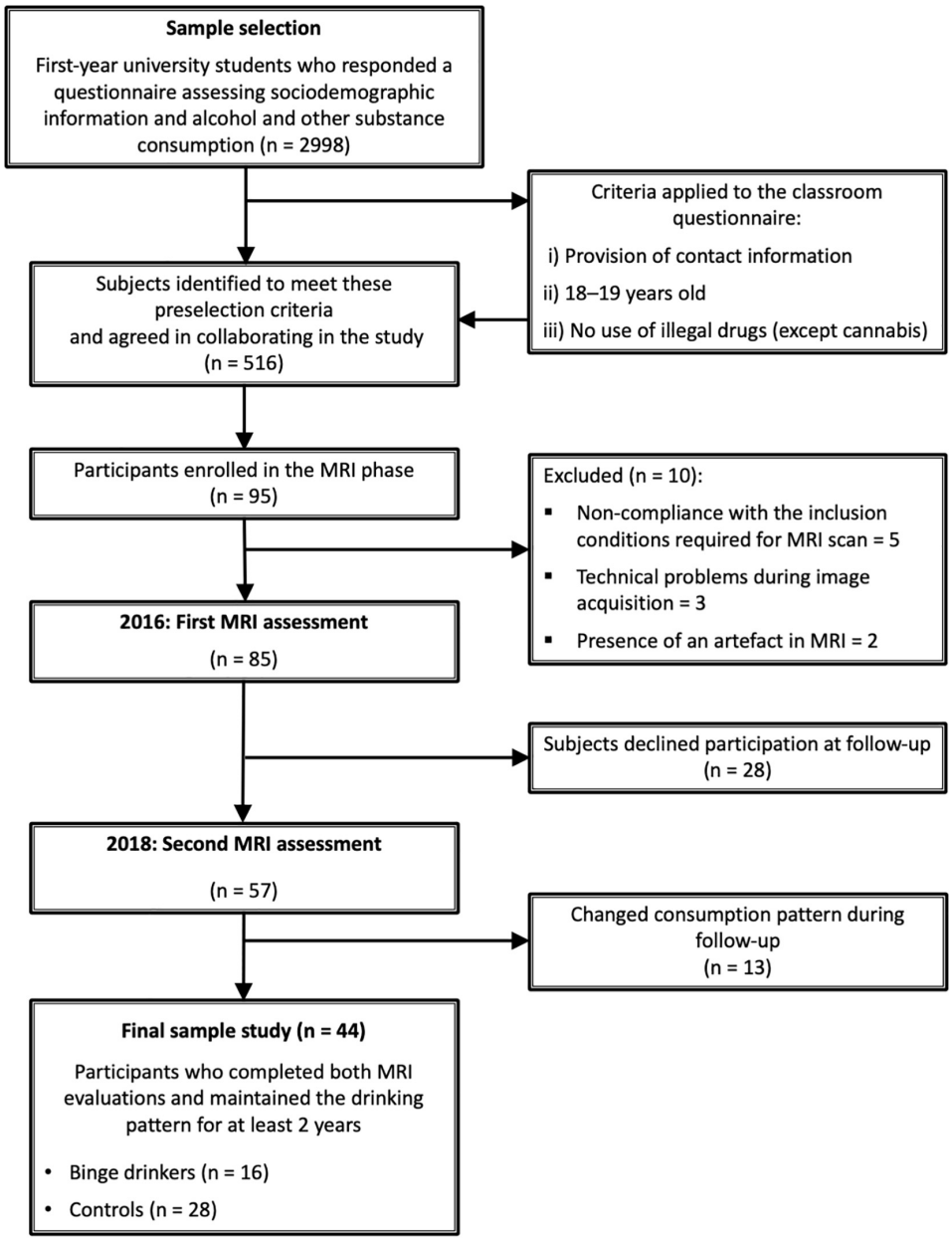

FIGURE 1 | Timeline with the phases of the study.

sociodemographic information and alcohol and other substance consumption (the study's timeline is shown in **Figure 1**). The questionnaire included the Galician adapted version of the Alcohol Use Disorders Identification Test (AUDIT) (42, 43), the short version of the Nicotine Dependence Syndrome Scale (NDSS-S) (44, 45) and the Cannabis Abuse Screening Test (CAST) (46, 47). To distinguish the most suitable subjects from the initial 2,998 questionnaires, the following pre-selection criteria were applied to the classroom questionnaire: (i) provision of contact information (telephone number and e-mail); (ii) 18–19 years old; and (iii) no illicit drug use except cannabis. From this sample, 516 subjects who met these criteria agreed to participate in the study. These participants then completed a semi-structured interview and a set of questionnaires including medical history, the Alcohol Timeline Follow-back calendar (TFLB) over the past 180 days, the Cannabis TLFB over the past 90 days (48), and the Spanish version of Symptom Checklist-90-Revised (SCL-90-R) (49). Those interviewees who met the inclusion/exclusion criteria (see **Table 1**) were considered for enrolment in the MRI phase. All participants gave written consent and received monetary compensation for their collaboration. The study was approved by the Bioethics Committee of the USC.

Subjects were classified as BDs if they reported one BD episode at least once a month over the last 6 months, or as controls if they did not meet the alcohol consumption threshold to be considered BDs. A BD episode was defined as the consumption of ≥ 50 g (females) or ≥ 70 g (males) of alcohol in one occasion, raising blood alcohol concentration above 0.08 g/dL (i.e., a measure that corresponds to the 4/5 standard drinks criteria specified in the NIAAA's definition of BD) (9). As the objective in this study was to compare longitudinal trajectories of consumption, only participants who met these criteria fulfilled in both time evaluations were selected. Hence, the final sample included 44 participants, with 16 continuous BDs (8 females) and 28 continuous controls (13 females). The sociodemographic and drinking characteristics of each group are summarized in **Table 2**.

Image Acquisition

Structural images were collected at both baseline and follow-up MRI scans on a 3T Achieva Philips body scanner (Philips Medical Systems, Best, NL) equipped with a 32-channel SENSE head coil (located at the University Hospital Complex of Santiago de Compostela, Spain). Three-dimensional T1-weighted anatomical images were acquired using a 3D turbo field-echo sequence with the following parameters: TR/TE = 7.7/3.4 ms, flip angle = 8°, FOV = 240 mm, voxel size = 0.8 mm^3, 200 transverse slices, acquisition time = 7 min. All images were inspected to assess any artifacts or abnormal structural features.

Image Preprocessing

Cross-Sectional and Longitudinal Processing Pipeline

The cortical surfaces and subcortical volumes were reconstructed and segmented using the FreeSurfer 6.0 image analysis suite[1] (50, 51). First, preprocessing from baseline and follow-up was conducted separately using the standard cross-sectional stream. Briefly, processing included removal of non-brain tissue, automated Talairach transformation, segmentation, intensity normalization, tessellation of the gray/white matter boundary, topology correction, and surface deformation. Then, the FreeSurfer longitudinal stream[2] was applied; this method included the creation of a within-subject template space and image from two cross-sectional time-points (baseline and follow-up) using robust registration (52, 53). Subsequent steps were initialized with common information from the within-subject template, increasing reliability and statistical power (53). For both cross-sectional and longitudinal processing pipelines, anatomical gray matter parcellations were labeled with reference to the Desikan-Killiany Atlas (54), while the subcortical segmentation was derived from Fischl et al. (55). When all reconstructions were completed, the resultant surfaces were used to calculate thickness, surface area, and cortical volume vertex-wise representations. The cortical volume is determined as the product of thickness and surface area for each cortical region; the thickness is defined as the shortest distance between the gray-white matter and pial surfaces, whereas surface area was calculated as the sum of the area within a given region on the white surface (56–58). Prior to the statistical analyses, individual thickness, surface area, and cortical volume maps were spatially smoothed using a Gaussian filter with full-width at half-maximum (FWHM) of 15 mm. Data outputs from each stage were inspected to ensure accuracy using the protocol developed by the ENIGMA consortium.[3]

In addition, based on our recent systematic review regarding the brain correlates that may be specific to BD in adolescents and young adults (5), the following bilateral regions of interest (ROIs) were selected: anterior cingulate (rostral and caudal divisions) and middle frontal gyrus (rostral and caudal divisions) defined according to the Desikan-Killiany atlas (54), and nucleus accumbens (NAcc) on the basis of the Aseg atlas (55). Consequently, cortical and subcortical structural values calculated in Freesurfer for each ROI (i.e., mean thickness in mm, surface area in mm^2, and volume in mm^3) were retrieved from the statistics files and exported to SPSS for statistical analysis.

[1] https://surfer.nmr.mgh.harvard.edu/

TABLE 1 | Exclusionary criteria established in the study.

Exclusion criteria
• Medical conditions affecting the normal cognitive functioning (hypothyroidism, diabetes, etc.)
• History of neurological disorders or history of brain injury with loss of consciousness for longer than 20 min
• History of diagnosed psychopathological disorders (axis I and II, according to DSM-IV-TR criteria)
• SCL-90-R score > 90th percentile on Global Severity Index (GSI) or at least two symptomatic dimensions
• Family history of major psychopathological disorders in first-degree relatives (clinically diagnosed by a professional)
• Family history of first-degree alcoholism or substance abuse
• Non-corrected sensory deficits and MRI contraindications
• AUDIT scores[a] > 20 at the start of the study
• Regular consumption of substances with psychoactive effects (psycholeptics)
• Use of illegal drugs (except occasional consumption of cannabis)[b]

[a] *AUDIT, Alcohol Use Disorders Identification Test.*
[b] *Subjects who consumed > 12 units over the last 90 days, or who regularly consumed cannabis (1 or more units per week), were not included.*

Statistical Analysis

Demographic and User Characteristics

Demographic and consumption variables were compared between the groups (BDs vs. controls) using Student's *t*-tests or chi-squared tests when appropriate. For longitudinal data, mixed-models repeated-measures analyses of variance (ANOVAs) were carried out for each consumption variable with the factor time (baseline vs. follow-up) as within-subject factor and group and sex as between-subject factors. *Post-hoc* comparisons were performed using the Bonferroni adjustment for multiple comparisons. All analyses were done with SPSS (version 22).

Whole-Brain Surface Analyses

All group whole-brain comparisons were executed in FreeSurfer using vertex-wise general linear models (GLMs) for each

[2] https://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalTwoStageModel
[3] http://enigma.ini.usc.edu/protocols/imaging-~protocols/

TABLE 2 | Demographic and alcohol use characteristics of the control and BD groups (mean [95% CI]).

	Baseline		Follow-up	
	Controls	**BDs**	**Controls**	**BDs**
n (females)	28 (13)	16 (8)	28 (13)	16 (8)
Age	18.55 [18.44–18.66]	18.56 [18.40–18.73]	20.57 [20.44–20.70]	20.51 [20.35–20.67]
Time between MRI assessments (months)	-	-	24.10 [22.98–25.21]	23.99 [22.09–25.89]
Age of onset on drinking***	16.58 [16.12–17.04]	15.50 [15.06–15.94]	-	-
Average # drinks per drinking occasion***	1.81 [1.30–2.32]	7.03 [5.68–8.38]	1.84 [1.36–2.31]	8.00 [6.42–9.58]
Average # drinks per week***	1.12 [0.47–1.77]	11.00 [8.02–13.98]	1.13 [0.49–1.77]	14.89 [7.38–22.40]
Number of BD episodes[a] (last 180 days)***	0.61 [0.03–1.19]	20.31 [14.90–25.72]	0.71 [0.17–1.26]	27.00 [17.15–36.85]
Total AUDIT score[b] ***	1.71 [0.93–2.50]	9.60 [7.67–11.53]	1.68 [1–2.35]	9.44 [7.14–11.73]

****p* ≤ 0.001.

[a]*BD episode: consumption of ≥ 50 g (females) or ≥ 70 g (males) of alcohol in one drinking occasion, raising blood alcohol concentration above 0.08 g/dL.*

[b]*In the BD group, missing scores for the second (participant 1) and the sixth and seventh items (participant 2) of the AUDIT at baseline were replaced by the BD group mean in each specific item.*

hemisphere independently. The estimated total intracranial volume was included as a covariate in the analysis of surface area and cortical volume to correct volumetric data for inter-individual differences in brain sizes (59). The longitudinal change was computed using the symmetric percentage change (SPC) rate. SPC is defined as a single metric that represents the percent change with respect to the average of thickness/volume/surface area across both time-points at each vertex for each participant (53). SPC is calculated using the formula:

$$\mathrm{SPC} = 100 * \frac{\text{measure at time 2} - \text{measure at time 1}}{(\text{interval between assessments}) * 0.5 * (\text{measure at time 1} + \text{measure at time 2})}$$

$$= 100 * \frac{\text{Rate}}{\text{Average}}$$

Both cross-sectional and longitudinal designs were conducted accounting for the interaction effects between group and sex. Whole-brain results from each GLM analysis were corrected for multiple comparisons using Monte Carlo Z simulation implemented in FreeSurfer (60), with a cluster-forming threshold of –log10 $p = 3.3$ (corresponding to $p < 0.0005$) and a cluster-wise p (CWP) threshold of < 0.05 (10.000 permutations).

Region of Interest Analyses

Group differences in cortical and subcortical ROI measures were tested using ANOVAs or Analyses of Covariance (ANCOVAs). The dependent variables were the mean ROI values (including SPC data) for each calculated metrics (i.e., thickness, surface area and volume [cortical and subcortical]) while group and sex were included as fixed factors. The estimated total intracranial volume was added as a covariate when outcome measures were surface area and volume (cortical and subcortical). To counteract the multiple comparison problem, the Bonferroni procedure was applied (dividing the significance level by the number of ROIs examined). Therefore, only *p*-values of < 0.00625 ($\alpha = 0.05/8$) for cortical regions (i.e., anterior cingulate, middle frontal gyrus) and $p < 0.025$ ($\alpha = 0.05/2$) for subcortical regions (i.e., NAcc) were considered significant. Bonferroni adjustment ($p < 0.05$) was applied to *post-hoc* comparisons where appropriate.

Correlation Analyses

Spearman's rho (controlling for estimated total intracranial volume in the case of volume and surface area) were performed between morphology parameters extracted from each cluster or/and ROIs presenting significant between-group differences and the following consumption variables at follow-up: (i) average drinks per drinking occasion; (ii) total AUDIT score. All tests were performed with a statistical significance threshold set at $p < 0.05$.

RESULTS

Sample Characteristics

Sample characteristics of each group for both baseline and follow-up are detailed in **Table 2**. No differences were observed between the groups in terms of sex, age, or interval between MRI assessments. As expected, alcohol consumption variables were significantly different between groups in both assessments: age of onset of alcohol consumption, $t_{(33)} = 3.540$, $p = 0.001$; average drinks per drinking occasion [$F_{(1,\ 40)} = 111.679$, $p < 0.001$, $\eta_p^2 = 0.736$]; average drinks per week [$F_{(1,\ 40)} = 62.161$, $p < 0.001$, $\eta_p^2 = 0.608$]; number of BD episodes [$F_{(1,\ 40)} = 120.270$, $p < 0.001$, $\eta_p^2 = 0.750$]; AUDIT score [$F_{(1,\ 40)} = 93.903$, $p < 0.001$, $\eta_p^2 = 0.701$]. Significant interactions were observed between time by sex [$F_{(1,40)} = 4.732$, $p = 0.036$, $\eta_p^2 = 0.106$] and group by time by sex for AUDIT score [$F_{(1,40)} = 8.757$, $p = 0.005$, $\eta_p^2 = 0.180$]. Specifically, the first interaction could be explained by a decrease in AUDIT score in females relative to males at follow-up (4.62 [95% CI = 3.33–5.90] vs. 6.47 [95% CI = 5.22–7.73]; $p = 0.044$). The second interaction revealed a decrease in AUDIT score in baseline vs. follow-up in BD females (9.79 [95% CI = 7.85–11.73] vs. 8.00 [95% CI = 5.97–10.03]; $p = 0.016$) but an increase in AUDIT score in BD males (9.41 [95% CI = 7.47–11.35] vs. 10.88 [95% CI = 8.85–12.90]; $p = 0.047$).

Furthermore, BD males scored higher than BD females only at follow-up ($p = 0.049$).

Magnetic Resonance Imaging Results

Cross-Sectional Analysis (Baseline and Follow-Up)

Baseline

Neither the whole-brain analysis, nor the ROI analysis revealed significant group differences in thickness, surface area or volume (cortical and subcortical) between BDs and controls.

Follow-Up

Whole-brain analysis showed that BD group, in comparison to controls, had significantly larger surface area (CWP = 0.045) in one cluster located in the left insula (MNI coordinates = −31.4, −26.2, 8.7, cluster size = 280.74 mm^2) (**Figure 2**). ROI analyses on thickness revealed a group by sex interaction [$F_{(1,\ 40)} = 8.857$, $p = 0.005$, $\eta_p^2 = 0.181$] in the rostral division of the right middle frontal gyrus (**Figures 3A,B**), with lower thickness observed in BD males compared to controls males ($p = 0.011$). In the BD group, a reduced thickness was also observed in this region in males relative to females ($p = 0.029$).

Longitudinal Analysis

Whole-brain analyses found no differences in the SPC in any of the measures examined (i.e., thickness, surface area, and cortical volume). ROI analyses on subcortical volume revealed a group by sex interaction [$F_{(1,\ 39)} = 7.596$, $p = 0.009$, $\eta_p^2 = 0.163$] in the right NAcc (**Figures 3C,D**), showing that BD males had reduced volume over time relative to control males ($p = 0.007$); in the control group, an increase of volume in males compared to females was observed ($p = 0.033$). Regardless of alcohol consumption, a significant main effect of sex was observed in the left rostral middle frontal gyrus thickness [males < females; $F_{(1,\ 40)} = 9.584$, $p = 0.004$, $\eta_p^2 = 0.193$].

Relationship Between Gray Matter Structural Measures and Alcohol Consumption Variables

Whole-brain cluster in the left insula (surface area, both groups combined): the surface area was positively correlated with the average drinks per drinking occasion (rho = 0.684, $p < 0.001$) and with AUDIT score (rho = 0.682, $p < 0.001$).

Right rostral middle frontal gyrus (thickness, males): thickness of this ROI was negatively correlated with the average drinks per drinking occasion (rho = −0.593, $p = 0.003$) and with AUDIT score (rho = −0.554, $p = 0.006$).

Right NAcc (SPC volume, males): correlation analysis of this ROI showed a negative association between SPC volume and the average drinks per drinking occasion (rho = −0.542, $p = 0.009$).

DISCUSSION

This study aimed to examine cross-sectionally and longitudinally the effect of the BD pattern on young brain development on three

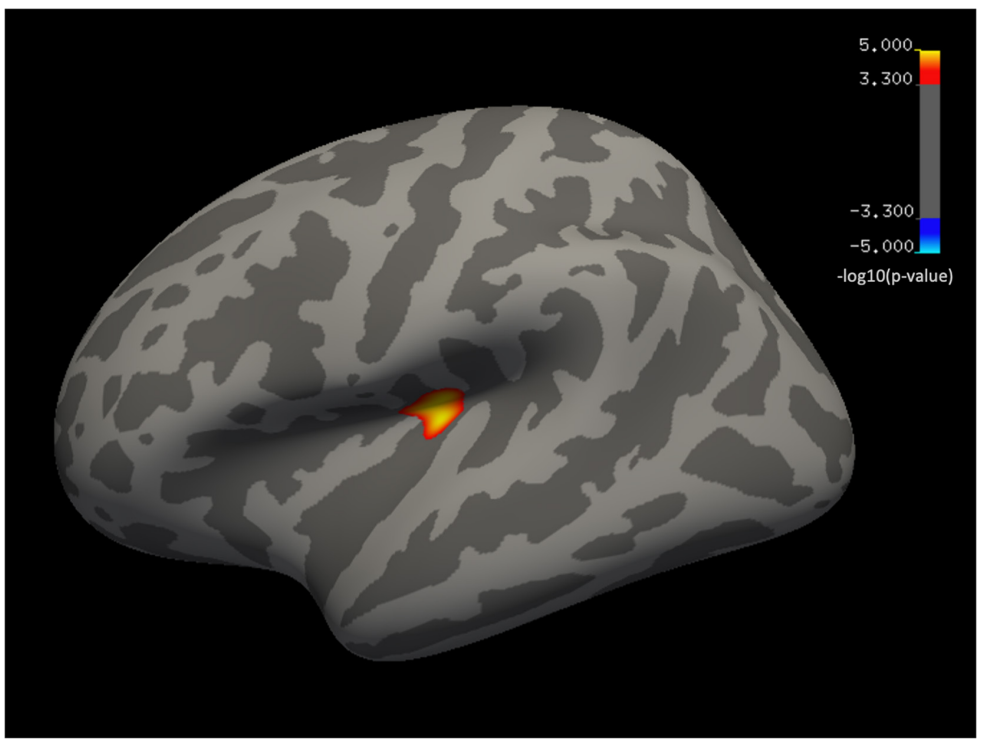

FIGURE 2 | Whole-brain vertex-wise analysis. Inflated cortical convolution maps showing group differences in a cluster located in the left insula, corrected for multiple comparisons (cluster-forming threshold $p < 0.0005$ and cluster-wise p-threshold < 0.05). Significance levels are on a -log(p) scale; positive values reflect the larger surface area in BDs vs. controls (warm colors).

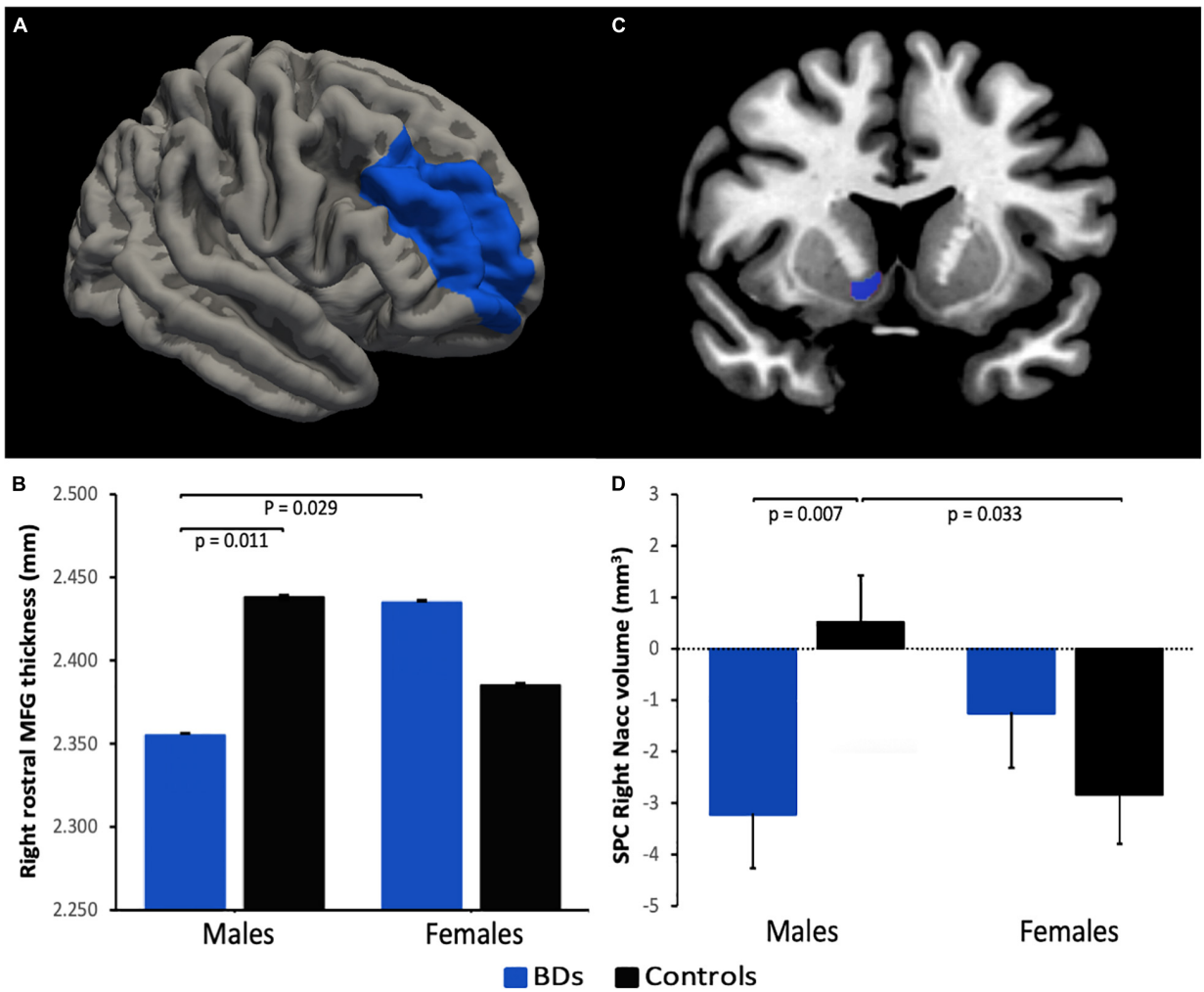

FIGURE 3 | Region of interest (ROI) analysis. **(A,C)** Areas in blue illustrate the brain labels (derived from FreeSurfer atlases) used to define ROIs. **(B,D)** Bar graphs represent significant group by sex interactions in rostral middle frontal gyrus (MFG) thickness at follow-up and right nucleus accumbens (NAcc) volume across time (i.e., symmetrized percent change, SPC), respectively. Errors bars represent the standard error of the mean. NAcc image is displayed in radiological convention (i.e., left is right).

different structural metrics: thickness, surface area, and volume. To this end, we tested for differences between emerging adult BDs and age-matched controls in both baseline and follow-up time-points, as well as in the SPC measure over 2 years.

Cross-Sectional Findings (Baseline and Follow-Up)

First, contrary to our hypothesis, we did not find differences in baseline time between groups, regardless of the type of analysis employed (e.g., whole-brain analysis or ROI). These results contrast with several cross-sectional studies which have consistently associated a BD pattern in adolescence and young adulthood with structural abnormalities, especially in prefrontal regions (i.e., middle frontal gyrus, anterior cingulate), and subcortical limbic areas (ventral striatum/accumbens) (19–24). Considering the similarity between our study and those previously mentioned in relation to sample characteristics together with the consumption pattern, we believe that the conservative significance threshold used in our analysis, both in ROI-based and surface vertex approach, could help to explain this discrepancy. Nevertheless, other additional factors, such as a longer maintenance of the BD pattern before the baseline assessment (e.g., 19) or the variability in the age range of the samples (which could correspond with different neurodevelopmental stages) (e.g., 23, 24) may also contribute to the inconsistency in results (see 5 for a systematic review on structural findings and methodological details of cross-sectional BD studies).

Second, as expected and partly in agreement with our predictions, anomalies not initially observed emerged at follow-up, as well as a significant group by sex interaction. Specifically, whole-brain analyses showed that young BDs had a larger surface area in a cluster in the left insula compared to controls.

The insular cortex subserves multiple brain processes, such as cognitive control, detecting interoceptive cues and emotional regulation (61). Furthermore, this brain area has been proposed as particularly relevant in the addiction cycle, mainly due to its role in the conscious urges to use drugs [for review see (62)]. Structural gray matter abnormalities implicating the insula in alcohol (63–68) and other drugs addictions (69) have been described. Interestingly, in accordance with our results, a recent study observed significantly higher bilateral insular surface in adult individuals with alcohol use disorder (68); nevertheless, it should be noted that meta-analyses of voxel-based morphometry studies in this population revealed reduced volume in the insula (70, 71). Previous longitudinal research has also shown insular structural alterations in both moderate and heavy alcohol use during emerging adulthood (30, 35, 72). However, these studies reported reductions in surface area (72) and volume (30, 35), without a consistent lateralization pattern of structural changes throughout the studies. To date, no insular anomalies have been detected in BDs, in contrast to several functional imaging studies that have shown altered brain activity (i.e., hyperactivation) in this region during decision-making (73), response inhibition (41, 74), and alcohol cue-reactivity tasks (75). We thus observed, for the first time, a larger surface area in the left insula in youth with a BD pattern. Although the surface area has not been explored as much as thickness or volume, neurodevelopment studies generally showed a decline in this feature across adolescence (76). As anticipated in the introduction, there are different possible explanations for understanding the meaning of the direction of gray matter anomalies. Our result fits with the hypothesis proposed by Squeglia et al. (25), suggesting that increases in gray matter measures in BDs may represent an alteration of healthy synaptic pruning processes due to alcohol exposure. This interpretation of a possible interference of neuromaturational processes would also be supported by other studies using BD samples with a similar university-age range, which revealed an increase in gray matter volume in cortical regions (19, 20).

On the other hand, ROI analyses reported a significant group by sex interaction on thickness in right rostral middle frontal gyrus at follow-up, showing that BD males had thinner cortices than both control males and BD females. The middle frontal gyrus is involved in executive functions, such as inhibitory control, working memory and cognitive flexibility (77). Studies focusing on young BDs have reported structural abnormalities in the middle frontal gyrus volume (19, 20, 23). Functional anomalies in this region during inhibition tasks prospectively predicted both binge and heavy drinking consumption throughout adolescence and alcohol-related problems in the future (78). Our finding is congruent with prior studies that reported reduced thickness or volume in BD males compared to control males in prefrontal regions (25, 26). Though, we found no differences in gray matter between BD females and their counterparts controls. One factor that may help explain this discrepancy is the significantly lower AUDIT score (as a measure of drinking severity) in BD females than BD males at follow-up.

Longitudinal Findings

Another main objective of this study was to explore potential longitudinal changes (i.e., SPC) in gray matter features in youth with a continuous BD pattern. ROI analyses reported a significant group by sex interaction in the right NAcc, showing that BD males had a greater volume decline over a 2-year follow-up than control males. The NAcc has been implicated in the reinforcing properties of acute alcohol consumption and plays a crucial role in neural models of addiction (79). Previous cross-sectional studies have found structural abnormalities in NAcc volumes in university-aged BDs (22, 24). Likewise, the reduction of NAcc volumes in BDs over time observed in our study agrees with several longitudinal investigations that have associated both binge (80) and heavy alcohol use (27, 30–34) during adolescence and emerging adulthood with a decrease of cortical and subcortical gray matter volumes. Various of these studies suggest that the decline of gray matter could be interpreted as an accelerated but non-beneficial pruning due to the neurotoxic effects of alcohol. Of note, a recent mega-analysis in the framework of the IMAGE project reported significantly lower NAcc volumes in alcohol-dependent individuals relative to non-dependent controls (81). Importantly, our finding is partially in line with the cross-sectional study by Kvamme et al. (26) which found a sex-specific decrease in NAcc volumes in university-aged BD males relative to control males, whereas females showed the opposite pattern. Given the longitudinal nature of the analyses used here, our results would further indicate that the maintenance of a BD pattern is associated with sex-related abnormalities in this structure over time, linked to the number of drinks per drinking occasion. These sex-differentiated effects of alcohol during early adulthood may be due to multiple factors. For example, one reason that may partially explain the sex differences observed in our sample is the increase in drinking severity over time (follow-up vs. baseline) in BD males along with the decrease observed in BD females. It is, therefore, possible that higher alcohol consumption over time aberrantly increases pruning in BD males relative to females. Another aspect to consider are the structural differences between males and females observed in neurodevelopmental studies which have typically been interpreted in terms of the rate and timing of synaptic pruning (82, 83).

Strengths and Limitations

To our knowledge, this is the first study on BD that combined cross-sectional data collected at two-time points over time with longitudinal change data, several morphological measures characterizing the cortical mantle (thickness, surface area, and volume), and a rigorous control for potential confounders to elucidate the structural changes in the young brain related to the BD pattern. However, despite its many strengths, our study also had some limitations to consider. Firstly, the strict exclusion criteria, together with the recruitment of subjects limited to students who completed all neuroimaging assessments and maintained the drinking pattern for a period of at least 2 years, resulted in a relatively small sample size. Secondly, the characteristics of the selected participants (university students),

such as high cognitive functioning and absence of associated pathologies, might limit the representativeness of our results to other populations. Finally, future studies with more than two follow-up assessments should be conducted to explore whether the abandonment of the BD pattern would imply a reversal or attenuation of the abnormalities previously observed.

CONCLUSION

Overall, our cross-sectional and longitudinal results suggest that continued BD in emerging adults may lead to structural gray matter anomalies in several regions strongly associated with reward processing, emotional regulation and executive functions. Remarkably, some abnormalities may vary depending on sex, reflecting a differential consequence of BD pattern on neuromaturation trajectories between males and females.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Bioethics Committee of the Universidade de Santiago de Compostela. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FC obtained funding for the study. FC, SR, MC, and SD designed the study. MC and SR were responsible for sample selection. JP-G, SS-S, and JB-R collected the data. JP-G, EC-R, and SD analyzed and interpreted the data. JP-G wrote the manuscript. All authors reviewed the manuscript and approved the submitted version.

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Forgetting Alcohol: A Double-Blind, Randomized Controlled Trial Investigating Memory Inhibition Training in Young Binge Drinkers

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Background: Binge Drinking (BD) has been associated with altered inhibitory control and augmented alcohol-cue reactivity. Memory inhibition (MI), the ability to voluntarily suppress unwanted thoughts/memories, may lead to forgetting of memories in several psychiatric conditions. However, despite its potential clinical implications, no study to date has explored the MI abilities in populations with substance misuse, such as binge drinkers (BDs).

Method: This study—registered in the NIH Clinical Trials Database (ClinicalTrials.gov identifier: NCT05237414)—aims firstly to examine the behavioral and electroencephalographic (EEG) correlates of MI among college BDs. For this purpose, 45 BDs and 45 age-matched non/low-drinkers (50% female) will be assessed by EEG while performing the Think/No-Think Alcohol task, a paradigm that evaluates alcohol-related MI. Additionally, this work aims to evaluate an alcohol-specific MI intervention protocol using cognitive training (CT) and transcranial direct current stimulation (tDCS) while its effects on behavioral and EEG outcomes are assessed. BDs will be randomly assigned to one MI training group: *combined* [CT and verum tDCS applied over the right dorsolateral prefrontal cortex (DLPFC)], *cognitive* (CT and sham tDCS), or *control* (sham CT and sham tDCS). Training will occur in three consecutive days, in three sessions. MI will be re-assessed in BDs through a post-training EEG assessment. Alcohol use and craving will be measured at the first EEG assessment, and both 10-days and 3-months post-training. In addition, behavioral and EEG data will be collected during the performance of an alcohol cue reactivity (ACR) task, which evaluates attentional bias toward alcoholic stimuli, before, and after the MI training sessions.

Discussion: This study protocol will provide the first behavioral and neurofunctional MI assessment in BDs. Along with poor MI abilities, BDs are expected to show alterations in event-related potentials and functional connectivity patterns associated with MI. Results should also demonstrate the effectiveness of the protocol, with BDs exhibiting an improved capacity to suppress alcohol-related memories after both *combined* and

cognitive training, along with a reduction in alcohol use and craving in the short/medium-term. Collectively, these findings might have major implications for the understanding and treatment of alcohol misuse.

Clinical Trial Registration: [www.ClinicalTrials.gov], identifier [NCT05237414].

Keywords: alcohol, craving, binge drinking, memory inhibition, randomized controlled trial, cognitive training, electroencephalograpy (EEG), transcranial direct current stimulation (tDCS)

INTRODUCTION

Besides being the most consumed drug in the world, alcohol represents a major risk factor for disease contributing largely to the number of deaths worldwide (World Health Organization [WHO], 2019). WHO data reveals that more than 30% of the deaths of American and European young males aged 15–29 years are somehow associated with alcohol (World Health Organization [WHO], 2011), which suggests that excessive alcohol consumption is particularly harmful for young people. One form of alcohol misuse that is common among youngsters and has received special attention in the last two decades, is binge drinking (BD) which is characterized by episodes of excessive alcohol use followed by periods of low consumption or abstinence (López-Caneda et al., 2019a; Maurage et al., 2020). This pattern is highly prevalent in most Western countries—including Portugal—being present in approximately 35% of people aged 15–24 years (Balsa et al., 2014; Kraus et al., 2016).

The high prevalence of BD at this age is of particular concern since adolescence and youth are periods especially vulnerable to the neurotoxic effects of alcohol, mainly due to the ongoing structural and functional changes occurring in the brain (Jones et al., 2018). Excessive drinking during this neurodevelopmental window might detrimentally influence maturation of cognitive functions, including working memory and/or inhibitory control, relying on still-maturing regions such as the prefrontal cortex (López-Caneda et al., 2014; Lees et al., 2020). Accordingly, BD has been associated with behavioral alterations in verbal memory and executive functions, particularly in inhibitory control and response inhibition to alcohol-specific stimuli (Townshend and Duka, 2005; Czapla et al., 2015; Carbia et al., 2018). Studies using neuroimaging and electroencephalography (EEG) techniques have also revealed abnormalities in the neural correlates of attention and executive functioning related to BD (Crego et al., 2012; Campanella et al., 2013; López-Caneda et al., 2013). Also, evidence from neurofunctional studies showed increased neural reactivity for alcohol-related information in young BDs (Petit et al., 2013, 2014; Brumback et al., 2015; Ryerson et al., 2017; Almeida-Antunes et al., 2022). The altered inhibitory control together with the augmented reactivity to alcoholic stimuli in BDs may constitute a risk factor for the development of alcohol dependence, since it may result in automatic action-tendencies to approach alcohol and difficulties to control alcohol intake (Peeters et al., 2012; Lannoy et al., 2020).

DLPFC has been frequently involved in addictive behaviors, namely in the top-down control processes aiming at regulating motivational reactions to drug cues (Hayashi et al., 2013; Volkow and Morales, 2015). Diminished DLPFC function has been related to reduced cognitive control and higher susceptibility to cue-induced relapse in alcohol abuse (Goldstein and Volkow, 2011). In addition, recent evidence has suggested that the DLPFC plays an important role in memory inhibition (MI), the ability to suppress unwanted or contextually relevant thoughts/memories (Anderson and Hulbert, 2021). MI is commonly studied through the Think/No-Think (TNT) paradigm, an adaptation of the classical Go/NoGo task typically used to evaluate suppression of motor responses (Huster et al., 2013). Briefly, this paradigm is usually divided into three phases (i.e., learning, TNT, and memory-test phases). In the first phase, participants are instructed to learn cue-target pairs, which can be composed of different types of material (i.e., words, pictures, or even autobiographical). During the TNT task, on each trial, a cue from a pair appears in green (Think trials) or red (No-Think trials). For Think trials, participants must remember the paired item and retain it in awareness; for No-Think trials, participants are asked to prevent the paired item from entering awareness. Lastly, the memory-test phase assesses memory for all pairs, with recall measured on Think, No-Think, and Baseline items (i.e., items that were studied during the learning phase but that did not appear in the TNT phase). Studies using this paradigm report consistently two main findings, supporting the assumption that people can voluntarily suppress retrieval (Anderson and Hanslmayr, 2014). Specifically, final recall for No-Think items is significantly reduced than final recall for Think items, suggesting that retrieval suppression reduces the benefits of reminders on memory. Most importantly, suppressing retrieval frequently decreases the memory for No-Think items below that exhibited for Baseline ones, resulting in the suppression-induced forgetting effect or MI (Anderson and Hulbert, 2021).

Growing research has also revealed that forgetting previously learned material involves DLPFC action, which reduces the hippocampus activity and, consequently, impairs memory retrieval (Anderson et al., 2004; Anderson and Hanslmayr, 2014). Recently, López-Caneda and colleagues developed the Think/No-Think Alcohol (TNTA) task, a paradigm aiming to examine the behavioral and neurophysiological mechanisms linked to MI in alcohol-related contexts (López-Caneda et al., 2019b). The authors found lower late parietal positivity (LPP) and increased frontal slow wave (FSW) during No-Think trials, suggesting the involvement of memory suppression mechanisms to drinking (alcoholic and non-alcoholic) contexts (López-Caneda et al., 2019b).

Despite little is known about the MI processes in cases of substance abuse, some studies have demonstrated that alcohol-dependent individuals display anomalies in the ability

to intentionally inhibit specific information in comparison with healthy subjects (Noël et al., 2009; Nemeth et al., 2014). Likewise, recent studies have proposed that MI seems to be impaired in several psychiatric disorders, namely in post-traumatic stress disorder (Catarino et al., 2015), attention deficit hyperactivity disorder (Depue et al., 2010) and depressive disorders (Joormann et al., 2009). In the same line, MI training revealed to be effective in enhancing the ability to selectively forget unpleasant memories in both healthy subjects and psychiatric patients (Jacobus and Tapert, 2013; Küpper et al., 2014).

Transcranial direct-current stimulation (tDCS) is one of the most commonly used neuromodulation paradigms in psychological research, which consists of the delivery of a weak electric current from a positive (anode) to a negative (cathode) electrode. It can raise (anodal) or decrease (cathodal) cortical excitability in target regions while also modifying the functional connectivity of the brain networks (Nitsche et al., 2008). This type of stimulation can be paired with cognitive or behavioral interventions to amplify neuroplasticity and boost better longer-term outcomes through synergistic effects (Ditye et al., 2012; Martin et al., 2013). The use of tDCS during multiple intervention sessions has proven to be effective in improving symptoms of several major psychiatric disorders (Kekic et al., 2016) and has recently been suggested as a novel treatment option for substance-use disorders (Ekhtiari et al., 2019). The most frequent anatomical target of these tDCS interventions has been the DLPFC (Boggio et al., 2008) and evidence has shown that tDCS applied over this region may reduce craving and/or alcohol use/relapse in alcohol use disorders (AUD) patients and heavy drinkers (Boggio et al., 2008; da Silva et al., 2013; Jansen et al., 2013; Klauss et al., 2014, 2018; den Uyl et al., 2015; Vanderhasselt et al., 2020). Furthermore, studies applying tDCS over DLPFC coupled with cognitive training (CT) sessions (e.g., cognitive/attentional bias modification; alcohol cue inhibitory control training) also revealed reduced craving in young heavy drinkers (den Uyl et al., 2016), lower relapse rate in recently detoxified patients (den Uyl et al., 2017, 2018; Dubuson et al., 2021) and modifications in the electrophysiological activity of young BDs during the performance of an alcohol-related inhibition task (Dormal et al., 2020). Evidence has shown that DLPFC and hippocampus—two regions specially involved in MI—are classical targets for the neurotoxic effects of alcohol (Jacobus and Tapert, 2013). However, to best of our knowledge, no study has explored the behavioral and neural mechanisms underlying MI neither in alcohol-dependent patients nor in BDs. Thus, based on the evidence that the TNTA paradigm may be a valuable instrument to measure the ability to suppress alcohol-related memories (López-Caneda et al., 2019b), in the present study we will use this task to evaluate the potential electrophysiological and behavioral abnormalities associated with MI, specifically those related to the suppression of alcohol-related memories in young BDs. For this purpose, the electrophysiological activity of 45 college BDs and 45 age-matched non/low-drinkers will be assessed while they perform the TNTA task (pre-training EEG assessment). During this session, psychological (i.e., craving levels), behavioral (i.e., recall accuracy and suppression abilities), and neurofunctional (i.e., Event-Related Potentials [ERPs] and Functional Connectivity [FC]) variables will be assessed. In addition, given that training of response inhibition has been shown to successfully contribute to the reduction –although limited to the short term- of alcohol consumption (Houben et al., 2011), we will develop a coupled tDCS and MI training protocol to investigate whether this training is able (1) to enhance MI capabilities and reduce alcohol cue reactivity (both assessed during the post-training EEG assessment), and (2) to decrease craving and/or alcohol use—monitoring up to 3 months after protocol implementation- in trained BD participants.

MATERIALS AND METHODS

Management and Ethics

Ethical requirements for human research will be followed in full accordance with the Code of Ethical Principles for Medical Research Involving Humans Subjects outlined in the Declaration of Helsinki (64th World Medical Association General Assembly, Brazil, 2013). The Ethics Committee for Social and Human Sciences of University of Minho approved the present protocol in December 12, 2018 (approval reference: CE.CSH 078/2018). Prior to enrolling in the study, subjects will be informed about the aims, conditions and procedure of the study and provided with two copies of the informed consent forms signed by the researchers and participants.. College students will receive gift vouchers in order to compensate for their participation.

Study Design and Setting

The authors confirm that all ongoing and related trials of this intervention are registered in the National Institutes of Health (NIH) Clinical Trials Database (ClinicalTrials.gov; identifier: NCT05237414). The CONSORT checklist is available as S1 CONSORT Checklist in **Supplementary Material**. Participant recruitment started at February 5, 2019 and the anticipated date for follow-up completion is May 15, 2022 (see **Figure 1**).

This study is composed of three different phases: (1) behavioral and electrophysiological analyses of MI abilities in young BDs as compared to age-matched non/low-drinkers; (2) a double-blind, randomized controlled trial aiming at assessing the effects of a MI training protocol at the behavioral and electrophysiological level; and (3) monitoring of self-reported alcohol consumption and alcohol craving 10 days and 3 months after the MI training (see **Figure 2**). Therefore, this experimental procedure aims to answer four main research questions and test specific hypotheses:

1. How does BD affect alcohol-related MI in young adults? Namely, are the behavioral and electrophysiological MI mechanisms—specifically those related to the suppression of alcohol-related memories—altered in BDs when compared to non/low-drinkers? At behavioral level, we hypothesized that BDs would perform worse on the TNTA task, showing an increased recollection of No-Think

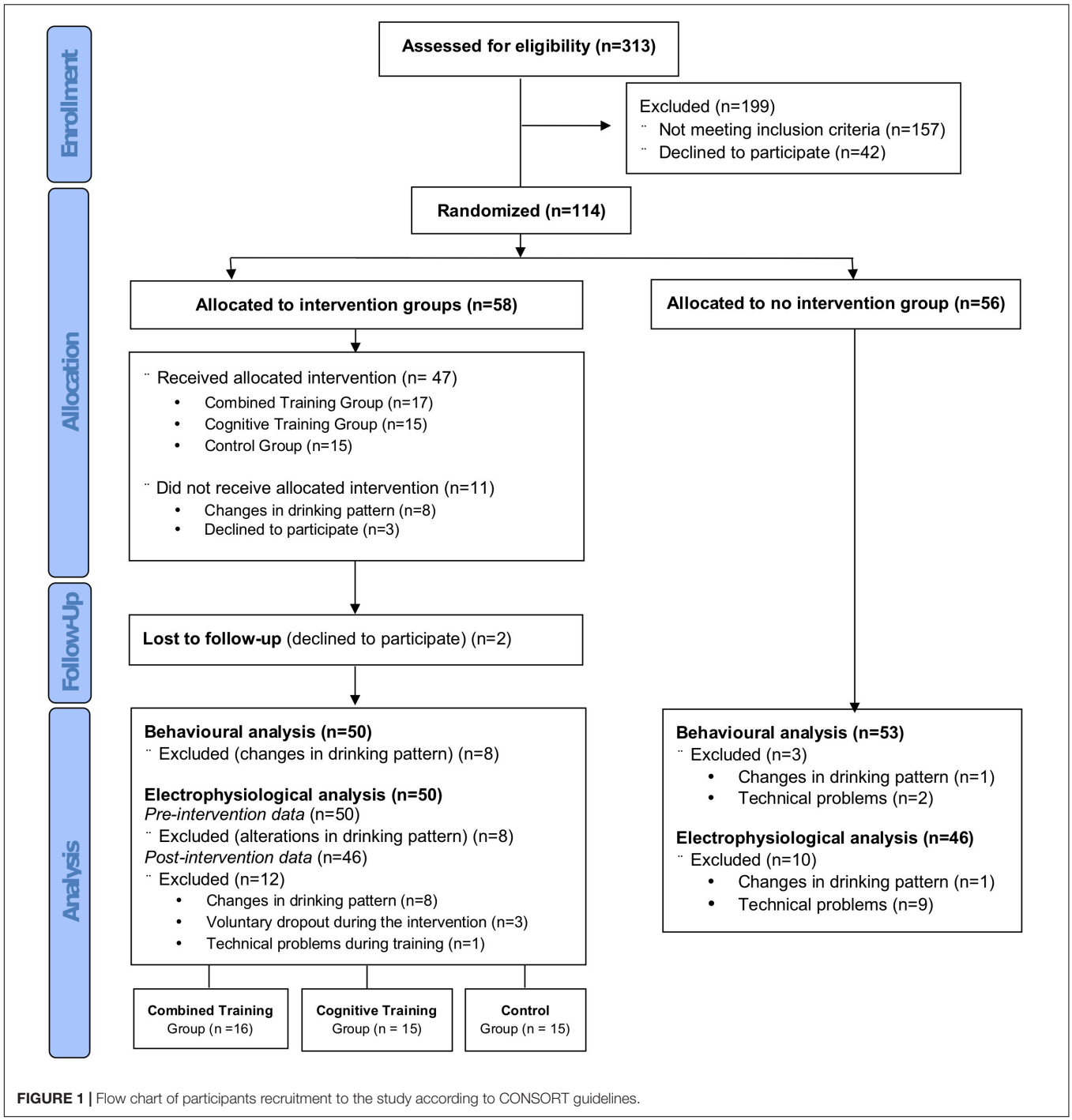

FIGURE 1 | Flow chart of participants recruitment to the study according to CONSORT guidelines.

images, mainly for alcoholic ones, in comparison to N/LDs (i.e., BDs will poorly inhibit alcohol-related pictures). At neurofunctional level, BDs are expected to show alterations in the amplitude of electrophysiological components linked to MI (e.g., N2 and LPP) as well as abnormal FC patterns within/between regions associated with MI (e.g., DLPFC and hippocampal/parahippocampal regions).

2. What is the effect of a MI training on behavioral TNTA task performance? Specifically, will the BDs show a reduced recollection of no-think images—mainly for alcoholic no-think—after training? The results should demonstrate the effectiveness of the training protocol, with BDs exhibiting an improved capacity to suppress alcohol-related memories after both *combined* and *cognitive* MI training.
3. Are the electrophysiological correlates underlying MI mechanisms and alcohol cue reactivity changed by MI training? The MI training protocol should lead to significant modifications in the ERP and FC patterns,

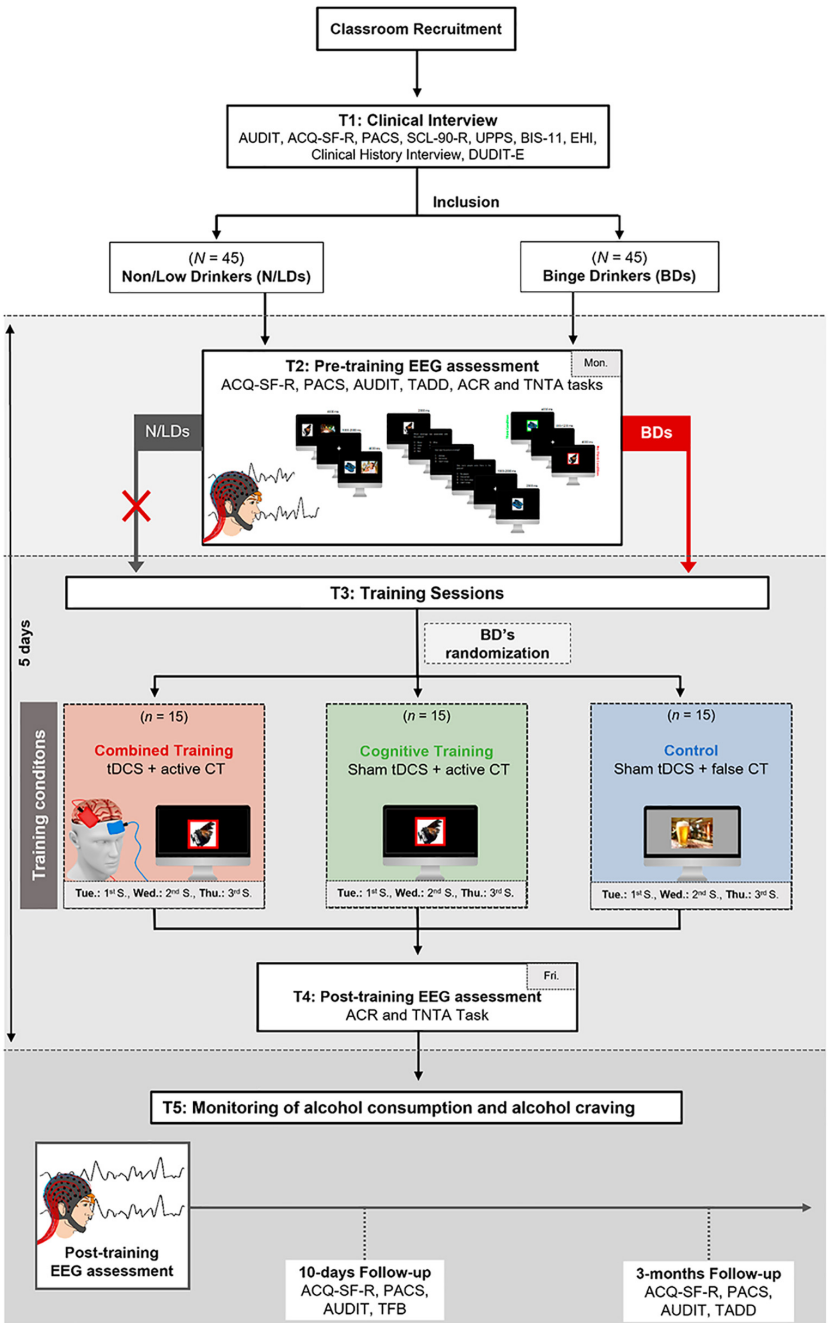

FIGURE 2 | Graphic representation of the procedure. Participants will perform a clinical interview (T1) to guarantee they fulfill the inclusion criteria and to assess baseline measures (e.g., psychological symptoms and impulsivity). Forty-five college students with a BD pattern will enter the study. To compare BDs with non/low-drinkers, the study will also include a group of 45 aged-matched non/low-drinkers, which will only perform the pre-training EEG assessment. During the pre-training EEG assessment (T2; Monday), alcohol craving and consumption levels will be measured, and participants will perform the TNTA task to assess the behavioral and electrophysiological MI mechanisms. Then (T3), BDs will be randomly distributed for one of three training conditions: Combined Training (i.e., verum tDCS and cognitive training [CT]), Cognitive Training (i.e., sham tDCS and verum CT), and Control (i.e., sham tDCS and sham CT). They will perform three sessions over three consecutive days (i.e., Tuesday, Wednesday, and Thursday). After the training sessions, BDs will perform a post-training EEG assessment (T4; Friday) with a procedure similar to T2. The monitoring of alcohol consumption and alcohol craving (T5) will be conducted 10 days and 3 months after T4. ACQ-SF-R, Alcohol Craving Questionnaire-Short Form Revised; ACR, Alcohol Cue Reactivity task; AUDIT, Alcohol Use Disorder Identification Test; BDs, Binge Drinkers; BIS-11, Barratt Impulsivity Scale-11; CT, cognitive training; DUDIT-E, Drug Use Disorders Identification Test-Extended; EEG, electroencephalogram; Fri, Friday; GSI, Global Severity Index; Mon, Monday; N/LDs, Non/low-drinkers; PACS, Penn Alcohol Craving Scale; SCL-90-R, Symptom Checklist-90-Revised questionnaire; TADD, Typical and Atypical Drinking Diary; TLFB, Alcohol Timeline Followback; Tue, Tuesday; Thu, Thursday; UPPS-P, Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency; Wed, Wednesday.

reflecting stronger MI capabilities and reduced alcohol cue reactivity in trained BD participants.

4. Will the MI training reduce alcohol consumption and craving levels in the short/medium term? BDs are expected to show a significant reduction in alcohol use and craving in the short/medium-term.

Target Population

The volunteers will be ninety college students (∼50% female), aged between 18 and 24 years: 45 non/low-drinkers and 45 BDs matched for age and gender. The sample size for the BD group (the group with pre- and post-intervention measures) was determined based on an *a priori* estimation of required sample size with G*Power software (Faul et al., 2009). Parameters for power calculation were: α level = 0.05, effect size = 0.25 (a moderate Cohen's η^2; Cohen, 2013), a desired power of 0.90, three manipulation groups (i.e., combined training, cognitive training and control) and three measurements (task performance, and self-reported alcohol use and craving levels). The *a priori* calculation yielded a required sample size of $N = 45$ (i.e., 15 participants in each BD sub-group).). All participants will be recruited through a screening questionnaire administered in the classroom of several courses taught at the University of Minho (UM). The screening will include the Alcohol Use Disorder Identification Test (AUDIT; Babor et al., 2001) along with other questions concerning alcohol and other drugs use.

Inclusion and Exclusion Criteria

To participate in the study, college students must meet the following eligibility criteria: report (i) drinking 5 or more drinks on one occasion at least once a month, and (ii) drinking at a speed of at least two drinks per hour during these episodes (which brings blood alcohol concentration to 0.08 gram percent or above (National Institute of Alcohol Abuse and Alcoholism [NIAAA], 2004), in order to be classified as BDs; or report (i) never drinking 5 or more drinks on each occasion and (ii) having an AUDIT score ≤ 4, to be considered as non/low-drinkers. The students who fulfilled the inclusion criteria will perform a clinical interview that will assess the following exclusion criteria: (a) use of illegal drugs except cannabis [as determined by the Drug Use Disorders Identification Test-Extended (DUDIT-E), Berman et al., 2007]; (b) alcohol abuse (i.e., AUDIT ≥ 20); consumption of medical drugs with psychoactive effects (e.g., sedatives or anxiolytics) during the 2 weeks before the experiment; (c) personal history of psychopathological disorders (according to DSM-V criteria); (d) history of traumatic brain injury or neurological disorder; (e) family history of alcoholism or diagnosis of other substance abuse; (f) occurrence of one or more episodes of loss of consciousness for more than 20 min; (g) non-corrected sensory deficits; (h) Global Severity Index (GSI) > 90 [Symptom Checklist-90-Revised questionnaire (SCL-90-R), Derogatis, 1983] or a score above 90 in at least two of the symptomatic dimensions.

Quality Assurance and Randomization

The protocol will be implemented by three skilled researchers with expertise in behavioral and EEG assessments and tDCS interventions. Researchers will not be aware of the results of the pre-training EEG assessment and will be blind to the randomization procedure that will follow. The randomization of the BD groups will be performed by an independent researcher using Microsoft Excel. BDs will receive one of the following interventions: (1) Combined training (CT and verum tDCS applied over the right dorsolateral prefrontal cortex); (2) Cognitive training (active CT and sham tDCS); or (3) Control (sham CT and sham tDCS).

EXPERIMENTAL TASKS

Alcohol Cue Reactivity Task

Firstly, the participants will perform the ACR task aiming at assessing the emotional response and the electrophysiological reactivity to alcohol-related cues. In this task, each trial starts with a white fixation cross in a gray background for a variable duration ranging from 1,000 to 1,500 ms. Subsequently, an alcoholic or non-alcoholic image is randomly presented at the center of the screen for 3,000 ms. Participants are asked to be focused on the fixation cross and then to look at the image whenever it appears. After the visualization of each image, participants have to register their emotional responses in terms of valence and arousal using the Self-Assessment Manikin (Bradley and Lang, 1994). The full task includes a total of 80 trials with 40 alcoholic and 40 non-alcoholic images obtained from the Amsterdam Beverage Picture Set (Pronk et al., 2015).

Think/No-Think Alcohol Task

The TNTA task is a version of the classical Think/No-Think paradigm (Anderson and Green, 2001), which was specially developed to examine MI mechanisms in alcohol-related contexts (López-Caneda et al., 2019b; see **Figure 3**). This task includes thirty-six pictures (18 related to alcohol and 18 non-related to alcohol) from the Galician Beverage Picture Set (GBPS; López-Caneda and Carbia, 2018) and 36 images of neutral objects obtained from the POPORO database (Kovalenko et al., 2012). The GBPS is a database of alcohol and non-alcohol pictures embedded in real-life scenarios which comprises 6 types of beverages: beer, wine, and liquor (alcoholic drinks), and water, juice, and milk (non-alcoholic drinks). The TNTA task includes 6 images from each of the 6 beverages. The pictures also differ in terms of orientation (vertical or horizontal) and number of people (no people, 1 person, 2 or more people). As such, within each type of beverage, 3 are vertical (each one with a different number of people: 0 people, 1 person, 2 or more people) and the other 3 are horizontal (also with 0 people, 1 person, 2 or more people). The task is divided into three phases, i.e., (1) the Learning phase, (2) the Think/No-Think (TNT) phase and (3) the Memory-Test phase, which are carefully described below.

Learning Phase

During the Learning phase (**Figure 3A**), participants are asked to memorize 36 image-pairs (i.e., a neutral image paired with an image including alcoholic or non-alcoholic drinks) divided into three blocks of 12 pairs. Each block starts with the presentation of

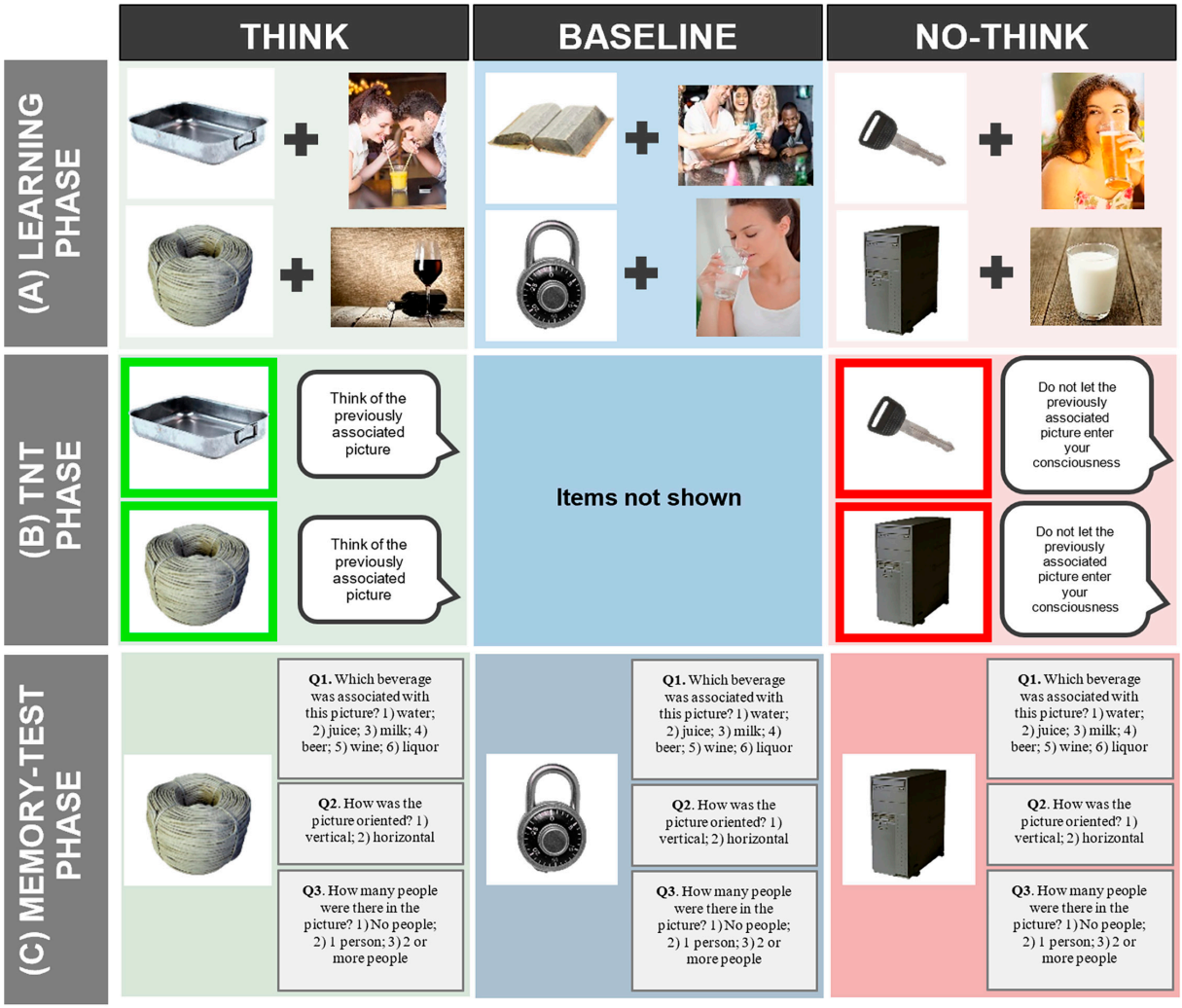

FIGURE 3 | Overall depiction of the Think/No-Think Alcohol (TNTA) task. **(A)** During the learning phase, participants will be asked to associate and memorize 36 pairs of neutral objects + alcoholic/non-alcoholic pictures. Then, only the neutral objects will be presented, and participants will have to try to remember the picture (alcoholic/non-alcoholic image) that was associated with this neutral object and answer three questions about the beverage depicted, the orientation of the picture and the number of people present in it. **(B)** After the learning phase, the Think/No -Think phase will comprehend two conditions: the Think (green square) and the No-Think (light red square). In the Think condition (depicted in the neutral images with a green frame) when participants are presented with the object, they will be instructed to "think of the previously learned alcoholic/non-alcoholic picture and keep it in mind during the entire presentation of the object." In the No-Think condition (depicted by neutral images with a red frame) they will be asked "not to let the previously associated picture enter your consciousness." **(C)** In the memory test phase, the 36 neutral images will be presented again, including the 12 neutral objects of the baseline condition that were not presented in the TNT phase. Participants will be asked to recall—answering the same three questions of the learning phase—the image (alcoholic/non-alcoholic) that was initially associated with the neutral object. Alcohol and non-alcohol images were obtained from Shutterstock (https://www.shutterstock.com) and with the permission of Shutterstock.

the 12 image-pairs at the center of the screen, each for 4,000 ms, in a randomized order, and with an inter-stimuli interval (ISI) ranging from 1,100 to 1,300 ms (with a 4,000 ms rest every 4 pairs). Subsequently, each of the neutral images is presented for 2,000 ms, and participants must try to remember the image that was associated with the neutral object through three questions: Q1. "Which beverage was associated with this picture?"; Q2. "How was the picture oriented?"; Q3. "How many people were there in the picture?" In each block, the 12 pairs and the questions are repeated three times. At the end of each block, feedback with the number of correct responses will be provided. Correct recall will only be considered when participants provide the right answer to the three questions. Thus, the combination of the potential answers to the three questions ($6 \times 2 \times 3 = 36$) ensured that each target image displayed a unique combination.

Think/No-Think Phase

In this phase (**Figure 3B**), there are two possible actions: to Think or to No-Think on the alcoholic/non-alcoholic image paired with the neutral object previously. Specifically, in the Think condition—determined by a green frame that circumvents the neutral image -, participants will be asked to focus on the

neutral image and think of the alcoholic/non-alcoholic image that was associated with it. In the No-Think condition—neutral image circumvented by a red frame—participants are instructed to focus on the image and not let the previously associated alcoholic/non-alcoholic picture enter their consciousness. Images will randomly repeated 15 times and presented for 3,000 ms (offset-onset ISI = 1,100–1,300 ms). From the initial set of 36 neutral images shown in the learning phase only 24 will be depicted during the TNT phase, 12 in each condition (i.e., Think and No-Think). The remaining 12 neutral images not depicted in this phase will be used as a baseline condition for the following Memory Test phase.

Memory Test Phase

During this phase (**Figure 3C**), the 36 neutral images from each pair are again presented, including the 12 images of the baseline condition. Participants are asked to remember the image (alcoholic or non-alcoholic) that was initially associated with the neutral object using the same three questions of the Learning phase. Three different versions of the task (where all the pictures were part of the three conditions: Think, No-Think and baseline) will be created and counterbalanced across participants.

Think/No-Think Alcohol Task Variations for Active and False Cognitive Training

Two variations of the TNTA task were developed for the active CT and for the false CT. The stimuli employed in these variations of the TNTA task were also obtained from the GBPS and POPORO databases; however, these stimuli differ from those used in the original TNTA task. The structure of the task for the MI active CT is the same as the original TNTA task. However, in this variation, the Learning phase is only composed of two blocks of 12-image pairs, and in the TNT phase, all the stimuli to be inhibited are alcohol-related images.

In the false CT version, the Learning phase also have only two blocks of 12-image pairs. Nevertheless, the TNT phase is replaced by a Forced-Choice Reaction Time task, during which the participants must only categorize alcoholic and non-alcoholic images answering to the question "What type of beverage was there in the image?" (answer: "Alcoholic drink" or "Non-alcoholic drink").

All the computerized tasks are programmed in open-source software Psychopy (Peirce, 2007).

PROCEDURE

T1: Clinical Interview

All the stages of the procedure are detailed in **Figure 2**. During the clinical interview (T1), we will verify the fulfillment of the exclusion/inclusion criteria and assess the baseline levels of some constructs (e.g., craving levels, impulsivity). Consequently, the following instruments will be used (see **Supplementary Figure 1**): (1) the AUDIT along with five additional alcohol use questions (i.e., speed of drinking [number of drinks consumed per hour], number and type of drinks consumed in a standard week, percentage of times getting drunk when going out, age of onset of regular alcohol use and BD); (2) the DUDIT-E to examine other drugs use; (3) the Penn Alcohol Craving Scale (PACS; Pombo et al., 2008) and the Alcohol Craving Questionnaire-Short Form Revised (ACQ-SF-R; Rodrigues et al., 2021); (4) the Barratt Impulsivity Scale-11 (BIS-11; Cruz and Barbosa, 2012) and the short form of the Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency (UPPS-P; Cyders et al., 2014) impulsive behavior scale; (5) the Symptom Checklist-90-Revised questionnaire (SCL-90-R) to evaluate the presence of psychopathological traits; (6) a clinical history interview to explore the personal/family history of psychopathological and neurological disorders as well as the overall medical history of the participants; and (7) the Edinburgh Handedness Inventory (EHI; Espírito-Santo et al., 2017) to evaluate the participants' handedness.

T2: Pre-training Electroencephalographic Assessment

During the pre-training EEG assessment (see **Figure 2**), psychological (i.e., craving levels), behavioral (i.e., alcohol consumption levels and task performance) and neurofunctional (e.g., ERPs, brain FC) outcomes will be assessed (for more details on the instruments used see **Supplementary Figure 1**). EEG data will be collected while participants perform the ACR and the TNTA task. Before the EEG recording, participants will be asked to perform a breathalyzer test to ensure that blood alcohol concentration is 0.0% (Alcoscan ALC-1). Along with the AUDIT, we will administer the Alcohol Timeline Followback (TLFB) and the Typical and Atypical Drinking Diary (TADD) in order to determine alcohol consumption levels during the previous week and the previous 3 months, respectively. After filling in the questionnaires, participants will perform the ACR task, which lasts from 5 to 10 min. Then, participants' resting brain activity will be recorded for 3 min during eyes-closed prior to the TNTA task. Finally, they will perform the TNTA task with a duration of 1 h and 10 min. Accordingly, the total duration of the pre-training EEG assessment will be approximately two and a half hours.

EEG data will be recorded using the ActiveTwo Biosemi System (Biosemi, Inc.) from 64 electrodes placed according the 10–10 system (Fregni et al., 2015) and digitized at a 512 Hz rate. Vertical and horizontal electrooculogram activity will be recorded to control for eye movements and blinks. Two additional electrodes will be placed on the mastoids, bilaterally, to provide the signal offline reference. Electrode impedances will be kept below 20 kΩ and the EEG signal will be filtered on-line with a 0.01–100 Hz band pass filter.

T3: MI Training Sessions

BDs will be randomly assigned to one of the three training subgroups: (a) *Combined training*; (b) *Cognitive training*; or (c) *Control* (see **Figure 2**). The participants' allocation to the training group will be done by an independent researcher who will be responsible to program the tDCS parameters.

Thus, both participants and research team will be blind to the randomization procedure.

During T3, subjects will perform the variation of the TNTA task corresponding to the group to which they will be assigned. After the first phase of the task (i.e., Learning Phase), neuromodulation (sham or active) will be performed using tDCS. Twenty minutes of 2 mA direct current will be applied to the scalp using a saline-soaked pair of 35 cm^2 surface sponge electrodes, through an Eldith DC Stimulator Plus (Neuroconn, Germany). To stimulate the right DLPFC, the anodal electrode will be placed over F4 according to the 10–20 international system for EEG electrode placement. The cathode electrode will be placed over the contralateral supraorbital area. During the active simulation, the current will fade in for 15 s, will be constant at 2 mA for 20 min, and then will fade out for 15 s. During the sham stimulation, the electric current will fade in for 15 s, then will be constant at 2 mA for 15 s and will fade out for 15 s. This procedure makes both active and sham stimulation indistinguishable for the participants. Before and after the stimulation, participants will answer to a continuous Visual Analog Scale that allows checking for possible secondary effects of the electrical stimulation.

T4: Post-training Electroencephalographic Assessment

During T4 (see **Figure 2**), participants will perform the ACR and TNTA tasks under the same procedure to the one undertaken during the T2.

T5: Monitoring of Alcohol Consumption and Alcohol Craving

Ten days after the T4, the primary craving and alcohol consumption outcomes will be assessed (see **Figure 2**). For this purpose, we will administer the PACS, the ACQ-SF-R and the AUDIT. Additionally, 3 months post-intervention, BDs will answer the same questionnaires and also the TADD aiming at assessing potential medium-term effects of the MI training.

DATA COLLECTION AND ANALYSIS

Data Collection

Data collection will occur, firstly, at university classrooms at the UM during the screening phase, and afterward at the facilities of the Psychological Neurosciences Laboratory at the School of Psychology of UM (Braga, Portugal). Participants will answer the questionnaires by using paper and pencil, and the data will then be entered into SPSS® (Version 27.0). Behavioral data obtained from the experimental tasks will be collected with PsychoPy (v1.84.0).

Electroencephalographic Data Processing

EEG data will be processed with FieldTrip package (Oostenveld et al., 2011). The signal will be corrected for vertical and horizontal ocular artifacts by independent component analysis (ICA) and re-referenced to the average reference For each subject, the normal distribution of raw signal (restricting its frequency range using band-pass filter for each type of artifact) will be calculated. Signals ≥ 2 standard deviations from mean score will be automatically marked as artifacts. Then, the correct artifacts removal will be visually inspected by an expert signal analyst. Therefore, every trial affected by movement or other kind of artifacts will be discarded from subsequent analysis. The data will be segmented into epochs of 2,500 ms (from −500 to 2,000 ms after stimulus onset) and trials marked as containing artifacts will be discarded from subsequent analysis. Only trials corresponding to originally learned items during the learning phase will be considered. Additionally, these epochs will be averaged separately according to the type of picture to be recalled or suppressed, thus obtaining four conditions: Alcohol Think, No-Alcohol Think, Alcohol No-Think and No-Alcohol No-Think.

Event-Related Potentials Analysis

To quantify the ERP data, we will calculate the mean amplitudes for each electrode in several time-windows, selected based on previous findings (e.g., López-Caneda et al., 2019b) and on the visual inspection of the ERP waveforms (predictably, 200–400 ms and 600–1,000 ms for fronto-central locations and 400–700 ms for parietal locations). We will use this selection in order to quantify the N2, FSW, and LPP components: to explore the N2 and the FSW amplitudes, we will extract the ERP data from six electrodes placed at left (F3, FC3), midline (Fz, FCz), and right (F4, FC4) frontal regions and to study the LPP component, the ERP data will be extracted from the following scalp electrodes: left parietal (P3, PO3), midline parietal (Pz, POz), and right parietal (P4, PO4).

Functional Connectivity Analysis

EEG data will be transformed into source space employing a realistic *Boundary elements model* (BEM) (Fuchs et al., 2001) as forward model and a Linearly Constrain, Minimum Variance (LCMV) beamformer (Van Veen et al., 1997) as inverse model. Cortical sources will be reconstructed in five classical bands—theta (4–8 Hz), alpha (8–12 Hz), low beta (12–20 Hz), high beta (20–30 Hz) and low gamma (30–45 Hz)-, using the Montreal Neurological Institute (MNI) template-based T1 images (ICBM 152) (Mazziotta et al., 2001). FC analysis will be calculated under the hypothesis of phase synchronization by means of the Phase Locking Value (PLV) (Bruña et al., 2018).

Statistics

The first step of the statistical analyses will be to examine the behavioral and EEG correlates of MI among college BDs and non/low-drinkers. For that purpose, the outcomes of the TNTA task collected during the pre-training assessment (T2) in BDs and non/low-drinkers will be compared and correlated with alcohol consumption (AUDIT) and alcohol craving measures (i.e., the PACS' and ACQ-SF-R's scores, and the ERPs and valence/arousal ratings recorded during the ACR task). Secondly, with the purpose of verifying the impact of the *combined, cognitive* and *control* training procedures applied to BDs on

psychological, behavioral, and neurofunctional measures, the pre-training data (T2) from the 45 BDs will be compared with data from T4 (post-training) and T5 (monitoring of alcohol consumption and alcohol craving). In addition, the three training groups will be compared with each other in order to determine potential differences between the training procedures at T4 and T5 stages.

With regard to the behavioral data, items learned during the learning phase and correctly recalled during the memory test phase will be considered correct responses. Accordingly, the percentage of correct responses (for Think, No-Think and Baseline items) will be computed according to the following formula:

$$\left(\frac{number\ of\ correctly\ recalled\ items}{number\ of\ previously\ learned\ items}\right) \times 100$$

A mixed-model analysis of variance (ANOVA) with one between-subject factor, Group (non/low-drinkers, BDs), and two within-subject factors, Condition (Think, No-Think, Baseline) and Content (Alcohol, Non-Alcohol) will be conducted on the recall accuracy rate to examine the participants' MI ability at T2. Afterward, a repeated-measures ANOVA with three within-factors: Moment (T2 and T4), Condition (Think, No-Think, Baseline) and Content (Alcohol, Non-Alcohol) will be performed to explore the training effects on the MI ability of BDs.

Furthermore, to examine the participant's emotional response to alcoholic cues (self-assessed during the ACR task using the Manikin test) at T2, two ANOVAs with Group (non/low-drinkers, BDs) as between-subject factor and with Content (Alcohol, Non-Alcohol) as within-subject factor will be conducted for valence and arousal ratings, separately. In addition, to evaluate possible variations in valence and arousal responses as a function of training sessions, new ANOVAs will be performed for each training group with two within-factors—Moment (T2 and T4) and Content (Alcohol, Non-Alcohol).

For the TNTA task, we will analyze the ERPs, specifically the mean amplitudes of N2, LPP, and FSW. A mixed-model ANOVA with one between-subject factor Group (non/low-drinkers, BDs) and four within-subject factors: Condition (Think, No-Think), Content (Alcohol, Non-Alcohol), Region (Left, Midline, Right), and Electrode (2 electrodes) will be conducted on the mean amplitude of each component to explore the MI neural mechanisms during T2. A repeated-measures ANOVA with five within-subject factors: Moment (T2 and T4), Condition (Think, No-Think), Content (Alcohol, Non-Alcohol), Region (Left, Midline, Right) and Electrode (two electrodes) will be conducted on the mean amplitude of each component separately, to explore the effects of MI training on the neural activity.

For the ACR task at T2, the mean amplitude of the P1, N1, and P2 ERP components will be analyzed by means of separate mixed-model ANOVAs with one between-subject factor Group (non/low-drinkers, BDs) and three within-subject factors: Content (Alcoholic, Non-Alcoholic), Region (Left, Midline, Right) and Electrode (2 electrodes). Furthermore, in order to investigate potential MI training effects on the electrophysiological reactivity to alcoholic cues, the amplitude of the abovementioned components will be analyzed through repeated-measures ANOVAs using within-subject factors: Moment (T2 and T4), Content (Alcoholic, Non-Alcoholic), Region (Left, Midline, Right) and Electrode (two electrodes). The behavioral and ERP correlates of MI and alcohol craving/reactivity will be correlated with the scores obtained from AUDIT, ACQ-SF-R, and PACS.

Regarding FC assessment, for the nodal strength—i.e., the level of connectivity of each node with the rest of the network-, the data will consist of a single value per source. These values will be compared between groups using a cluster-based permutation test (CBPT) (Oostenveld et al., 2011). For the seed-based analysis, and according to the literature concerning MI, prefrontal (e.g., DLPFC) and medial temporal (e.g., perirhinal and parahippocampal cortex, hippocampus) regions will be used as seeds. Lastly, the regions defined by the clusters showing significant differences between both groups in the nodal strength analysis will also be used as seeds.

DISCUSSION

At the present, the literature is still scarce regarding both the core functional anomalies in BDs and the neurobiological factors that underlie the evolution from pre-clinical (e.g., hazardous alcohol use, BD) to clinical conditions related to alcohol (i.e., AUD) (Witkiewitz et al., 2019). This study protocol constitutes an important step to fill in the existing gap and an opportunity to shed new light on a broad and more comprehensive understanding of the memory suppression mechanisms and their potential implication on heavy alcohol use. To the best of our knowledge, this protocol will be the first to describe the design and implementation of a randomized controlled trial that examines MI in BDs and tests the effectiveness of different types of MI training using both CT and neuromodulation by tDCS with the aim of reducing alcohol use and craving. Examining the extent to which BDs may have difficulties to inhibit alcohol-related information, what its behavioral and neurophysiological underpinnings are and how they can be potentially modified by training, will extend previous research on inhibition training in social and problem drinkers (Petit et al., 2012; Jones et al., 2014; Di Lemma and Field, 2017; Smith et al., 2017; Kilwein et al., 2018). Moreover, findings resulting from this research could hold important clinical implications for alcohol misuse treatment, particularly for that focused on the training of response inhibition to alcohol cues (Houben et al., 2011, 2012; Tschuemperlin et al., 2019).

Besides its innovative character granted by the use of a neuromodulation technique and the collection of behavioral and electrophysiological data, the protocol involves the longitudinal assessment of important psychological variables and measurements of alcohol craving/consumption registered at follow-up periods of up to 3 months. This monitoring will allow a comprehensive proximal and distal characterization of potential changes in BD behavior resulting from the MI training.

Ultimately, the present study may be particularly important as it can provide a new and useful tool for the clinical community

and, consequently, contribute to improving the quality of life of individuals suffering from problems related to alcohol and/or other substances. Moreover, our findings might encourage other researchers to conduct new studies on this topic and, thus, lead to a build-up of a strong and more comprehensive body of knowledge involving MI in substance misuse that can be translated into measurable societal impact.

ETHICS STATEMENT

This study, involving human participants, was reviewed and approved by Ethics Committee for Social and Human Sciences of University of Minho (approval reference: CE.CSH 078/2018). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EL-C: conceptualization. EL-C, AC, and AS: funding acquisition and methodology. EL-C and AC: project administration. EL-C, AC, AS, NA-A, MV, and RR: validation. NA-A and MV: visualization and writing – original draft. EL-C, AC, AS, and RR: writing – review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.914213/full#supplementary-material

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Binge drinking indirectly predicts a negative emotional memory bias through coping motivations and depressive symptoms: The role of sex/gender

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Background: In this three-part study, we investigate whether the associations between binge and problematic drinking patterns with a negative emotional memory bias (NMB) are indirectly related through coping motivations and depressive symptoms. We also address potential sex differences in these relations.

Methods: Participants (N=293) completed the Timeline Followback to assess binge drinking, the Alcohol Use Disorder Identification Test (AUDIT) to assess problematic alcohol use, the Drinking Motives Questionnaire-Revised to assess coping motivations, and the Depression, Anxiety, and Stress Scales-21 to assess depression. Participants were asked to identify whether 30 emotional sentences were self-referent or not in an incidental encoding task; 24h later they were asked to recall as many sentences as possible and a negative memory bias score was calculated.

Results: Across all three studies, we found significant bivariate relations between AUDIT scores, coping, depression, and an NMB, particularly for sentences participants deemed self-referent. In two undergraduate samples, there were significant indirect effects through coping motivations and depressive symptoms between binge drinking and an NMB in females as well as between AUDIT scores and an NMB in females only. In the community sample, there was only an indirect effect through coping motives, but this was observed in both females and males.

Conclusion: These findings support a relation between binge drinking as well as problematic alcohol use and a self-referent NMB in the context of coping motivations for alcohol use and depressive symptoms. Moreover, the pattern of findings suggests this model primarily holds for females, yet may also apply to males at higher levels of problematic alcohol use.

KEYWORDS

alcohol, binge drinking, emotional memory, depressive symptoms, coping motivations, sex factors

Introduction

Psychopathology-congruent memory biases are a purported cognitive mechanism underlying mental health conditions and maladaptive behaviors (Blaut et al., 2013; Zupan et al., 2017; Carbia et al., 2020). For instance, the occurrence of a negative emotional memory bias (NMB), defined as the propensity to preferentially recall negative information (Duyser et al., 2020), has recently been associated with frequent binge drinking (BD) in female undergraduate students (Carbia et al., 2020). However, not everyone who BDs frequently shows an NMB, which begs the question, what sets apart those who do? In this vein, the NMB is potentially indicative of emotional dysregulation, seen through increased attention to and identification with negative stimuli (see Disner et al., 2011). Emotional dysregulation is also a central feature of the negative reinforcement model of addiction (Koob, 2013), which posits that repeated heavy alcohol consumption serves to relieve unpleasant states (e.g., negative mood). Thus, the NMB may be more likely to occur among individuals for whom this model is most salient, whether in the form of BD or other problematic alcohol use.

Importantly, contemporary conceptualizations of the negative reinforcement model propose that individuals who engage in excessive drinking behavior tend to endorse coping with negative affect as a motivation for alcohol use (Webb et al., 2020), and report greater depressive symptoms (Keough et al., 2015), which by extension, may also relate to an NMB. Indeed, greater alcohol consumption is associated with using alcohol as a coping mechanism (Patrick and Schulenberg, 2011; Decaluwe et al., 2019), which may facilitate alcohol-related neurological changes that, in turn, increase recall of negative information (Stephens and Duka, 2008). Additionally, greater alcohol consumption and drinking-related consequences are related to depression (Kuria et al., 2012; Connell et al., 2015) which is further associated with the NMB (Bradley and Mogg, 1994; Blaut et al., 2013; Zupan et al., 2017). Thus, given the relations among excessive alcohol use with coping motivations and depressive symptoms, here, we investigate the potential intervening roles of coping motivations and depressive symptoms on the relation between BD, more general problematic alcohol use, and the NMB.

Problematic drinking and a negative emotional memory bias

Over time, excessive alcohol consumption is associated with structural brain changes (Carpenter-Hyland and Chandler, 2007; Spear, 2018) in regions that play key roles in encoding and retrieving emotional memories (Tyng et al., 2017). To elaborate, the pattern of intoxication-withdrawal characteristic of repeated BD episodes may dysregulate the amygdala and prefrontal cortex (Stephens and Duka, 2008). Related reductions in prefrontal-mediated inhibitory control coupled with amygdala hyperactivity may thus predispose individuals who BD frequently to preferentially attend to and recall negative information (Stephens and Duka, 2008; Tolomeo et al., 2021). Importantly, despite differing patterns of use, young adults who BD frequently exhibit cognitive and emotional profiles similar to those observed in repeatedly detoxified individuals with prolonged alcohol use disorders (Duka et al., 2004; Stephens and Duka, 2008). Thus, it is prudent to understand the NMB in the context of BD and problematic drinking more generally (Disner et al., 2011).

Despite longstanding investigations of the NMB in conditions involving emotional dysregulation (Bradley and Mogg, 1994; Disner et al., 2011; Duyser et al., 2020), its relation to alcohol use remains relatively understudied. In a recent exception, Carbia et al. (2020) observed that higher frequencies of BD episodes among female (but not male) college students predicted greater recall of negative compared to neutral words across immediate learning trials and after a 30-min delay. However, given that emotional stimuli generally tend to elicit superior recall relative to neutral stimuli (Tyng et al., 2017), it is also important to establish preferential recall of negative relative to positive stimuli when determining the presence of an NMB. In addition, longer delays ($\geq$ 1 day) are often more sensitive to observing explicit memory biases, which are thought to reflect time-dependent processes of emotional effects on memory consolidation. Here, we investigate the above association, extending the delay to 1 day, and explore relations of the NMB with more general problematic alcohol use as well as assess potential mediating factors: Namely, use of alcohol to cope and symptoms of depression.

Role of coping motivations for alcohol use

Coping motivations for alcohol use (i.e., using alcohol to relieve negative affect) may contribute to the association between alcohol consumption and the NMB. Indeed, endorsement of coping motivations underlying alcohol consumption is associated with greater frequency of BD episodes, greater quantities of alcohol consumed per episode (Stewart et al., 2011; Decaluwe et al., 2019), as well greater cumulative years of BD (Patrick and Schulenberg, 2011). All such factors may lead to more pronounced neurological consequences that may render individuals more vulnerable to the NMB. Furthermore, coping motivations are associated with implicit memory associations formed while drinking in a negative affective state. For example, coping motivation is related to an alcohol-related interpretative bias reflected by a tendency to identify external negative situations as being contextually related to alcohol (Salemink and Wiers, 2014). Similarly, repeated drinking during periods of negative affect may result in a learned association between internally "feeling bad" and cravings for alcohol (Zack et al., 1999, 2002). Thus, certain external triggering situations and internal negative affect may cue a craving for alcohol in those who drink to cope, thereby perpetuating a negative reinforcement cycle (Zack et al., 2002; Cox et al., 2006; Kessler et al., 2013). As such, elicitation of alcohol

cravings in negative situations and increased consumption as a function of coping motivations may also explain the pathway from problematic drinking to an NMB.

Role of depression

The co-occurrence of depression is posited to exacerbate the emotional and cognitive consequences of excessive alcohol use (Connell et al., 2015). For example, the biased recall of alcohol-related stimuli accompanying alcohol dependence is stronger in those with comorbid depression (Fridrici et al., 2014). Furthermore, depressed individuals high on BD measures attend to negative stimuli more quickly compared to those who are either nondepressed or do not BD as often (Connell et al., 2015). As previously noted, depression is also linked to an NMB (Disner et al., 2011; Duyser et al., 2020), that is, especially pronounced for self-referent information (Bradley and Mogg, 1994; Taylor and John, 2004; Zupan et al., 2017). This "self-NMB" may result from pervasive negative self-views in depression that increase the salience of negative information referent to self-concept, rendering it more competitive for retrieval (Disner et al., 2011, 2017; Zupan et al., 2017). The NMB is further proposed to relate to difficulty disengaging from negative information, thus perpetuating negative self and world views, two central features of depression (Beck, 1967; Disner et al., 2011). As such, we propose that depression plays a role in the path from excessive alcohol use to an NMB for self-referent information.

Current aims

In sum, individuals who engage in problematic forms of drinking are at risk of developing an NMB. Moreover, this relation may be explained by intervening relations with coping motivations and depressive symptoms. Here, we fit a serial multiple mediation model to assess whether greater alcohol use predicts a tendency to use alcohol to cope with negative emotions (negative reinforcement), thereby predicting depressive symptoms due to excessive drinking and emotional dysregulation, and ultimately perpetuating an NMB. Further, we expect that the NMB will be most pronounced for sentences deemed self-referent as is seen in depression (Disner et al., 2011). We recognize that the aforementioned factors might act in a reciprocal manner, thus resulting in a feedback loop, and as such fit other possible models to assess the relative fit of our hypothesized predictive path.

We first explore this model with a female undergraduate sample to assess indirect effects in an extension of the sex-specific findings reported by Carbia et al. (2020). Study 2 then aims to replicate this in a sample of male and female undergraduate students to assess potential sex/gender differences in the aforementioned model. Finally, Study 3 assesses the generalizability of findings to a community sample.

Study 1

Methods

Participants

We recruited 62 female participants through an undergraduate psychology research pool; 5 were excluded from analyses due to missing data and 3 were excluded due to consuming alcohol on Day 1 (i.e., were at risk of being intoxicated during testing). Sample characteristics of the remaining 54 participants are presented in Table 1. We engaged with participants *via* secure videoconferencing (Zoom Video Communications, Inc.) for course credit; cameras were off during self-report portions to minimize undue social influence. The Toronto Metropolitan University REB approved the project (Studies 1–3) in accordance with the Canadian Tri-Council Policy Statement (TCPS2) on ethical conduct for research involving humans and all participants (Studies 1–3) provided informed consent.

Cognitive tasks

Digit-span

Participants completed the forward digit-span task requiring them to repeat verbally presented sequences of numbers of progressive length (3–9 digits). This task served as a distraction to minimize expectation that memory would also be assessed for the sentence task.

Self-referent sentences task

Participants completed an incidental encoding task. Participants were asked whether they felt 30 short sentences (e.g., "I am rational") described them ("yes" or "no") to determine self-reference. Sentences contained 10 positive, 10 neutral, and 10 negative adjectives from the English Word Database of Emotional Terms (EMOTE; Gruhn, 2016), presented in a random order. The items were selected from the EMOTE database based on the following ranges (on a scale of 1–7): negative 1–2.5, neutral 3–5, and positive 5.5–7. Moreover, items within each valence category were matched for numbers of letters and syllables, word frequency, imagery, concreteness, meaning, and familiarity (ps > 0.05). To further validate the emotional dimensions in our sample, participants rated the valence and arousal of each sentence after the memory task on the second day. Negative sentences were rated as more negative in valence than neutral sentences, $d = -2.05$, $p < 0.001$, and positive sentences were rated as more positive in valence than neutral sentences, $d = 1.50$, $p < 0.001$. There were no significant differences in arousal ratings, $F(2, 112) = 1.23$, $p = 0.30$, $\eta_G^2 = 0.02$, supporting that an NMB would be primarily driven by valence.

TABLE 1 Sample characteristics across the three studies.

	Study 1 Student	Study 2 Student		Study 3 Community	
	Female	Female	Male	Female	Male
n	54	94	50	47	48
Age	23^{bc}(7.1)	21.5^{c} (7.3)	23.6^{bc} (7.4)	25.3^{ab}(4.9)	27.4^{a} (5.0)
Ethnicity (%)					
White/European	52	39	40	45	52
South/East Asian	22	34	30	32	19
Middle Eastern	9	4	14	6	8
Black	7	9	4	13	19
Hispanic	2	5	0	4	2
Multiracial	7	10	12	0	0
AUDIT	6.9^{b} (5.9)	4.6^{b} (4.5)	7.7^{b} (5.9)	6.4^{b} (6.9)	12.2^{a} (10.1)
BD episodes	2.3 (4.4)	2.8 (6.4)	3.9 (6.0)	1.8 (4.2)	1.0 (1.8)
DMQ-R					
Coping	10.9^{b} (5.3)	9.4^{b} (5.4)	10^{b} (4.8)	10.8^{b} (5.1)	12.6^{a} (5.5)
Enhancement	13.2 (5.3)	12.2 (5.1)	13.8 (5.1)	11.8 (5.3)	14.6 (6.8)
Social	16.1 (5.4)	14.9 (5.8)	16.2 (5.3)	13.4 (5.1)	14.4 (5.7)
Conformity	8.4^{b} (3.9)	8^{b} (3.7)	8.2^{b} (4)	9.4^{b} (5)	12^{a} (4.7)
DASS-21					
Depression	14.4^{a} (10.1)	12.7^{a} (9.8)	12.8^{a} (10.5)	10.7^{b} (9.3)	10.6^{b} (7.2)
Anxiety	15.3 (10.6)	11.5 (9.6)	10.3 (8.8)	9.8 (9)	11 (7.9)
Stress	18.9^{a} (9.5)	14.3^{b} (9.3)	14.6^{b} (9.8)	13.7^{b} (10.1)	13.2^{b} (7.6)
Recall Performance					
Total Recall	1.78 (1.46)	3.68 (2.70)	2.76 (2.18)	2.98 (2.6)	3.44 (2.31)
Negative					
Self	0.32^{b} (0.56)	0.66^{a}(0.96)	0.38^{b} (0.64)	0.30^{b} (0.51)	0.19^{b} (0.45)
Not-Self	0.56 (0.72)	0.90 (1.15)	0.78 (1.10)	0.74 (1.03)	0.96 (1.09)
Positive					
Self	0.72^{b} (0.79)	1.61^{b}(1.44)	1.1^{b} (1.04)	1.66^{b} (1.78)	2.17^{a} (1.63)
Not-Self	0.17 (0.52)	0.51 (0.90)	0.50 (0.93)	0.28 (0.62)	0.12 (0.33)

Data represent Means (SDs). ^{a,b,c} Superscripts reflect significant differences between and within the three study samples for the respective variables based on Welch's t tests, where a > b > c; groups with the same superscript(s) do not differ significantly from one another. AUDIT, BD, age, and recall scores had a somewhat positive skew.

Free recall

Approximately 24 h after the incidental encoding of sentences, we asked participants to type out as many sentences as they could recall from the sentences task within 2 min. Memory bias scores were calculated by subtracting correctly recalled negative sentences from correctly recalled positive sentences, such that negative bias scores reflect an NMB and positive scores reflect a positive memory bias. Bias scores were further defined according to whether the respective sentences had previously been deemed self-referent or not by each participant on Day 1.

Questionnaires

Alcohol use disorders identification test (AUDIT)

The AUDIT (Saunders et al., 1993) consists of 10 items rated on a 5-point scale (0–4) that assesses the frequency and amount of alcohol consumption and alcohol-related problems (e.g., feeling guilty after drinking) in the past year. A score of 8 or more indicates risky drinking habits. The AUDIT has been validated across genders and various ethnicities (Saunders et al., 1993; World Health Organization, 2001) and has demonstrated good internal consistency (Cronbach's $\alpha = 0.83$; Selin, 2003).

Timeline followback method- alcohol (TLFB)

Participants reported estimates of their daily alcohol consumption during a 60-day TLFB (Sobell and Sobell, 1995) interview to measure the number of BD (5 standard drinks in males, 4 in females) episodes. The TLFB has been validated in males and females over the age of 14 in clinical and nonclinical samples (Sobell and Sobell, 1995) and demonstrates high test-retest reliability for BD episodes (ICC = 0.79; Cohen and Vinson, 1995).

Drinking motives questionnaire-revised (DMQ-R)

The DMQ-R (Cooper, 1994) contains 20 statements representing four categories of drinking motivations, including coping, enhancement, social, and conformity. Here,

we focus on the coping subscale to address our *a priori* hypotheses. Motivations are rated on a 5-point scale based on how frequently they occur (Never/Almost Never to Always/Almost Always). The DMQ-R was validated in samples of adolescents and adults (Cooper et al., 1992; Cooper, 1994), its subscale structure holds across gender, ethnicities, and age, and it shows good internal consistency (Cronbach's $\alpha = 0.84$; Harbke et al., 2019).

The depression anxiety stress scale (DASS-21)

The DASS-21 (Lovibond and Lovibond, 1995) measures self-reported symptoms of depression, anxiety, and stress symptoms experienced in the past week. Each subscale contains seven items rated on a 4-point scale. Scores range from 0 to 42 with greater numbers indicating greater severity. This scale shows good internal consistency (Cronbach's $\alpha = 0.83–0.85$), as well as good construct validity across ethnicities (Norton, 2007) and in clinical and nonclinical samples (Osman et al., 2012).

Bidimensional impression management index (BIMI)

Social desirability was assessed using the BIMI (Blasberg et al., 2013), which distinguishes between agentic (exaggeration of social status or intellect) and communal impression management (denying socially deviant impulses and exaggerating virtuous attributes). The mean score on the agentic subscale in our sample exactly equals the norm from Blasberg et al. (2013) for honest responses (Welch's t $d = 0$, $p = 1.0$), and is significantly lower (i.e., more honest) than the norms for 'faking good', $d = -0.92$, $p < 0.001$. Scores on the communal subscale from our sample were significantly greater than the norms for honest, $d = 0.33$, $p = 0.05$, but were also significantly lower than norms for 'faking good', $d = -0.38$, $p = 0.01$. These patterns together with the fact that this study was not looking at prosocial behavior support an honest profile of responses by the current sample.

Statistical analyses

As some alcohol consumption and recall variables were positively skewed, we assessed bivariate correlations using Spearman's rho among the variables of interest: Number of BD episodes, AUDIT, coping, depression, bias scores, and total recall. Based on these relations and our hypotheses, we used PROCESS v3.5 in R (Model 6; Hayes, 2017) to assess serial indirect relations between alcohol use and an NMB through depression and coping. Predictor, mediator, and outcome variables were converted to standardized scores. Significance of indirect effects is interpreted relative to 95% confidence intervals (CIs) constructed with 5,000 bootstrap samples with a consistent randomly selected seed (31216) across analyses; p values are reported for direct and total effects. Regression assumptions were satisfied for all models.

Results

Memory performance

Overall recall ranged from 0 to 5 sentences (see Table 1 for descriptive statistics). Using Wilcoxon signed-rank test, there was no significant difference in overall recall for negative and positive sentences ($p = 0.89$). However, for sentences deemed self-referent there were significantly fewer negative than positive sentences recalled ($p < 0.01$); the reverse was true for sentences rated not self ($p < 0.01$). Self-bias scores ranged from −2 to 2 and not-self bias from −3 to 2. Thus, despite an overall positive bias, there was variation across individuals in demonstrating an NMB or positive memory bias.

Correlations and regressions

As seen in Table 2, greater scores on the AUDIT were significantly related to lower self-bias scores, consistent with a self-NMB. BD episodes, however, were not significantly related to a self-bias score. Higher AUDIT and more BD episodes were both significantly correlated with endorsement of coping motivations; AUDIT was also highly positively correlated with depressive symptoms whereas BD failed to reach significance. Moreover, greater depression and endorsement of coping motivations significantly predicted lower bias scores only for self-referent sentences. In contrast, bias scores for sentences deemed "not-self" only revealed very small (rhos <0.15) and nonsignificant relations with variables of interest. Likewise, total recall performance was not significantly related to BD, AUDIT, depression, or coping motivation scores. The above results indicate that a tendency toward an NMB in individuals high on the aforementioned variables primarily occurs for information deemed self-referent.

To better understand the observed relations of AUDIT and depression with the self-bias scores, we used multiple regression to assess the relative contributions of recall for self-referent negative and positive sentences. Together they explain 8% of the variance in AUDIT ($R^2 = 0.08$, $p = 0.05$) and 13% of the variance in

TABLE 2 Correlation matrix among the alcohol, clinical, and memory variables of interest in Study 1.

	AUDIT	BD episodes	Depression	Coping
Depression	**0.46*****	0.05		
Coping	**0.65*****	**0.37****	**0.51*****	
Self-Bias	**−0.38****	−0.10	**−0.46*****	**−0.27***
Not-self	0.05	0.03	0.14	0.09
NMB				
Total recall	−0.18	−0.16	0.12	−0.13

AUDIT, Alcohol Use Disorders Identification Test; BD, Binge Drinking. Correlation coefficients are reported as Spearman's rho. Bold values are significant relations between main variables of interest.

*$p < 0.05$.

*$p < 0.01$ Self-Bias = self-positive–self-negative recalled.

***$p < 0.001$ Not-self Bias = not-self positive–not-self negative recalled.

depression scores ($R^2 = 0.13$, $p < 0.01$). In both cases, higher scores on these measures were associated with a pattern of recalling more negative ($\beta = 0.21$, $\beta = 0.36$, respectively) and fewer positive self-referent sentences ($\beta = -0.26$, $\beta = -0.19$, respectively).

Serial multiple mediation through coping and depression

Given Carbia et al.'s (2020) findings of the association between BD and an NMB, we first assessed the serial mediation model on self-bias scores with number of BD episodes as the predictor; the current lack of bivariate relation does not preclude the presence of meaningful indirect effects (Hayes, 2017). With BD as the predictor, the specific total indirect effect was significant such that a greater frequency of BD days predicted a tendency to endorse coping motives, which predicted greater depressive symptoms, and, in turn, lower self-bias scores, $\beta = -0.12$, [−0.28, −0.01]. An increase of 1 SD or approximately 4 BD episodes in the 60-day period corresponded with a 12% lower self-bias score through endorsement of coping motivations and depression. The direct effect of BD on self-bias memory scores did not explain significant unique variance ($p = 0.61$).

The overall relation (total effect) between AUDIT and self-bias memory scores was significant ($p = 0.02$), as were the individual components of the indirect pathway, supporting the predictive value of AUDIT scores on coping motivations, of coping motivations on depressive symptoms, and of depressive symptoms on the self-bias scores (see Figure 1). The specific total indirect effect (i.e., serial path), however, just failed to reach significance, $\beta = -0.15$ [−0.33, 0.003]. The direct effect of AUDIT on a self-NMB was not significant ($p = 0.22$), supporting that the relation between alcohol use and a self-NMB is primarily explained *via* coping motivations and depressive symptoms.

Model validation

Although our cross-sectional design cannot support causal inference, the mediation verbiage represents the underlying theory. That is, the theoretical basis behind the above models is that excessive alcohol use (either problematic drinking or BD) predicts lower self-bias scores through greater coping motivations, which predicts greater depression. To test the above models, we examined alternatives by reordering the predictor and the intervening variables. In the BD model, swapping the order of mediator variables resulted in no significant pathways, whereas in the AUDIT model, only the specific indirect effect through depression was significant, $\beta = -0.22$ [−0.47, −0.002]. With depression as the predictor in both AUDIT and BD models, the direct effects were significant ($p = 0.02$; $p = 0.01$) whereas none of the indirect pathways were significant. Comparatively, with coping motivations as the predictor in the AUDIT model, neither direct nor indirect effects were significant. With coping motivations as the predictor in the BD model, only the specific indirect pathway through depression was significant, $\beta = -0.27$, [−0.51, −0.03]. Additionally, the other DMQ-R subscales of enhancement, social, and conformity motivations failed to show significant indirect effects when controlling for coping motivations. Likewise, anxiety and stress subscales of the DASS-21 failed to show significant indirect effects when controlling for depression. These findings further support that problematic drinking and BD are primarily related to lower self-bias memory scores through the respective indirect effects of depression and coping motivations in the predicted manner.

Discussion

As expected, problematic drinking, coping, and depression scores were particularly related to a tendency to preferentially recall self-referent negative information, as opposed to sentences that participants deemed not self-referent. This aligns with previous findings that the NMB tends to be stronger for self-referent stimuli in individuals with depression (Zupan et al., 2017). Moreover, an indirect path through coping motivations and depression explained the relations between BD and problematic drinking with lower memory bias scores for self-referent sentences.

Notably, the relation between alcohol use and an NMB has so far only been found in females (Carbia et al., 2020). Study 1 built upon this relation in assessing the mediating role of coping motivations and depression in females. Sex and gender are important, although somewhat complex, considerations in the discussion of alcohol use and emotional dysregulation. Sex refers to a biological trait that influences the development of the brain and body (Sanchis-Segura and Becker, 2016) and contributes to how individuals interact with their environment. Gender refers to individual embodiments or expressions that interact with but may not align with sex (Sanchis-Segura and Becker, 2016). Gendered environmental experiences may subsequently influence the brain and alter behavior (Sanchis-Segura and Becker, 2016). For example, experiences of sexual trauma are significantly more common in women (Olff, 2017), which may dysregulate brain functioning and emotional responses and result in greater use of alcohol to cope with related symptoms (Ullman et al., 2013; Hammerslag and Gulley, 2016). Thus, both sex and gender involve biological and environmental interactions and play a key role in vulnerabilities and responses to substance use. These factors warrant attention in relation to self-NMB.

Study 2

Study 2 provides a replication of the mediating roles of coping motivations and depression in the relation between alcohol use and an NMB. Given that Carbia et al. (2020) only observed significant NMB relations with BD in women, we also investigate whether sex/gender moderates the above indirect relations. Of note, our current aims were not to disentangle sex and gender effects, and as detailed below these variables were largely redundant in our study; thus, we refer to sex only

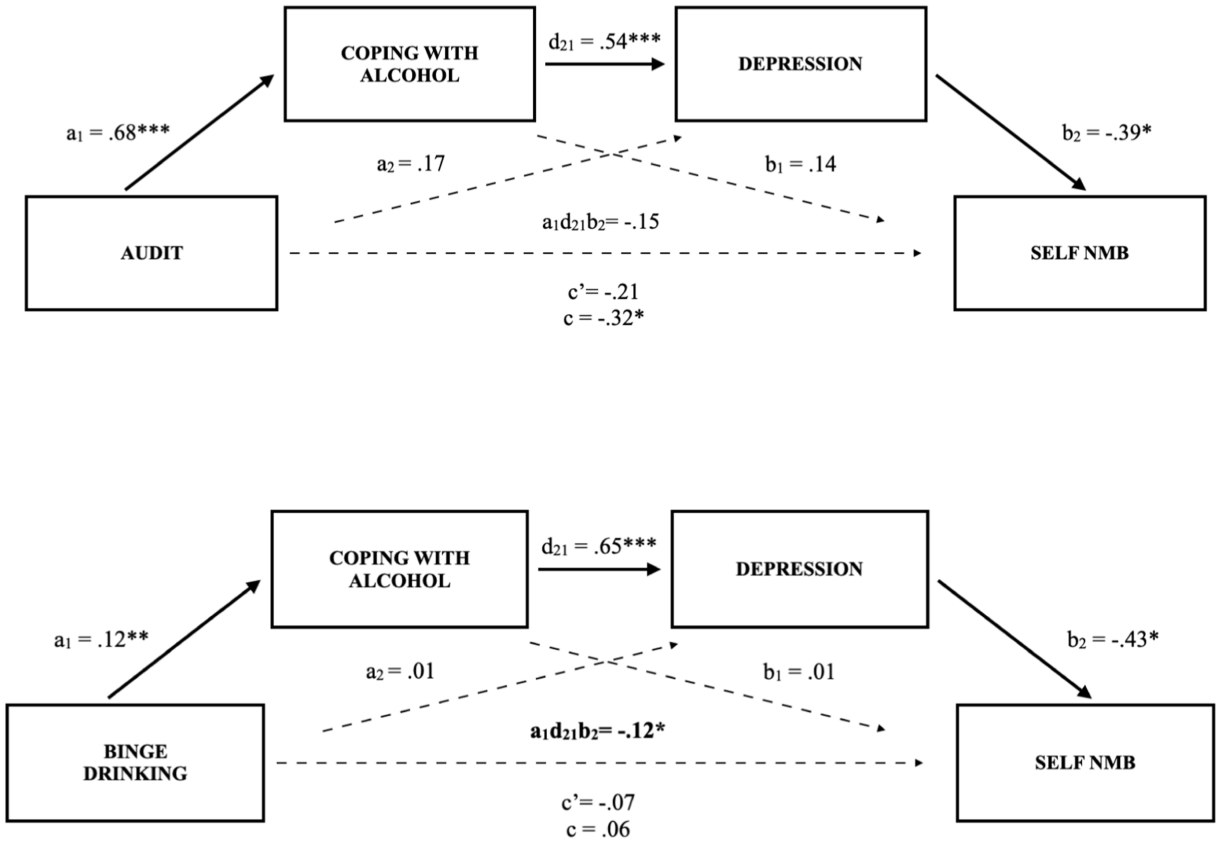

FIGURE 1
Serial multiple mediation model of the relations between problematic drinking (AUDIT scores) and binge drinking with negative self-referent memory bias (self-NMB) through coping motivations and depressive symptoms in undergraduate female students. (Study 1). Solid lines and bolded parameters reflect significant relations: *p<0.05, **p<0.01, ***p<0.001.

throughout. Further, as outlined below, given low overall recall in Study 1, we modified the memory paradigm to enhance task sensitivity.

Methods

Participants

Using the coefficients obtained from the model with AUDIT scores as the predictor, which just failed to reach significance in Study 1 (see Figure 1), we applied Schoemann et al.'s (2017) application that estimated a target sample size of n = 70 for a serial mediation effect with 80% power. Thus, we aimed to recruit a minimum of 70 females and 70 males to target serial mediation within each sex. Across two terms, we recruited 138 female and 76 male students *via* the same undergraduate pool as for Study 1. There was limited discrepancy between sex and gender identifications (i.e., 98% of females identified as women and 97% of males identified as men). Thus, as noted, analyses were conducted by sex; however, results may be indicative of either sex-based (i.e., biological) differences or gendered (i.e., environmental) experiences.

In contrast to Study 1 where 7% of students reported abstaining from alcohol (i.e., a score of 0 on the AUDIT), this percentage was almost five times higher in the Study 2 sample (33%). As the reasons for abstinence may vary, this high proportion of the sample reporting no use may impede clear interpretation of the relations with problematic alcohol use. To address this concern, we analyzed the data with and without those who reported no consumption; the ratio of males:females across the original and alcohol-using samples was similar (0.55; 0.53, respectively; see Table 1). The pattern of findings was similar across these analyses in terms of the strength of relations and their interpretation relative to significance decision thresholds. We report the findings from the smaller sample to better represent the relations with problematic drinking (AUDIT scores).

Materials and procedure

Questionnaires administered were the same as in Study 1 along with the inclusion of the Personal Attributes Questionnaire (PAQ; Spence and Helmreich, 1978) to assess individuals' alignment with gender roles; descriptive statistics are reported in Table 1. AUDIT showed good internal consistency in the Study 2 sample (Cronbach's α = 0.85), the depression subscale of the

DASS-21 showed excellent internal consistency ($\alpha = 0.90$), and the coping motivations subscale of the DMQ-R showed acceptable internal consistency ($\alpha = 0.77$). To enhance overall recall and sensitivity of the bias scores, however, we made a number of modifications to the main memory task in this iteration of the study. First, we increased the focus on the positive and negative stimuli of interest, and presented 14 negative and 14 positive sentences in a random order. Only 2 neutral sentences were included at the beginning and end of the Self-Referent Sentences Task to control for primacy and recency effects. In addition, we included a second task that asked participants to identify the valence ("positive" or "negative") of the adjectives from the Self-Referent Sentence Task in order to re-expose them to the key stimuli. On Day 2, participants were asked to recall as many sentences as they could, with one of the neutral sentences used as a reminder of the task (e.g., "I am rational").

In contrast to the direct interaction and interview style used in Study 1, we also moved Study 2 to an anonymous online survey format. More specifically, participants completed the study remotely *via* Qualtrics[1] and Pavlovia[2] online platforms. Results of the BIMI agentic and community subscales were significantly lower than the student norms for 'faking good' ($d = -1.60$, $p < 0.001$; $d = -0.56$, $p < 0.001$), indicating honest response styles.

Statistical analyses

Following bivariate correlation and regression analyses as for Study 1, we conducted a conditional process analysis *via* PROCESS v3.5 (Model 92; Hayes, 2017) to assess the serial mediation models by sex. We also explored bivariate relations with femininity and masculinity. Regression assumptions were satisfied for all models.

Results

Memory performance

Recall ranged from 0 to 14 sentences ($M = 3.4$, $SD = 2.6$), indicating that alterations to the paradigm were successful in raising overall recall levels compared to Study 1, Welch's $t(168) = 5.38$, $p < 0.001$. In both sexes, there were significantly fewer self-negative sentences recalled relative to self-positive (Wilcoxon signed-rank test; female, $p < 0.001$; male, $p < 0.001$). For sentences rated "not-self," there were more negative relative to positive sentences for females, $p < 0.01$, whereas there was no significant difference for males, $p = 0.18$. Notably, there was variation in memory biases across individuals as self-bias and not-self bias scores ranged from-4 to 5 and-5 to 5 in females, respectively, and from −2 to 3 and −5 to 4 in males, respectively.

1 www.qualtrics.ryerson.ca

2 www.pavlovia.org

Correlations and regressions

Replicating the pattern of results from Study 1, the relations between AUDIT, coping motivations, and depression with lower self-referent memory bias scores were of similar magnitude among females in Study 2; moreover, all three relations were significant (see Table 3). In males, depressive symptoms were significantly related to lower self-referent bias scores. Further, more BD episodes revealed small-medium relations to lower self-referent bias scores, but failed to reach significance, whereas AUDIT and coping motivations did not relate to bias scores in males (Table 3).

Regression models were fit to examine the unique relations of self-positive and self-negative sentences recalled to the above three variables for females and the two small-medium relations for males. In females, higher AUDIT, coping, and depression scores were associated with significantly greater recall of negative self-referent sentences ($\beta = 0.17$, $p < 0.05$, $\beta = 0.26$, $p < 0.01$, $\beta = 0.38$, $p < 0.001$, respectively); depression was also associated with significantly lower recall of positive self-referent sentences ($\beta = -0.28$, $p < 0.01$). Comparatively, only depression was significantly related to greater recall of negative self-referent sentences in males ($\beta = 0.34$, $p = 0.02$).

To explore potential relations with gender, and specifically alignment with gender roles, we examined the relations of femininity and masculinity scores with the five key variables of interest (self-bias, AUDIT, BD, coping, depression). Among females, femininity was moderately correlated with higher AUDIT scores rho = 0.25, $p < 0.05$, and more BD episodes, rho = 0.29, $p < 0.01$, whereas masculinity related to more positive self-bias memory, rho = 0.28, $p < 0.01$, and lower depression, rho = −0.47, $p < 0.001$. There were no significant relations among these measures for males.

Moderated serial multiple mediation through coping and depression

Supporting assertions on the same model in Study 1, we found that in females the specific total indirect (i.e., serial) pathway was significant such that more problematic alcohol use predicted greater coping motivations, which predicted greater depressive symptoms, which predicted a lower self-bias score, $\beta = -0.08$, [−0.19, −0.02] (see Figure 2). That is a 1 SD greater AUDIT score predicted an 8.3% lower self-referent bias score, through endorsement of coping motivations and greater depressive symptoms. The same was not true for male students with AUDIT scores, for whom the specific total indirect effect failed to reach significance, $\beta = -0.03$, [−0.10, 0.01]. Despite the sex difference in significance of the indirect pathway, the index of moderated mediation failed to reach significance, $\beta = -0.05$, [−0.20, 0.05]. After accounting for coping motivations and depression, the direct effects of AUDIT on self-bias scores were also nonsignificant in females ($p = 0.43$) and males ($p = 0.51$).

In the model with BD as the predictor, the specific total indirect pathway was again significant for females, such that a greater number of BD days was associated with greater coping

TABLE 3 Correlation matrix among female (below diagonal) and male (above) student alcohol, clinical, and memory variables of interest in Study 2.

	AUDIT	BD days	Depression	Coping	Self-Bias	Not-Self Bias	Total Recall
AUDIT		**0.51****	**0.26***	**0.58****	−0.04	0.25	0.02
BD days	**0.60****		0.08	0.23	0.23	−0.08	0.13
Depression	**0.21***	0.04		**0.37****	**−0.27***	0.34	0.09
Coping	**0.46****	**0.23****	**0.47****		0.04	0.28	<0.01
Self-Bias	**−0.25***	−0.16	**−0.38****	**−0.27****		−0.40	−0.40
Not-Self Bias	0.11	<0.01	−0.33*	0.23	−0.38***		0.12
Total Recall	0.08	0.13	0.05	0.05	0.35*	0.24	

AUDIT, Alcohol Use Disorders Identification Test; BD, Binge Drinking. Correlation coefficients are reported as Spearman's rho. Bold values are significant relations between main variables of interest.

*$p < 0.05$.

**$p < 0.01$ Self-Bias = self-positive– self-negative recalled.

***$p < 0.001$ Not-self Bias = not-self positive–not-self negative recalled.

motivations, which predicted greater depressive symptoms, which predicted a lower self-bias score, β = −0.05, [−0.12, −0.004], consistent with Study 1. That is 1 SD greater BD episodes (~ 4 more episodes) predicted a 4.9% lower self-bias score. Comparatively, the serial indirect pathway for males was of a similar magnitude, but again not significant, β = −0.04 [−0.11, 0.01]. The index of moderated mediation was also not significant, β = −0.01 [−0.10, 0.08]. As expected, the direct paths failed to account for unique variance in self-bias memory scores (females, $p = 0.86$; males, $p = 0.18$). Notably, in both AUDIT and BD models, the separate specific indirect pathways through only depression or only coping were not significant (see Figure 2).

Discussion

In sum, with both problematic alcohol use and BD episodes as predictors, we replicated a significant indirect relation with more negative self-referent memory biases as explained through coping motivations and depression among females. Although the pattern was similar and relations were of similar magnitude for males, these associations failed to reach significance.

Study 3

We conducted Studies 1 and 2 on undergraduate student samples given characteristically elevated rates of alcohol consumption and depressive symptoms in this population (Geisner et al., 2012). Here, we expand our investigation to a community sample to assess the generalizability of proposed models.

Methods

Based on *a priori* power analyses detailed in Study 2, we recruited 165 Canadian community participants *via* the Honeybee Hub recruitment platform[3] for a $10 incentive ($5/day). Due to incomplete or invalid survey responses, 44 male and 27 female responses were excluded, leaving 47 male and 48 female participants. Only 9.4% of the remaining sample reported no alcohol consumption on the AUDIT. Sample characteristics are summarized in Table 1. The procedures and measures were otherwise identical to Study 2. The AUDIT showed good internal consistency in the Study 3 sample (Cronbach's α = 0.89), as did the depression subscale of the DASS-21 (α = 0.87), and the coping motivations subscale of the DMQ-R (α = 0.89). Scores on the BIMI were significantly lower than the norms reported for the online community sample in Blasberg et al. (2013) for "faking good" on both the agentic, d = −2.39, $p < 0.001$, and community subscales, d = −3.23, $p < 0.001$, indicating honest response styles. Regression assumptions were satisfied for all models.

Results

Memory performance

Recall ranged from 0 to 11 sentences (M = 3.2, SD = 2.5). In females and males, there were significantly fewer self-negative sentences recalled relative to self-positive (Wilcoxon signed-rank test, both $p < 0.001$) and, conversely, more not-self negative sentences relative to not-self positive (females $p = 0.01$; males $p < 0.001$). In females, self-bias and not-self bias scores ranged from −1 to 7 and −3 to 2, and in males from −1 to 8 and −4 to 1, respectively.

Correlations and regressions

As seen in Table 4, higher scores on the AUDIT, depressive symptoms, and coping motivations in males revealed medium-sized and significant relations to a greater NMB for self-referent sentences. Further, males showed small-medium relations between BD days with a negative self-memory bias, though these

3 www.honeybeehub.com

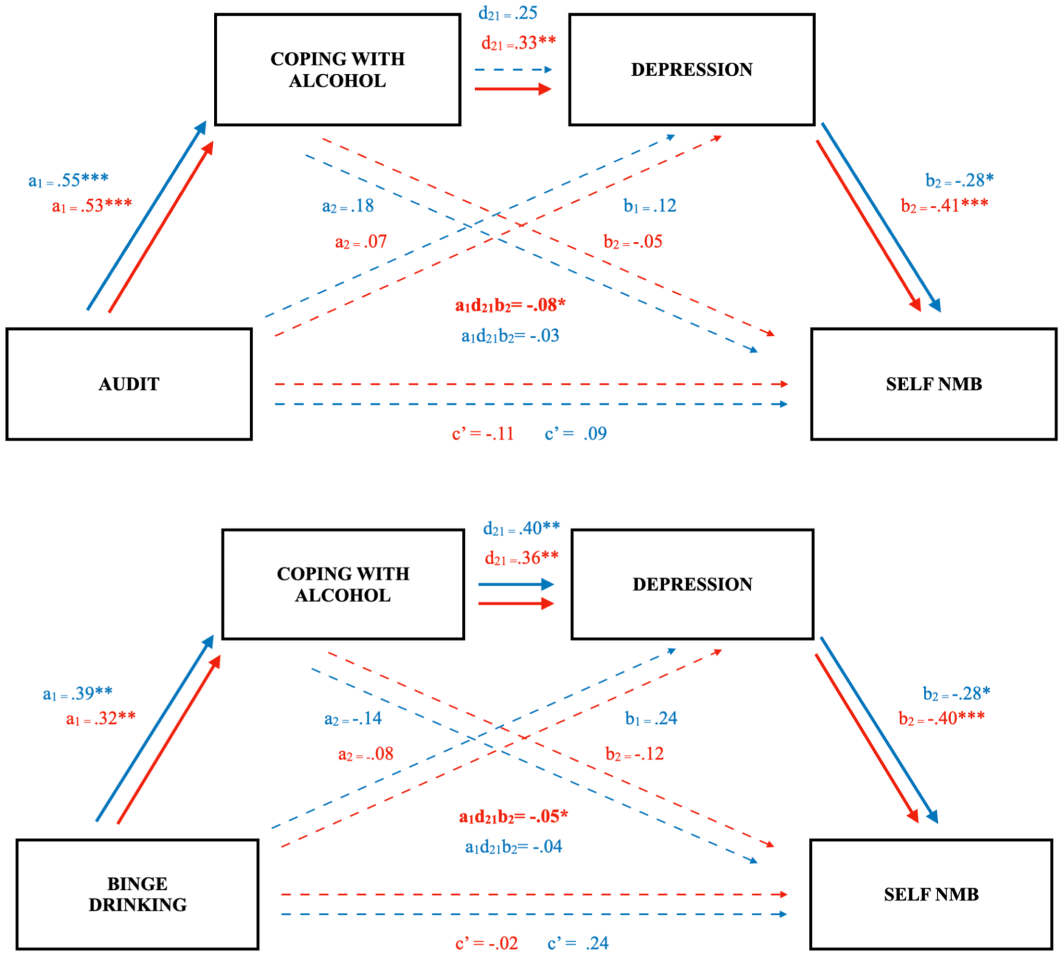

FIGURE 2
Indirect effects of coping motivations and depression on the relation between problematic drinking, binge drinking, and a self-referent memory bias in undergraduate females, but not males (Study 2). Figure depicts separate serial mediation models with females in red, males in blue. Solid lines and bolded parameters reflect significant relations: *p<0.05, **p<0.01, ***p<0.001.

failed to reach significance. Unlike Studies 1 and 2, among females from the community, only greater endorsement of coping motivations revealed a small-medium, but nonsignificant relation to lower self-bias scores. Notably, in females, greater alignment with feminine gender roles was moderately related to lower depression, but failed to reach significance (rho = −0.24, p = 0.09). Masculinity and femininity were not related to variables of interest in males.

Nonetheless, depression scores among females predicted significantly greater recall of negative self-referent sentences (β = 0.35, p = 0.02) through regression analyses. Similarly, depression in males was also associated with significantly greater recall of negative self-referent sentences (β = 0.29, p = 0.04), while coping motives were related to significantly lower recall of self-referent positive sentences (β = −0.39, p < 0.001).

Moderated serial multiple mediation through coping and depression

As in Study 2, we assessed the moderated serial multiple mediation models in the community sample. In contrast to the undergraduate samples, the paths from depression to self-bias scores were nonsignificant, precluding the total specific indirect paths through both coping and depression (see Figure 3).

Notably, however, with BD as the predictor, the specific indirect pathway through coping was significant in both females, β = −0.09, [−0.39, −0.01] and males, β = −0.24, [−0.61, −0.05]. As such, 1 SD greater BD episodes (2 episodes for females and 3 for males) predicted 9 and 24% lower self-bias scores, respectively (see Figure 3). Again, the index of moderated mediation was not significant, β = 0.15, [−0.18, 0.52]. Finally, the direct effect between BD and self-referent memory bias was not significant in either females (p = 0.37) or males (p = 0.81).

For females, the specific indirect effect for AUDIT through coping was significant (β = −0.43, [−0.79, −0.13]; see Figure 3), such that 1 SD increase in AUDIT scores predicted a 43% lower self-bias score through coping motivations in community females. In males, this relation was half the magnitude and not significant, β = −0.22, [−0.48, 0.07]. Despite discrepancy in path coefficients between the sexes, the index of moderated mediation was not significant, β = −0.21, [−0.67, 0.17]. The

TABLE 4 Correlation matrix for females (below diagonal) and males (above) in the community sample for alcohol, clinical, and memory variables of interest in Study 3.

	AUDIT	BD days	Depression	Coping	Self-Bias	Not-SelfBias	Total Recall
AUDIT		**0.63*****	0.26*	**0.72*****	**−0.32***	−0.16	0.11
BD days	**0.74*****		**0.39****	**0.45*****	−0.27	0.18	0.10
Depression	0.10	0.13		−0.02	**−0.14***	0.04	0.02
Coping	**0.70*****	**0.53*****	**0.27***		**−0.33***	0.04	0.26
Self-Bias	0.06	0.06	−0.13	−0.27		0.24	0.72*
Not-Self Bias	−0.18	0.23	0.13	0.28	−0.45***		0.55*
Total Recall	−0.05	−0.01	0.17	0.10	0.68*	−0.52*	

AUDIT, Alcohol Use Disorders Identification Test; BD, Binge Drinking. Correlation coefficients are reported as Spearman's rho. Bold values are significant relations between main variables of interest.

*$p < 0.05$.

**$p < 0.01$ Self-Bias = self-positive–self-negative recalled.

***$p < 0.001$ Not-self Bias = not-self positive–not-self negative recalled.

direct effect for AUDIT was not significant for females ($p = 0.10$) or males ($p = 0.91$).

As males and females in the community sample were significantly older than students in Studies 1 and 2 (Table 1), we assessed the relations between age and bias scores; however, it was not significant (rho = 0.27, $p = 0.07$).

To partially address modest sample size limitations in the above three studies, we ran omnibus conditional process analyses pooling the data from all participants (N = 292); results revealed a significant index of moderated mediation, supporting a difference in relations among problematic alcohol use (AUDIT), depression, endorsement of coping motivations, and a self-bias score in females relative to males β = −0.07, [−0.14, −0.02]. Indeed, the full mediation model was significant in females β = −0.07, [−0.12, −0.02], but not for males, β = 0.003, [−0.03, 0.04]. Similarly, results for the BD model supported the full mediation model in females β = −0.05, [−0.10, −0.02] and not males, β = −0.01, [−0.03, 0.01], although the index of moderated mediation failed to reach significance, β = −0.04, [−0.09, 0.001].

Discussion

We found an indirect effect of endorsement of coping motivations on the relation between alcohol consumption variables (both AUDIT scores and BD episodes) and an NMB in community females. Interestingly, we also found that endorsement of coping motivations was a significant intervening variable for only the BD model in community males, in contrast to Study 2 findings. Study 3 supports the relevance of maladaptive behaviors linked with emotional dysregulation (i.e., drinking to cope with negative affect), in the proposed relation between excessive alcohol use and preferential recall of self-referent negative stimuli. When pooling all three studies, we also found support for the full indirect effect in AUDIT and BD models in females only, and moderated mediation in the AUDIT model supported a significant difference between females and males.

General discussion

In this three-part study, we examined whether coping motivations and depressive symptoms serially explain the relationship between problematic drinking and BD with a self-referent NMB in undergraduate and community samples, as well as the moderating role of sex. Overall, results generally replicated across studies with minor nuances in findings. Across all three samples, we found bivariate relations between a self-referent NMB and problematic drinking (AUDIT scores), depressive symptoms, and endorsement of coping motives. Further, across both student samples, multiple linear regression models found that greater recall of self-referent negative sentences was associated with higher levels of problematic drinking and depressive symptoms, and that lower recall of self-referent positive sentences associated with depressive symptoms. More central to our study aims, findings from both student samples supported the serial mediation model with an indirect pathway through coping motivations and depressive symptoms among females for both BD and problematic drinking, whereas this path was weaker for males and nonsignificant. Comparatively, in the community sample, the proposed model was partially replicated as only the specific indirect pathways through coping motivations were significant for both sexes with BD episodes and in females with AUDIT scores.

The role of sex in alcohol consumption behaviors and consequences

In female undergraduate students, excessive alcohol use patterns *via* the AUDIT consistently related to a greater tendency to recall self-referent negative stimuli. Excessive alcohol use is purported to give rise to an NMB related to lower prefrontal-cortex inhibition of the amygdala (Stephens and Duka, 2008). In the current study, the more robust pattern of findings in undergraduate females relative to males may relate to different neural vulnerabilities and responses to alcohol consumption. For example, high levels of sex-steroid receptor expression in the

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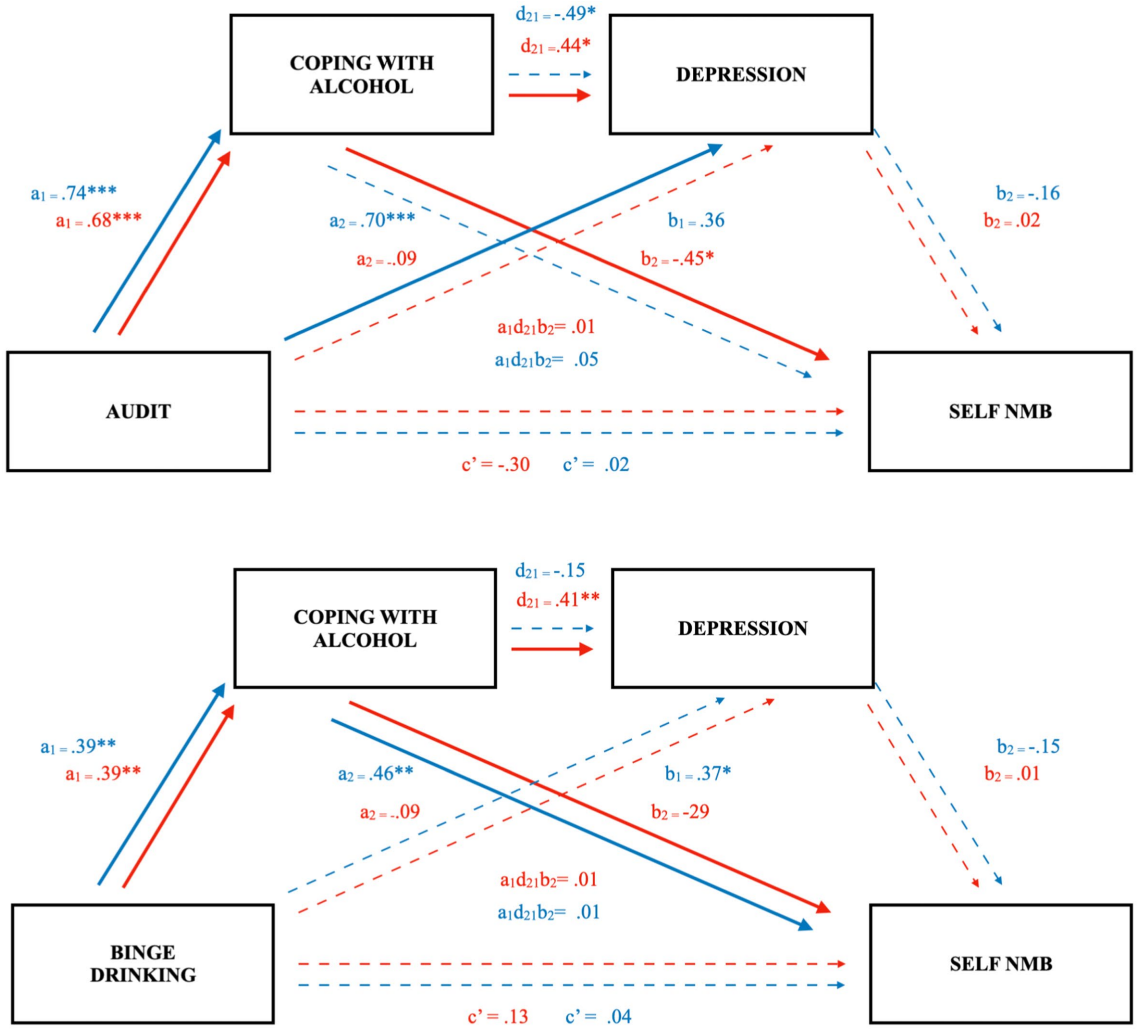

FIGURE 3
Coping mediates the relation between problematic drinking and a self-referent negative emotional memory bias in community females but not males (Study 3). Figure depicts separate serial mediation models with females in red, males in blue. Solid lines and bolded parameters reflect significant relations: *p<0.05, **p<0.01, ***p<0.001.

prefrontal cortex and amygdala relate to sexually dimorphic pubertal development and functionality of these regions, resulting in a greater impact of alcohol consumption on dysregulation of emotions in females, relative to males (Hammerslag and Gulley, 2016). Thus, female students who excessively consume alcohol during university, a formative developmental period, may be particularly vulnerable to alcohol-induced neurological changes in regions associated with processing emotional memories (e.g., hippocampus, amygdala, and prefrontal cortex; Stephens and Duka, 2008). Further, emotional dysregulation associated with excessive alcohol consumption may manifest in the form of experiencing depressive symptoms and turning to maladaptive coping mechanisms for negative emotions (Koob, 2013).

Comparatively, problematic alcohol use among male participants in the community sample was significantly correlated with the self-NMB, whereas this was not the case for female participants. Though somewhat unexpected based on findings of the student samples in Study 1 and 2, along with previous research (Carbia et al., 2020), this may be explained by the higher rates of alcohol consumption observed in community males (nearly double their female counterparts, as well as both male and female students). Thus, whereas certain vulnerabilities, whether neural or behaviorally based, may render females more sensitive to an NMB at lower levels of consumption, more severe patterns of problematic drinking may still contribute to emergence of an NMB in males. Further, although there was no longer a bivariate relationship for females, alcohol use remained a predictor of a self-NMB *via* endorsement of coping motivations. Future research will be useful for exploring potential dose-dependent relationships across sexes and other demographics (e.g., age and student status).

Serial mediation through coping motivations and depressive symptoms

As hypothesized, across all models, alcohol variables did not reveal a direct effect on the NMB after accounting for coping motivations and depression. Rather, we observed a significant intervening effect of coping motivations in females whether independently (Figure 3) or as part of a serial mediation with depressive symptoms (Figures 1, 2). Individuals who are motivated to consume alcohol to cope with negative affect may be more likely to experience an NMB *via* reinforcement of alcohol cravings in response to negative affective cues, greater cognitive and emotional dysregulation, and higher levels of alcohol consumption (Zack et al., 1999, 2002; Stephens and Duka, 2008; Foster et al., 2014; Decaluwe et al., 2019). In fact, the serial models in Studies 1 and 2 for undergraduate females support that excessive use of alcohol may influence an individual to use it as a coping mechanism through negative reinforcement (Koob, 2013) and that this may precipitate onset or worsening of depressive symptoms (Connell et al., 2015), further contributing to the self-referent NMB (Disner et al., 2011).

Interestingly, depression was not supported as a mediator in Study 3. The discrepancies among undergraduate and community female samples may in part be explained by differences in prevalence of depressive symptoms, such that Study 1 students had the highest levels, followed by Study 2 students, and community members reporting the lowest. Additionally, whereas relations between alcohol measures and coping were robust and remarkably similar between sexes for all samples (Tables 3, 4; Figures 2, 3), the relations with depression were more discrepant and its relations with the NMB were relatively weak in the community sample. Furthermore, the community sample was on average older than the student samples, which is potentially indicative of a protective effect of age (Reed and Carstensen, 2012). Indeed, previous studies have also found that the NMB is especially pronounced in younger depressed participants and decreases with age (Zupan et al., 2017). Thus, relations between alcohol use and the NMB may be less reliant on depressive symptoms with age, whereas the full serial model appears especially relevant for adolescents and young adults.

The role of sex in the serial mediation model

Research on sex/gender differences in the tendency to endorse coping motivations is mixed, with adolescent girls between the ages of 13–19 years reporting greater coping motives than boys, whereas no gender differences are seen in college-aged students (for review see Kuntsche et al., 2006). In Study 3, we observed that coping motivations explained the relation between BD and an NMB in both males and females. Further, in Study 3, the male community sample endorsed significantly higher rates of coping motivations relative to male undergraduates. As such, in tandem with elevated alcohol consumption levels in the community males, cognitive emotional biases related to higher rates of maladaptive coping that are thought to underlie the NMB may explain the significant effect of coping motivations in this group. Interestingly, we found that in both male samples, coping motivations were not significantly related to depressive symptoms in the serial mediation models, whereas this relationship was significant for all female samples. This corresponds with previous findings that in females, endorsement of coping motivations was significantly related to higher depressive symptoms, whereas this relationship was not significant in males (Foster et al., 2014).

Sex and/or gender can play a role in the prevalence of and response to depression. For example, a significant increase in depression is seen in only females during Tanner stage III in mid-puberty (Hammerslag and Gulley, 2016). Moreover, socialization and gender inequalities may contribute to negative self-referent biases and lower self-esteem in vulnerable individuals (van der Aar et al., 2018; Bone et al., 2021). To elaborate, gender-informed cognitive models of depression suggest that adolescent girls are more vulnerable to depression due to differences in rumination and negative inferential style, a greater likelihood of experiencing negative life events, and a greater tendency to develop depressive symptoms in response to such events (Hankin and Abramson, 2001). This coincides with the finding that in undergraduate females, alignment with feminine gender roles was related to greater alcohol consumption whereas greater endorsement of masculine gender roles was associated with lower depression scores. Conversely, in males, gender role alignment did not relate to variables of interest, which may suggest experiences of gender and gender roles play a bigger part for females with respect to alcohol consumption, depression, and potentially cognitive sequelae, while this does not appear true for males. Surprisingly, this contradicts previous research that found that alignment with feminine roles assessed by the same measure was negatively related to alcohol consumption (Peralta et al., 2010). However, Peralta et al. (2010) did not disaggregate findings by sex identification, possibly obscuring differences. This may also be reflective of differences in socio-cultural context by time or location of samples.

It is important, however, not to overstate the immutability of sex/gender differences. While literature shows females are likely to experience depression and have a greater tendency toward an NMB than males (Hammerslag and Gulley, 2016; Dir et al., 2017; Hardee et al., 2017), males who are depressed may also show differential responses relative to males who are not depressed. That is, while there may be differences between males and females in general, the differences between males and females with depression may be less striking. Indeed, in both undergraduate and community males and females, depressive symptoms predicted greater recall of self-negative sentences, indicating a common cognitive risk. Further, the pathway from depressive symptoms to the NMB was significant in both female and male students. As such, future research may investigate these relations in a sample of males with diagnosed depressive disorders, who may be more likely to present with negatively biased cognition.

Strengths, limitations, and future directions

The strengths of our investigation include assessment of the proposed mediation model across three samples and variation in task design. Indeed, our three studies showed that bivariate relations largely replicated across male and female participants in both student and community samples. Furthermore, coping motives significantly mediated the relationship between alcohol use and an NMB across all three samples. Another methodological strength of our study is the 1-day delay, which is conducive to observing the biasing of emotional memories that occurs during the extended consolidation process (Bogie et al., 2019). Lastly, the incidental encoding of sentences provides ecological validity in reflecting everyday experiences when individuals are not actively trying to remember information. Nonetheless, the associated low overall recall performance with this approach may have limited sensitivity to detect some relations. Some procedural modifications were made to the memory task in Study 2 to increase recall performance that inherently introduced differences from Study 1. Similar patterns were observed between the female student samples in these studies; however, and identical methods were used in Studies 2 and 3.

Each study had modest sample sizes, particularly after correcting for invalid survey responses in community members; however, the pooled analysis with a larger sample supported mediation effects in females but not males. It should be noted there were about half as many student males as females in Study 2 as well as the pooled analysis, potentially limiting power for male findings. Indeed, the pattern of path coefficients in Study 2 was generally similar for male and female participants, and the individual paths were significant in the binge-drinking model for males (see Figure 2). As such, replication of the mediation models with a larger sample size and a more balanced sex distribution is warranted. Moreover, the samples were not equated in terms of demographics or the distributions of the model variables (levels of problematic alcohol use, depressive symptoms, and coping motivations), obscuring comparisons across samples. Although the patterns generally replicated, there were some differences across samples, such that depression did not play a role in the proposed model for community samples whereas it did for students. Furthermore, while we found a consistent pattern of relations between alcohol use, endorsement of coping motivations, and a self-referent NMB, the multiple analyses conducted raised the risk of Type I error. In addition, there was a low prevalence of BD episodes in all three samples of the current study, ranging from a mean of 0.5 in the male community sample to 2 episodes per month in student samples, respectively. In contrast, for example, Carbia et al. (2020) reported means of 2.2 to 2.8 BD episodes in their student samples. Finally, some procedural modifications were made to the memory task in Study 2 to increase recall performance that inherently introduced differences from Study 1. Nonetheless, similar patterns were observed between the female student samples in these studies and identical methods were used in Studies 2 and 3.

Conclusion

Problematic drinking, whether in the form of BD or more generally, poses a problem for an individual's emotional wellbeing and mental health; one way this materializes is through an NMB, particularly for information deemed self-referent. Results support that engaging in alcohol use as a coping mechanism for negative affect or experiencing elevated depression may explain why the NMB presents in some individuals who drink excessively but not others. Moreover, this preliminary evidence suggests that relations among alcohol use, coping motivations, and the NMB are more likely to occur in males if they have very high alcohol consumption patterns, whereas in females it occurs more consistently at moderately high levels of alcohol consumption. Future research may investigate whether the above models and observed sex/gender differences hold in clinical samples (i.e., people with co-occurring alcohol use disorder and depression diagnoses).

Data availability statement

Study 1: The datasets presented in this article are not readily available because participants consented to data sharing under the discretion of the researchers and the institutional review board. Requests to access the datasets should be directed to the corresponding author [TAG]. Studies 2 and 3: The original contributions presented in the study are publicly available. This data can be found at: https://doi.org/10.32920/ryerson.21499290.v1.

Ethics statement

The studies involving human participants were reviewed and approved by Toronto Metropolitan University (formerly Ryerson) Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SJ, KC, and TG designed the study and wrote and edited the article. SG collected, analyzed, and interpreted the data and designed the visualizations. All authors revised and made significant contributions to the final manuscript. All authors have approved the final article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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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.2022.998364/full#supplementary-material

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Alterations of theta power and synchrony during encoding in young adult binge drinkers: Subsequent memory effects associated with retrieval after 48 h and 6 months

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Introduction: Young emerging adults commonly engage in binge drinking which is associated with a range of neurocognitive deficits, including memory impairments. However, evidence on neural oscillations mediating episodic memory in this population is lacking. To address this gap, we recorded theta oscillatory activity in young binge (BDs) and light drinkers (LDs) during memory encoding and analyzed it prospectively as a function of subsequent retrieval. Theta underlies successful encoding of novel items in memory through corticolimbic integration. Subsequent memory effects (SMEs) are reflected in stronger theta activity during encoding of the items that are later remembered compared to those that are later forgotten.

Methods: In the present study, 23 BDs (age: 23.3±3.3) and 24 LDs (age: 23.4±3.3) rated emotionally evocative images with negative, positive, and neutral themes during implicit encoding. They performed a recognition memory task on two follow-up occasions after a short (48h), and long retention delay (6months). Electroencephalography (EEG) signal was recorded during the encoding session and analyzed in time-frequency domain with Morlet wavelets in theta band (4–7Hz). To evaluate SMEs, the event-related theta oscillations acquired during encoding were analyzed based on recognition outcomes after the two retention intervals.

Results: The BD and LD groups did not differ on recognition memory. However, BDs showed attenuated event-related theta power during encoding of images that were successfully retained after 6 months compared to LDs. In addition, theta synchronous activity between frontal and left posterior regions during encoding successfully predicted recognition of the images after both retention delays in LDs but not in BDs. These SMEs on theta power and synchrony correlated negatively with high-intensity drinking in the previous 6 months. No differences between men and women were observed for any analysis.

Discussion: It has been well established that long-range neural synchrony between cortical and limbic nodes underlies successful memory encoding and retention which, in turn, depends on neural excitation/inhibition (E/I) balance. Given that binge drinking is associated with E/I dysregulation, the observed SME deficiencies are consistent with other evidence of neural

hyperexcitability in BDs, and may be indicative of increased risk of developing alcohol use disorders.

KEYWORDS

binge drinking, EEG, subsequent memory effects, memory encoding, theta power, phase-locking synchrony

Introduction

Memory plays a fundamental role in connecting the past and the present while providing a conceptual framework needed to predict the future and to manage ongoing activities as they unfold in real time (Tulving, 2000; Hawkins and Blakeslee, 2007). Remembering a stimulus relies on successful encoding, consolidation, and retrieval of information (Tulving, 1972). A typical memory-probing paradigm comprises two experimental occasions: during an encoding session, participants are presented with a list of items. During the subsequent recognition session, the participants are asked to classify each item as old (previously encountered) or new. Behavioral experiments have shown that high rates of recognition with or without recollecting details of the encoding episode persist for long periods of time (Gardiner and Java, 1991; Dewhurst et al., 2009; Erk et al., 2010).

EEG-based methods have been used extensively to study the neural underpinnings of memory processes, and have provided insight into their dynamics with an emphasis on theta oscillations (Friedman and Johnson, 2000; Jacobs et al., 2006; Werkle-Bergner et al., 2006; Bäuml et al., 2008). Intracranial EEG (iEEG) human studies have established that hippocampal theta underlies successful encoding through interactions with cortical and limbic areas, confirming that the distributed oscillatory neural activity enables coherent integration across multiple brain areas (Lega et al., 2012; Lin et al., 2017; Zheng et al., 2019). Evidence obtained during word encoding indicates that increased frontal and temporal theta power predicts better subsequent word recognition (Sederberg et al., 2003). Similarly, both magnetoencephalography (MEG) and scalp EEG studies have reported greater theta power during encoding of the photos that were later recognized compared to those that were later forgotten (Klimesch et al., 1997; Summerfield and Mangels, 2005; Hanslmayr et al., 2009). This line of evidence suggests that theta oscillations mediate the long-range synchronous coactivation of the hippocampus and the cortex, and the long-range cortico-cortical connections during encoding of new information (Wang et al., 2005; Hasselmo and Stern, 2014; Hsieh and Ranganath, 2014). Memory consolidation, or the establishment of stable memories over time, relies on the hippocampus to guide reorganization of the information encoded in distributed cortical regions (Squire et al., 2015). Greater activity during encoding of the subsequently remembered, compared to the subsequently forgotten items, has been termed the subsequent memory effect (SME), also known as difference due to memory [Dm] effect (Sanquist et al., 1980; Paller and Wagner, 2002). Studies using the SME paradigm have reported higher theta power during encoding of the items that were later recalled, highlighting its importance for successful encoding (Klimesch et al., 1997; Sederberg et al., 2003; Osipova et al., 2006).

It has been well established that acute alcohol intoxication disrupts memory encoding (Weissenborn and Duka, 2003; White, 2003; Mintzer, 2007; Doss et al., 2018). However, exceedingly few studies have investigated alcohol-induced changes of oscillatory activity during memory tasks. Krause et al. (2002) reported a decrease in event-related theta during both encoding and subsequent retrieval of auditory stimuli during acute alcohol administration, which is consistent with alcohol-induced increase of neural inhibition (Kumar et al., 2009; Doss et al., 2018; Correas et al., 2021). Even though it is known that excessive alcohol consumption has detrimental impact on memory (Oscar-Berman et al., 2014; Fama et al., 2021), to our knowledge, there is currently no available evidence on oscillatory dynamics underlying episodic memory impairments associated with alcohol use disorder (AUD). In contrast, multiple studies have examined other cognitive functions such as inhibitory control and attention, and have reported alterations in theta oscillations following chronic excessive alcohol exposure (Kamarajan et al., 2004; Porjesz et al., 2005; Rangaswamy and Porjesz, 2014). The anomalies in event-related theta oscillations during cognitive tasks have also been observed in the offspring of individuals diagnosed with alcohol use disorder (AUD) (Kamarajan et al., 2006; Rangaswamy et al., 2007), suggesting that event-related theta oscillations could serve as an endophenotype for susceptibility to alcohol addiction (Porjesz et al., 2005; Porjesz and Rangaswamy, 2007).

Heavy episodic drinking, also termed binge drinking, is a pattern of alcohol consumption that elevates one's blood alcohol concentration to or above the legal intoxication level (0.08 g/dl, National Institute of Alcohol, Abuse and Alcoholism, 2022). It is commonly practiced among young, emerging adults, and is associated with neurocognitive deficits, including low academic performance (Miller et al., 2007; Pascarella et al., 2007; Petit et al., 2014; Lannoy et al., 2019). Consistent with these reports, some studies have confirmed a linkage between binge drinking and poor performance on both verbal (Sneider et al., 2012; Mota et al., 2013; Carbia et al., 2018) and visual memory tasks (Weissenborn and Duka, 2003; Hartley et al., 2004), as well as face-name encoding deficits (Folgueira-Ares et al., 2017). However, the

changes in oscillatory brain dynamics characterizing memory formation in healthy, young adults with a history of binge drinking have yet to be investigated.

To address this gap, the present study examined theta-based indices of memory encoding that predict recognition outcomes as a function of habitual binge drinking. During an implicit encoding session, young adults with or without a history of binge drinking were presented with pictures depicting a range of emotional scenes and were asked to rate how they felt about each picture (Huang et al., 2018). Subsequently, the strength of their memory trace was probed with recognition tasks conducted with delays of 48 h (hrs) and 6 months (mos) respectively. To characterize SMEs, event-related theta oscillations were examined during encoding as a function of recognition outcomes recorded after these two intervals and compared between the two groups. Furthermore, given the importance of neural synchronization for memory formation (Clouter et al., 2017; Eichenbaum, 2017), we investigated the strength of theta co-oscillations during encoding as a function of the recognition delay. We hypothesized that the recognition rates, event-related theta power during encoding of the pictures, as well as theta co-oscillations, would be attenuated in individuals who engage in binge drinking as compared to the demographically matched moderate social drinkers, particularly for the 6-mos retention interval.

Materials and methods

Participants

Sixty-eight young, healthy adults (average age 23.3 ± 3.3 yrs., age range: 18–30 yrs., 34 women) were recruited from the local community through flyers and ads. They were all right-handed and reported no illegal drug, cannabis, or tobacco use at least 1 month prior to the study, no history of seizures, brain injury, neurological or neuropsychiatric disorders, no vision, hearing, or learning problems, and no medication use at the time of the study. This information was obtained in an initial online screening survey, and was queried in greater detail in a follow-up phone interview. Based on questionnaires querying their current and recent drinking patterns, they were assigned to Binge Drinking (BD) and Light Drinking (LD) groups (Table 1). The BD group comprised 34 participants (17 women) who reported at least five binge episodes in the past 6 months and at least one binge episode in the previous month, with 13.2 ± 8.9 binge episodes on average. A binge episode was defined as consuming at least 6 (men) or 5 (women) drinks within a two-hour time span. This criterion was adopted based on the evidence suggesting that this level of drinking is likely to result in blood alcohol concentration (BAC) of 0.08% or above (Lange and Voas, 2001). The remaining 34 participants (17 women) who reported no more than one binge episode in the past 6 months were assigned to a LD group. No abstainers were recruited as all LDs reported consuming at least 1 drink per week on average. The two groups were matched on age, sex, education, ethnicity/race, and family history of AUD (Table 1). They took part in an encoding session (ENCODE), followed by a recognition session scheduled 48 h later. In addition, 19 BDs and 25 LDs participated in a third session probing recognition after a 6-mos long retention interval.

Procedure

Participants completed a battery of questionnaires including handedness (Oldfield, 1971), medical history, drinking habits including the frequency and quantity of alcohol consumption (modified from Cahalan et al., 1969), the severity of alcoholism-related symptoms (Self-Administered Short Michigan Alcoholism Screening Test, SMAST; Selzer et al., 1975), and motives for engaging in alcohol use (Drinking Motive Questionnaire Revised Short Form, DMQ-R SF; Kuntsche and Kuntsche, 2009). A modified version of the Family History Assessment Module (FHAM; Rice et al., 1995) was administered to assess family history of AUD. Family history positive (FHP) participants were those who reported at least one first-degree and one first-or second-degree relative, or at least three second-degree relatives. Prospective participants with a maternal history of alcohol misuse were excluded from the study to avoid possible fetal alcohol exposure confounds. Family history negative (FHN) participants reported no first-or second-degree biological relatives with problem drinking or AUD. A subset of participants (6 BDs and 4 LDs) did not meet the criteria for either negative or positive family history. In addition, participants completed questionnaires measuring depression (9-item Patient Health Questionnaire, PHQ-9; Kroenke and Spitzer, 2002) and anxiety (7-item anxiety scale, GAD-7; Spitzer et al., 2006). The participants also completed the NIH-Toolbox Cognitive Battery comprising the List Sorting Working Memory Test to assess working memory capacity, Dimensional Change Card Sort (DCCS) Test to assess cognitive flexibility, Pattern Comparison Processing Speed Test to measure processing speed, and Picture Sequence Memory (PSM) Test which probed episodic memory (Gershon et al., 2013).

Participants came to the lab on three occasions. The first (ENCODE) and the second (48-h) experimental sessions were scheduled exactly 48 h apart and the third session followed after 6 mos. The participants were asked to refrain from consuming any alcohol at least 48 h prior to each experimental session. Upon arrival at the lab, they provided a urine sample and all tested negative on a 12-panel multidrug test (American Screening Corporation, United States). In the ENCODE session, participants completed an emotional rating task the results of which have been reported in a separate manuscript (Huang et al., 2018). This rating task served as an implicit encoding of the pictorial stimuli while the EEG signals were recorded from the electrodes placed on the scalp. In the two subsequent sessions participants took part in recognition tasks probing their recent (48-h) and remote (6-mos) memory of these pictures. Participants were monetarily compensated for taking part in the study.

TABLE 1 Participant characteristics [Mean±SD or *n* (%)] for the BD and LD groups assessed at enrollment and at a 6-month retention interval.

	At enrollment			After a 6-month retention interval			Main effects of Time (change after 6 months)	
	BD (*n* = 34)	LD (*n* = 34)	*p*	BD (*n* = 19)	LD (*n* = 25)	*p*	BD (*n* = 19) *p*	LD (*n* = 25) *p*
Demographics								
% Women	50%	50%	1.0[a]	52.6%	60%	0.63[a]		
% White/non-Hispanic	67.6%	70.6%	0.79[a]	63.2%	68.0%	0.74[a]		
Age	23.3 ± 3.3	23.4 ± 3.3	0.81	23.8 ± 3.5	23.3 ± 3.2	0.69		
Age range	18–30	18–29		18–30	18–29			
% Fam. hist. of AUD	50.0%	41.2%	.47[a]	42.1%	48.0%	0.70[a]		
Education years	15.7 ± 2.0	16.3 ± 2.3	0.18	15.4 ± 1.9	16.3 ± 2.4	0.28		
Undergraduate GPA	3.15 ± 0.46	3.46 ± 0.37	**0.004**	3.02 ± 0.51	3.54 ± 0.24	**0.001**		
BMI	24.92 ± 3.94	23.19 ± 3.22	0.06	25.71 ± 4.64	23.11 ± 2.56	**0.04**		
Drinking-related variables								
Age of drinking onset	16.0 ± 1.4	18.5 ± 2.0	**< 0.001**					
Alcoholism sympt. (SMAST)	3.51 ± 3.60	0.53 ± 0.86	**<0.001**	2.63 ± 3.35	0.24 ± 0.52	**<0.001**	0.62	0.16
In the past 6 months:								
Drinks per week	17.3 ± 8.4	3.0 ± 1.9	**<0.001**	14.1 ± 11.1	3.3 ± 2.7	**<0.001**	0.15	0.29
Intoxications per month	5.6 ± 4.5	1.9 ± 1.7	**<0.001**	6.4 ± 6.5	0.8 ± 1.0	**<0.001**	0.56	. 07↓
Binge episodes	13.2 ± 8.9	0.09 ± 0.3	**<0.001**	7.6 ± 5.6	0.2 ± 0.6	**<0.001**	0.41	0.10
Alcohol-induced blackouts	4.4 ± 3.5	0.03 ± 0.2	**<0.001**	3.3 ± 3.4	0	**<0.001**	0.28	0.33
Max. Drinks per occasion	12.7 ± 5.8	4.7 ± 2.1	**<0.001**	12.0 ± 7.7	4.1 ± 2.3	**<0.001**	0.39	0.72
Drinking motives (DMQ-R)								
Enhancement	2.21 ± 0.46	1.77 ± 0.50	**0.001**					
Social	2.52 ± 0.44	2.08 ± 0.54	**0.001**					
Conformity	1.41 ± 0.48	1.35 ± 0.41	0.66					
Coping	1.66 ± 0.58	1.24 ± 0.32	**0.001**					
Internalizing variables								
Anxiety (GAD-7)	4.03 ± 5.11	2.12 ± 2.55	0.22	3.11 ± 2.99	1.79 ± 2.11	0.19	0.71	0.41
Depression (PHQ-9)	4.39 ± 4.80	1.88 ± 1.62	0.09	3.06 ± 2.44	1.96 ± 1.99	0.12	0.47	0.50
Cognitive battery								
NIH-Toolbox Cognitive Tests								
Working Memory/List Sorting	107.66 ± 13.01	104.01 ± 13.26	0.35					
Cognitive Flexibility/DCCS	104.74 ± 9.38	108.39 ± 8.05	0.10					
Processing Speed/Pattern Comparison	129.14 ± 14.35	132.71 ± 18.40	0.24					
Episodic Memory/PSM	113.89 ± 15.08	115.08 ± 12.72	0.56					

Fam. hist. of AUD, family history of AUD; sympt., symptoms; SMAST, Self-Administered Short Michigan Alcoholism Screening Test; Max., maximum number of; DMQ-R, Drinking Motive Questionnaire Revised Short Form; GAD-7, 7-item anxiety scale; PHQ-9, 9-item Patient Health Questionnaire; DCCS, Dimensional Change Card Sort; PSM, Picture Sequence Memory. [a]Chi-square test. ↓Decrease from enrollment to a 6-month retention interval. Bold values refer to p values that reach the significance level ($p < 0.05$).

Material

During all three sessions participants were presented with color pictures depicting scenes with negative, neutral, or positive valence, which were selected mostly from the International Affective Picture System (IAPS; Lang et al., 2008). In the ENCODE session, 264 pictures were included in the emotional rating task. EEG analyses were carried out only on these initial 264 pictures. They were used as "old" (previously seen) items in both 48-h and 6-mos recognition sessions (Figure 1). In each recognition session, additional 96 pictures were presented as "new," not previously seen items. Importantly, the "new" pictures included in the 48-h recognition session were used as lures in the 6-mos recognition session, but were excluded from the behavioral analysis of that session. The "old" and "new" sets were randomly selected from a larger picture set and were equated in valence, arousal ratings, and the presence of human faces. The stimulus set contained an equal number of pictures with positive, neutral, and negative emotional valence. For more details on picture selection and characteristics please see a related article (Huang et al., 2018).

Task descriptions

In all three experiments, each trial started with a fixation cross shown on the screen for 1,000 ± 250 ms, followed by a picture presented for 1,000 ms in the center of a 24-inch color monitor subtending a visual angle of 6.0° × 4.5° at a viewing distance of 180 cm. Pictures were presented in a randomized order in eight blocks. After the offset of each picture, a scale was shown on the screen for 2,700 ms. In the emotional rating task during ENCODE, participants were instructed to judge how each image made them feel on a 9-point visual Likert scale ranging from 1 (very negative) to 9 (very positive) by using a joystick. In the subsequent 48-h recognition session, participants were asked to judge whether they had seen each picture during ENCODE (remembered/old) or not (new) and to indicate the confidence level on a 4-point rating scale (1 = high-confidence new, 2 = low-confidence new, 3 = low-confidence old, 4 = high-confidence old) with a joystick. Similarly, in the 6-mos delay recognition session, they judged whether they had seen the picture before and the confidence level on the same scale. The experiment was conducted with a PC using the Presentation software (Neurobehavioral Systems Inc.). Before each recording, participants practiced the task with additional 20 images that were excluded from the actual experiment.

EEG recording

EEG signals were recorded from a 64-channel actiCap DC Brain Vision system (Brain Products GmbH, Germany) and were continuously sampled at 500 Hz. The nose served as the reference and an electrode attached to the forehead as ground. Eyeblinks and eye movements were monitored with bipolarly referred electrodes attached above and below the left eye. The electrode impedance was maintained below 5 kΩ.

EEG data were analyzed with customized MATLAB (Mathworks, Natick, MA) routines that incorporated modules from publicly available packages including Fieldtrip (Oostenveld et al., 2011) and EEGLAB (Delorme and Makeig, 2004). The continuous EEG data were bandpass filtered from 0.1 to 100 Hz, and segmented into epochs extending from-300 to 1,000 ms relative to each stimulus onset. A 300 ms long padding was added to each end of the epoch to account for edge artifacts during the wavelet analysis. The data were carefully inspected and the trials that contained obvious artifacts were rejected. An independent component analysis was used to detect and remove artifacts caused by eyeblinks and heartbeat (Delorme and Makeig, 2004). Complex power spectra were calculated for each trial using Morlet wavelets (Oostenveld et al., 2011) in 1 Hz increments with 500 ms cycle length and 2–4 cycles across all frequencies in theta range (4–7 Hz) (Marinkovic et al., 2012). Theta band wavelet results were visually inspected and any additional trials that were contaminated by artifacts were rejected. Analysis of the raw theta power in the baseline showed no group or condition differences, indicating that any observed stimulus-related differences were due to event-related changes in theta power and not to the overall differences in the baseline. Event-related theta power was averaged across theta band frequencies (4–7 Hz) and across trials for each condition and expressed as percent signal change from the average theta power during the-300 to 0 ms prestimulus baseline. To examine signal distribution across the scalp, event-related theta indices were averaged into five electrode clusters representing the frontal (comprising AFz, AF3, AF4, Fz, F1, F2, F3, F4, F5, F6 electrodes), central (FCz, FC1, FC2, FC3, FC4, FC5, FC6, Cz, C1, C2, C3, C4, C5, C6), parietal (CPz, CP1, CP2, CP3, CP4, CP5, CP6, Pz, P1, P2, P3, P4, P5, P6), left

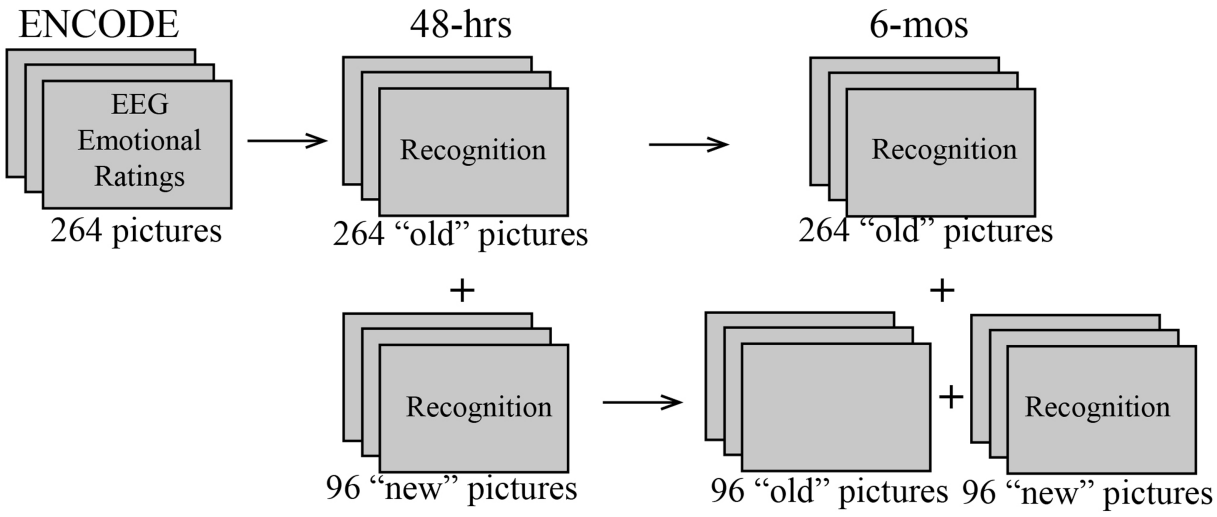

FIGURE 1
Schematic diagram of the study design showing picture sets that were used in the ENCODE, and 48-h and 6-mos recognition sessions. To examine subsequent memory effects (SME), EEG data from the ENCODE session were analyzed as a function of recognition outcomes observed in the 48-h and 6-mos sessions. In the 6-mos session, the unmarked pictures were used as lures but were not analyzed for recognition accuracy.

temporal (FT7, T7, TP7, TP9, P7), and right temporal (FT8, T8, TP8, TP10, P8) montage areas (López-Caneda et al., 2013, 2014). Co-oscillations between the midline frontal (Fz) and the electrodes positioned over the left and right temporal areas were estimated by calculating phase-locking values (PLV) which reflect the consistency of phase differences in theta frequency band irrespective of the amplitudes of the neural activity (Lachaux et al., 1999; Tallon-Baudry and Bertrand, 1999; Beaton et al., 2018; Correas et al., 2019; Marinkovic et al., 2019). PLVs were expressed as percent signal change from the baseline. All event-related changes were quantified by analyzing a time window capturing the peak activity.

Statistical analyses

The subsequent memory effects (SMEs) for the encoding EEG signals were analyzed as a function of retrieval after two retention delays. Specifically, the EEG trials recorded during the ENCODE session were divided into the trials that were later remembered with high-confidence, and those that were later forgotten, as indicated by recognition performance after 48 h and 6 mos, respectively. Event-related theta power and PLV indices were analyzed with mixed-design analyses of variance (ANOVAs) with Group (BD vs. LD) as a between-subject factor and SME (Later Remembered and Later Forgotten) as a within-subject factor.

To examine the behavioral indices of changes in memory retrieval as a function of delay, mixed-design ANOVAs with Group (BD vs. LD) and Delay (48-h and 6-mos) were carried out on the *d-prime* (*d'*) derivation based on recognition with high (H-*d'*) and low (L-*d'*) confidence. D′ was calculated from hit rate (HIT) and false-alarm rate (FA) using the formula $d' = Z_{HIT} - Z_{FA}$ where Z represents a transformation of the two distributions allowing for comparison of measures with different ranges of absolute values (Macmillan and Creelman, 1990). Trials were aggregated across all emotional categories to ensure optimal power for the EEG analyses. Moreover, the Emotion × SME interaction effects on behavioral HIT and FA rates were comparable for BD and LD groups, all $ps > 0.12$. The factor of Sex was included initially in an overall analysis model for both the EEG and behavioral data. However, there were no main effects or interactions including Sex, so it was omitted from the reported analyses. Moreover, the factor of Brain Region (frontal, central, parietal, left temporal, right temporal) was included in an initial analysis of the theta activity, but no effects on SMEs were found, $ps > 0.10$ (Supplementary Table S1). However, the analyses focused on the frontal electrodes where the memory modulations of theta activity appeared most prominent. To estimate fronto-temporal interactions, PLVs were primarily calculated for the Fz-C5 and Fz-C6 electrode pairs, which permitted laterality comparisons. PLV values for all other calculations between Fz and other lateral electrodes are available in the Supplementary Table S2.

To investigate the changes in participant self-reports across the 6-month time period, the questionnaire scores were analyzed with mixed model ANOVAs with Group as a between-group factor and Delay (at enrollment vs. 6 months later) as a within-subject factor. Group differences in dispositional variables were evaluated with the Mann–Whitney *U* tests for independent sample comparisons given that many variables violated the assumption of normal distribution. A Chi-square test was used for categorical variables such as sex and race/ethnicity. Spearman's rank correlation analyses were performed on the intensity of drinking behaviors/symptoms and the strength of the EEG-based brain activity. Of note, one BD participant who reported a number of binge episodes beyond three standard deviations of the mean was excluded from all correlation analyses.

Results

Drinking-related variables, personality characteristics, and cognitive functions

As expected, group differences were observed on all variables associated with alcohol consumption (Table 1), as BDs reported consuming more alcohol, engaging in more binge episodes, and experiencing more blackouts and other alcohol-related consequences than LDs. However, the BD and LD groups did not differ on NIH-Toolbox tests of cognitive functions including working and episodic memory. A follow-up after 6 months confirmed all group differences in drinking habits.

Recognition performance

Figure 2 displays d' for both groups based on high-confidence (H-d') or low-confidence judgments (L-d') during the recognition task. As expected, participants showed higher overall H-d' after a 48-h, compared to a 6-mos delay, $F(1, 42) = 184.43$, $p < 0.001$, indicating a decrease in H-d' across time. There was no main effect of Group, $F(1, 42) = 0.42$, $p = 0.52$, or an interaction effect of Group × Delay on H-d', $F(1, 42) = 0.59$, $p = 0.45$. Similarly, while a reduction of L-d' was observed after a 6-mos relative to a 48-h delay, $F(1, 42) = 116.58$, $p < 0.001$, there was no group difference, $F(1, 42) = 0.11$, $p = 0.74$, and no Group × Delay interaction, $F(1, 42) = 0.11$, $p = 0.74$.

Subsequent memory effects: ENCODE event-related theta as a function of recognition outcomes after 48-h and 6-mos retention delays

48-h delay

We examined theta acquired during the ENCODE session by averaging trials that were remembered with high confidence vs. those that were forgotten after a 48-h delay. One participant in each group was excluded from the analysis due to insufficient number of trials ($n < 15$) in either condition. On average, 128 trials that were later remembered and 73 trials that were later forgotten remained in the EEG analysis for the 48-h delay. As shown in

Figure 3A, a main effect of SME on encoding theta was observed within a latency interval of 300–600 ms, $F(1, 64) = 17.50$, $p < 0.001$, with higher theta power evoked by the later remembered than by the later forgotten pictures. There was no effect of Group on the overall theta power, $F(1, 64) = 0.001$, $p = 0.97$, nor on the theta power associated with recognition success, expressed as SME-related theta power difference between later remembered and forgotten, $t(64) = 0.75$, $p = 0.45$. SME-related theta power difference did not correlate with drinking/dispositional variables, all $ps > 0.17$.

6-mos delay

For the analysis of ENCODE theta based on SMEs after a 6-mos long retention interval, two BDs and five LDs were excluded from the analysis due to insufficient trials, resulting in 43 remembered and 153 forgotten trials on average. A significant interaction between Group and SME within a 200–450 ms latency window was found, $F(1, 35) = 9.08$, $p = 0.005$. During encoding, only the LD group showed greater theta on the trials that were recognized vs. those that were forgotten 6-mos later, $t(19) = 4.11$, $p < 0.001$. In contrast, no SME on theta was observed in the BD group after a 6-mos delay, $t(16) = 0.15$, $p = 0.88$. SME-modulated theta power difference (later remembered – later forgotten) correlated negatively with the number of self-reported binge episodes in the past 6 months, $rs = -0.47$, $p = 0.004$, the maximum number of drinks imbibed on a single occasion in the past 6 months, $rs = -0.44$, $p = 0.007$, alcohol-induced blackout in the past 6 months, $rs = -0.38$, $p = 0.02$, and strength of social drinking motives, $rs = -0.35$, $p = 0.036$, all surviving the Benjamini-Hochberg FDR correction (Figure 3B). In a later time window (500–700 ms), SME modulated the event-related theta power, $F(1, 35) = 5.28$, $p = 0.028$, reflected by higher theta responses to the later remembered compared to the later forgotten items. However, there was no main effect of Group, $F(1, 35) = 1.73$, $p = 0.20$, or a Group × SME interaction, $F(1, 35) < 0.001$, $p = 0.98$, within this time window. The SME-modulated theta difference did not correlate with any drinking/dispositional characteristics at this latency, $ps > 0.13$. Further, we observed that the standard deviations of the SME theta power distribution in the later 500-700 ms time window (later-remembered $SD = 0.54$; later-forgotten $SD = 0.29$) appeared to be greater than that in the early 200-450 ms time window (later-remembered $SD = 0.39$; later-forgotten $SD = 0.23$). It is worth noting that none of the individual theta values exceeded three standard deviations above the group mean. The absence of group differences could be additionally attributed to the relatively small number of participants who completed the memory recognition task after a 6-mos retention interval.

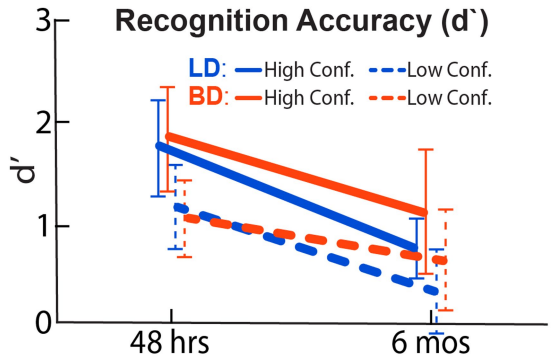

FIGURE 2
Recognition accuracy expressed as a standardized, d-prime (d') index calculated from the hit and false-alarm rates. BD and LD groups did not differ at either 48-h or 6-mos delay. As expected, lower recognition accuracy was found after a 6-mos retention delay.

Neural synchrony during encoding: SMEs after 48-h and 6-mos retention delays

48-h delay

PLVs were calculated between the frontal (Fz) and a left central (C5) electrode location to examine the oscillatory synchrony dynamics during memory encoding as a function of retention delay. For the 48-h delay, there was an interaction between Group and SME in the 300–600 ms time window, $F(1, 64) = 4.69$, $p = 0.031$. Specifically, SME (later remembered > later forgotten) was observed for LDs, $t(32) = 2.98$, $p = 0.005$, but not for BDs, $t(32) = 0.025$, $p = 0.98$. SME-related Fz-C5 PLV difference was negatively correlated with the number of reported binge episodes in the past 6 mos, $r_s = -0.28$, $p = 0.024$, the maximum number of drinks consumed on a single occasion in the past 6 months, $r_s = -0.27$, $p = 0.028$, enhancement drinking motives, $r_s = -0.32$, $p = 0.009$, social drinking motives, $r_s = -0.26$, $p = 0.036$, coping drinking motives, $r_s = -0.27$, $p = 0.034$, and alcoholism symptoms (SMAST), $r_s = -0.26$, $p = 0.036$, all surviving the Benjamini-Hochberg correction. While the Fz-C5 PLV time courses are shown in Figure 4 to illustrate the effect, similar effects were observed for other electrode pairs (Fz with FC5, C5, T7, CP5, TP7, C6, CP6), showing left-hemisphere dominance (Figure 4A, bottom panel, statistical comparisons are available in Supplementary Table S2 and additional timecourses are included in Supplementary Figure S1).

6-mos delay

There was an interaction between Group and SME on Fz-C5 PLVs within the 200–450 ms latency, $F(1, 35) = 5.34$, $p = 0.027$, with greater neural synchrony SME in the LD compared to the BD group. In the LD group, the Fz-C5 PLV synchrony during encoding was greater for the later remembered relative to later forgotten pictures, $t(19) = 2.53$, $p = 0.021$. In contrast, there were no SME modulations of PLVs for the BD group, $t(16) = -0.74$, $p = 0.47$. Furthermore, SME-modulated Fz-C5 PLVs correlated negatively with the reported binge episodes, $r_s = -0.35$, $p = 0.039$, the maximum number of drinks imbibed in a single occasion in the past 6 months, $r_s = -0.41$, $p = 0.013$, and social drinking

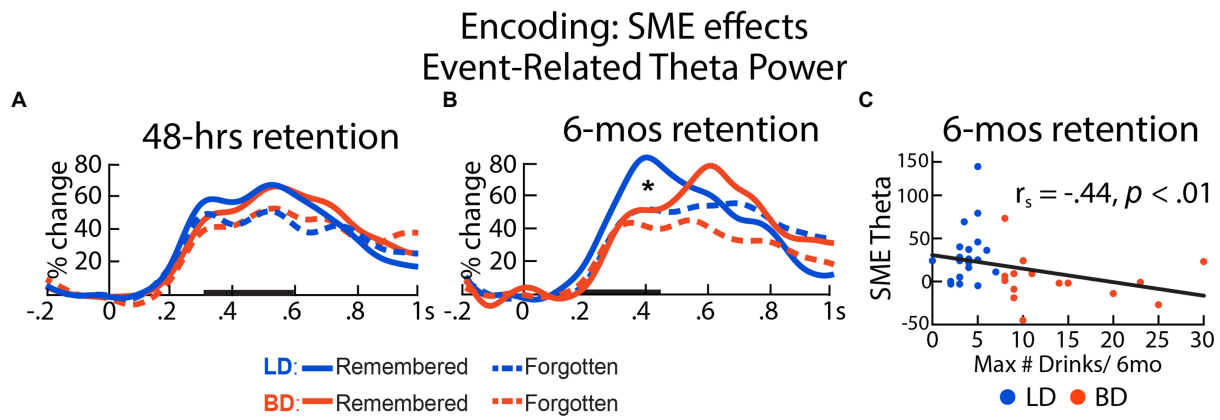

FIGURE 3
Event-related theta power during initial encoding associated with later remembered vs. forgotten pictures for LD and BD groups as a function of recognition **(A)** after 48h and **(B)** after 6 mos. Event-related theta power is expressed as percent signal change from the baseline. **(C)** SME-related theta power difference (remembered – forgotten after 6 mos) correlated negatively with self-reported maximum number of drinks consumed on a single occasion in the past 6months. *$p \leq 0.05$. Bolded bars on the *x*-axis mark the time windows of interest.

motives, $r_s = -0.38$, $p = 0.025$. Similar effects were observed for two other left-lateralized electrode pairs (Fz-FC5 and Fz-CP5, Figure 4B bottom panel; Supplementary Table S1; Supplementary Figure S1).

Discussion

The present study examined the SMEs on event-related theta power and phase-locked co-oscillations as a function of short (48-h) and long (6-mos) retention delays in young adult binge and light drinkers. Our findings confirm that stronger SMEs are reflected in greater event-related theta power overall. Equivalent recognition accuracy was observed in both groups after both retention delays. However, BDs showed reduced theta power during picture encoding associated with SMEs after a 6-mos retention interval. The SME correlated negatively with high-intensity drinking in the previous 6 months. In addition, only LDs but not BDs displayed SME-induced fronto-posterior theta phase synchrony in relation with both retention intervals. The SMEs for the PLVs also correlated negatively with high-intensity drinking reported for the previous 6months.

SME-associated event-related theta power and PLVs

In the present study, the BD and LD groups differed in SMEs reflected in theta power and co-oscillations. However, we found no group differences in behavioral performance, which is broadly aligned with extant evidence. Binge drinking seems to exert a subtle impact on verbal memory performance, and only a small proportion of studies have reported impaired performance on visual memory tasks in young binge drinkers (see Carbia et al., 2018 for review; Scaife and Duka, 2009). Of note, an EEG study that demonstrated deficits in SME-associated event-related potentials (ERPs) during encoding in binge drinkers did not identify group differences in behavioral performance, either (Folgueira-Ares et al., 2017). Moreover, a recent review of EEG studies on binge drinking (Almeida-Antunes et al., 2021) reported that behavioral differences between BDs and non/low drinkers were observed in fewer than 25% of studies that employed cognitive tasks. Indeed, group differences are typically observed in studies using neural measures, often in the absence of behavioral deficits (Crego et al., 2012; Petit et al., 2014; Huang et al., 2018; Holcomb et al., 2019; Lannoy et al., 2019), suggesting the subtlety of deficits at the behavioral level. Moreover, the BD group comprised highly functional individuals whose performance did not differ from LDs on neuropsychological tests of episodic memory, working memory, processing speed, or cognitive flexibility, corroborating that EEG indices are more sensitive to neural alterations in young BDs than behavioral measures (Maurage et al., 2009; López-Caneda et al., 2017; Huang et al., 2018; Correas et al., 2019; Holcomb et al., 2019).

In the present study, SMEs were reflected in greater event-related theta power during encoding which predicted better recognition performance after a long retention delay. This finding is consistent with recent reports of increased frontal midline theta recorded during encoding of items that are subsequently remembered (see Hsieh and Ranganath, 2014 for review). Intracranial EEG (iEEG) recordings in humans indicate that theta oscillations are primarily generated in superficial cortical layers and may represent widespread integration across different cortical areas (Wang et al., 2005; Halgren et al., 2015, 2018; Solomon et al., 2019). Intracranial EEG evidence also suggests that the coherent theta-band activity in the hippocampus supports successful encoding of new items by coordinating cortical rhythmic activity (Hasselmo and Eichenbaum, 2005; Lega et al., 2012; Berens and

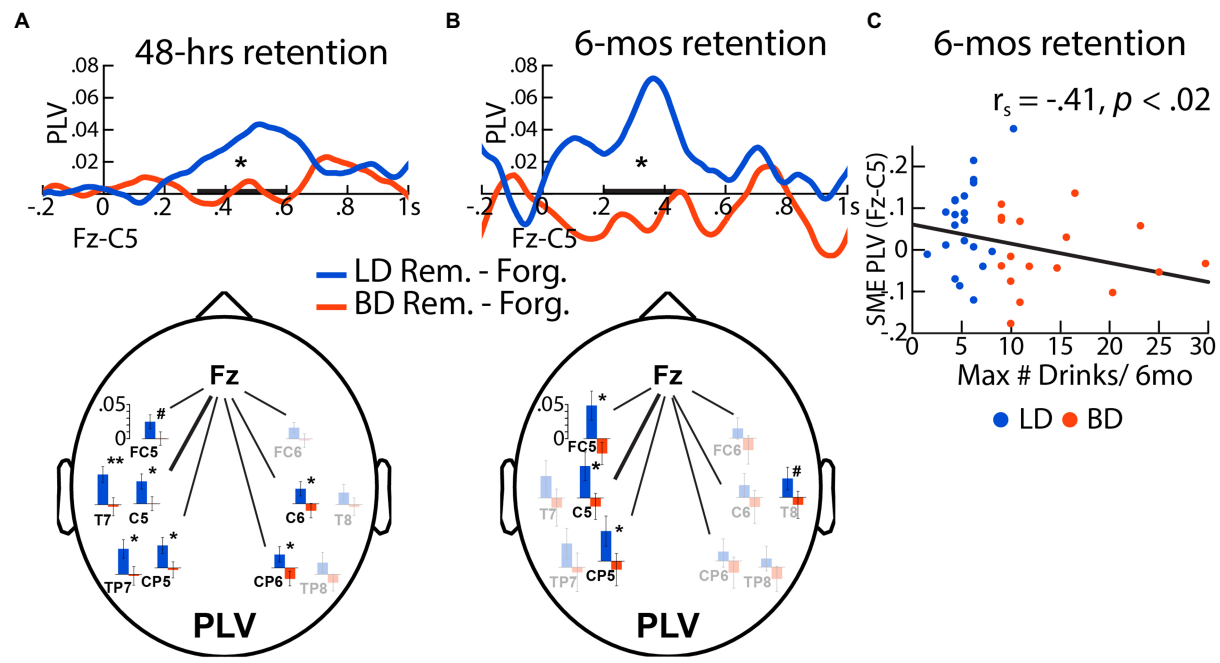

FIGURE 4
The SMEs on phase locking values (PLVs) during encoding were expressed as differences in PLVs between later remembered and later forgotten items assessed after **(A)** 48h and **(B)** 6 mos for BD and LD groups. Here shown are the PLVs for the Fz-C5 electrode pair. **(C)** SME-evoked Fz-C5 synchrony during encoding associated with 6-mos recognition was negatively correlated with the self-reported maximum number of drinks consumed on a single occasion during the previous 6 mos. The electrode maps show the SME effects on the theta-entrained synchrony between Fz and other electrodes associated with a 48-h and a 6-mos interval, respectively. Fully colored bar graphs show the electrode pairs with significant LD – BD group differences. No group differences are marked with faint-colored bar graphs. *p<= 0.05; #p<= 0.10; bolded bar on the x-axis represents the time window of interest.

Horner, 2017; Zheng et al., 2019). Consequently, it has been proposed that theta oscillations recorded from neocortical areas during memory formation reflect activity of the hippocampo-cortical feedback loops (Klimesch et al., 1997; Jones and Wilson, 2005; Eichenbaum, 2017). In support of this idea, our results indicate that theta activity in the neocortex, which is likely coordinated by hippocampal theta, is important for creating the integrated representations of novel items in the memory system (Siapas et al., 2005; Sauseng et al., 2007; Benchenane et al., 2010; Nyhus and Curran, 2010).

Consistent with the integrative role of theta during encoding, our PLV results indicate elevated fronto-posterior theta phase-locking during SME in the LD group. Specifically, the LD group showed greater theta-entrained PLVs between the frontal and the left-dominant posterior brain regions to the pictures that were subsequently remembered with high-confidence, relative to those that were subsequently forgotten after both retention intervals. These PLV findings align with other scalp EEG studies documenting increased theta phase synchronization between the frontal and posterior cortices during episodic memory formation (Schack and Weiss, 2005; Summerfield and Mangels, 2005; Staudigl and Hanslmayr, 2013). Such enhanced fronto-posterior theta synchrony during encoding adds to the evidence that formation of episodic memories is subserved by neural synchrony integrating diverse brain regions including the frontal and the lateral and medial temporal lobes (Paller and Wagner, 2002). Further, the stronger SMEs on theta oscillations between frontal and left posterior locations are aligned with the prior evidence of left-lateralized SME on theta oscillatory activity (Staudigl and Hanslmayr, 2013; Miller et al., 2018) and the importance of the left entorhinal cortex for successful encoding (Solomon et al., 2019). Even though the great majority of studies have probed verbal memory (Staudigl and Hanslmayr, 2013), left-lateralized theta during pictorial encoding is also sensitive to successful memory (Pu and Yu, 2019).

Deficits in SME-associated theta oscillations in binge drinkers

While there were no group differences in SMEs on event-related theta power for a short retention interval, the SME

theta modulations were attenuated in BDs when considered for the 6-mos interval. It points to selective deficits in oscillatory neural networks subserving encoding processes that dissipate over time and are not maintained over a longer delay. Similarly, the PLV data unveiled the absence of SMEs on the theta phase-locking between the frontal lobe and the posterior regions in BDs. Indeed, greater functional connectivity (Sneve et al., 2015) between the hippocampus and other areas, as well as more robust DTI connectivity with the prefrontal cortex (Cohen, 2011) result in stronger and longer lasting memory. The present finding of weaker or absent SMEs for both, event-related theta and synchronous co-oscillations in BDs compared to LDs, mirrors prior evidence of the deficient neural synchrony subserving integrative cognitive processing following acute alcohol consumption or among young binge drinkers (Beaton et al., 2018; Correas et al., 2019; Marinkovic et al., 2019).

These observations are consistent with the convergent evidence of alcohol-induced disturbances in the brain areas critical for memory formation such as the hippocampus and the prefrontal cortex (Oscar-Berman and Marinkovic, 2007; Oscar-Berman et al., 2014; Sullivan, 2017; Fama et al., 2021). Relatedly, fMRI evidence has documented atypical activation patterns in the hippocampus mediating novel encoding in teenage binge drinkers, suggesting that binge drinking may alter the neural substrate of the encoding processes in the developing brains (Schweinsburg et al., 2010). Studies in rodents have confirmed morphological changes in the hippocampus such as decreased numbers of pyramidal and dentate gyrus granule neurons (Nixon et al., 2002; Herrera et al., 2003) as well as suppressed induction of long-term potentiation (Roberto et al., 2002) following chronic exposure to ethanol. Neurodegeneration and inhibition of neurogenesis following long-term exposure to ethanol have also been documented in frontal regions in animal model studies (Crews et al., 2000; Crews and Nixon, 2009). These extensive findings from animal models provide substantial explanatory evidence for the neurophysiological underpinnings of the impairments in long-term episodic memory reported in humans with AUD (Oscar-Berman and Marinkovic, 2007; Oscar-Berman, 2012; Stavro et al., 2013).

These alterations in theta activity and fronto-posterior theta phase synchrony during encoding for long-term memory among young BDs are suggestive of a selective dysregulation of excitation/inhibition (E/I) balance that underlies the long-range co-oscillatory synchrony between the principal cortical and limbic nodes implicated in long-term memory as function of binge drinking (Klimesch et al., 2001; Siapas et al., 2005). Indeed it has been well established that neural inhibition, as effectuated by the gamma amino butyric acid (GABA), the primary inhibitory neurotransmitter, plays an essential role in stabilizing neural networks and memory consolidation (Barron, 2021). However, alcohol misuse is associated with reduced inhibitory function (Koob and Le Moal, 2008; Roberto and Varodayan, 2017). Indeed, recent evidence indicates that binge drinking is associated with lower GABA concentration (Marinkovic et al., 2022) and neural hyperexcitability (Correas et al., 2021). GABA reduction in the hippocampus is associated with neural hyperactivity and memory impairments in animal (Li et al., 2021) and human studies (Jiménez-Balado et al., 2021). Over time, alcohol-induced neurochemical changes may contribute to the allostatic neuroadaptations in limbic brain structures that are critical for memory consolidation (Koob, 2003; Koob and Le Moal, 2008; Wise and Koob, 2014). Such neuroadaptive effects observed in young BDs tip the E/I balance towards excitation, making it more difficult to encode information and retain it over longer time intervals. The altered theta-mediated memory processes may underpin the more frequent alcohol-induced blackouts that contribute to memory loss for the events occurring during intoxication (Read et al., 2013; Hingson et al., 2016), and lower academic achievement (Miller et al., 2007; Pascarella et al., 2007; Huang et al., 2018; Holcomb et al., 2019), which have been reported in college binge drinkers.

While these findings provide evidence for disrupted theta activity during memory encoding in young BDs, these deficits are broadly consistent with dysregulated theta observed in BDs during tasks probing attention (Correas et al., 2019), inhibitory control (Holcomb et al., 2019) and emotional processing (Huang et al., 2018). Furthermore, theta dysfunction during cognitive tasks has also been observed in individuals with AUD (Kamarajan et al., 2004, 2012; Jones et al., 2006) and adolescents at high risk for alcohol addiction (Porjesz and Rangaswamy, 2007). This convergent evidence suggests that theta alterations during memory processing is one aspect of a more general deficit in neurocognitive functioning in relation to binge drinking. Furthermore, binge drinking is theorized to be a transitional phase towards alcohol dependence (McCarty et al., 2004; Enoch, 2006). Therefore, these theta disturbances during mnemonic processes among BDs may be the precursor to memory impairments characterizing AUD (Oscar-Berman and Marinkovic, 2007). In addition, our results are aligned with proposals that altered theta synchrony during cognitive processes may serve as an effective neurophysiological marker of a predisposition towards the development of AUD (Porjesz et al., 2005; Rangaswamy and Porjesz, 2014). However, due to the relatively small sample size impeding the statistical power especially for the recognition assessment after a 6-mos delay, the observed group differences should be interpreted with caution. Moreover, to ensure sufficient power for the EEG analyses, trials were aggregated across emotional picture categories. Given the previous reports of altered EEG indices of emotional processing in binge drinkers (e.g., Huang et al., 2018), future studies could be designed to allow comparisons between emotional categories to examine the impact of emotional processing on SME-related EEG outcomes. Another limitation involves the potential confounding effect of volume

conduction on the estimate of the theta synchronization between different electrode locations. It is recommended that future researchers endeavor to apply advanced methods (e.g., Bruña et al., 2018) to mitigate such possible effects.

Conclusion

In conclusion, in the absence of BD vs. LD group differences in pictorial memory performance, SME theta power associated with long-term (6 mos) memory retention was attenuated in BDs compared to LDs. This observation suggests that during encoding, LDs were able to engage a distributed neural network reflected in increased theta power, supporting item retention in remote memory. In contrast, the BD group was characterized by an inefficient network-level interactive engagement of the brain areas that mediate memory formation, particularly for the items that were prospectively retained over 6 months in remote memory. This SME deficit is further substantiated by dysregulated long-range synchronous co-oscillations in BDs. The importance of excitation/inhibition (E/I) balance for the long-range corticolimbic neural synchrony that mediates memory encoding and retention is well established. At the same time, convergent animal and human mechanistic evidence indicates that E/I dysregulation is associated with alcohol misuse represented by binge drinking. Thus, the observed SEM deficits in BDs are consistent with suboptimal neural activity in the corticolimbic circuitry during encoding. Aligned with other evidence, the divergence between the behavioral and EEG results endorses the argument that direct neural measures are selectively sensitive to deficits in young BDs that are otherwise too subtle to be detected with behavioral tests (Lannoy et al., 2019; Almeida-Antunes et al., 2021). These findings address a gap in the memory literature on binge drinking and expand our current understanding of possible neural underpinnings of the early stages of alcohol use disorder. Furthermore, these results may have clinically relevant implications for the development of diagnostic and prevention strategies for problematic alcohol use by underscoring the importance of the elements that focus on memory disturbances.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University of California, San Diego (UCSD) Human Research Protection Program (HRPP). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SH and KM designed the study. SH was responsible for collecting, analyzing, interpreting the data, and writing the manuscript. KM oversaw and contributed to all aspects of the study, including data interpretation and writing. DW assisted with data analysis and figure creation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.1061016/full#supplementary-material

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Sex-specific decision-making impairments and striatal dopaminergic changes after binge drinking history in rats

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Binge drinking (BD) is a harmful behavior for health and is a predictive factor for the development of alcohol addiction. Weak decision-making (DM) capacities could play a role in the vulnerability to BD which in turn would lead to DM impairments, thus perpetuating BD. Longitudinal preclinical studies are however lacking and necessary to understand this complex relationship. Both DM and BD are influenced by sex and involve dopamine release in the core of the nucleus accumbens, a central mechanism regulated by dopamine D2/3 autoreceptors. In this context, we used an operant self-administration procedure of BD in male and female rats, and longitudinally assessed DM capacity, memory and anxiety-like behavior. To better understand the mechanisms potentially involved in the relationship between DM and BD, *ex vivo* dopamine transmission was assessed short term after the end of the binge exposure in the core of the nucleus accumbens (NAc) using the fast-scan cyclic voltammetry (FSCV) technique and the D2/3 agonist quinpirole. We found important basal sex differences in DM, with female rats showing better performances at baseline. Choice processes were impaired exclusively in males after BD history, associated with a decrease in impulse control in both sexes, while memory and anxiety-like behavior were not affected. Our neurobiological results demonstrate that BD did not affect basal dopamine signaling in the NAc core, regardless of the sex, but reveal changes in the sensitivity to the inhibitory effects of quinpirole in females. DM impairments were neither associated with changes in basal dopamine signaling nor pre-synaptic D2 activity. Overall, our findings show that BD affects both DM processes and dopamine transmission in the core of the NAc in a sex-related manner, further suggesting that these effects may play a role in the vicious cycle leading to BD perpetuation and the early onset of AUD. Our results may inform novel strategies for therapeutic and prevention interventions.

KEYWORDS

binge drinking, decision making, dopamine, nucleus accumbens core, sex

1 Introduction

Binge drinking (BD) definition has yet to find an international consensus but it is characterized by an intense and episodic alcohol consumption, with recurring alternations between intense intoxication episodes and abstinence periods (Lannoy et al., 2019). BD is particularly worrying because of its health consequences (Kuntsche et al., 2017; Rolland and

Naassila, 2017; Tavolacci et al., 2019) and its contribution to alcohol dependence vulnerability (Tavolacci et al., 2019).

Many factors have been associated with BD such as decision-making (DM) and impulsivity, two hallmarks of alcohol dependence. First, DM refers to a fundamental cognitive process allowing us to select a particular option among several alternatives, in order to select advantageous choices over disadvantageous one in everyday life [for review, (Ernst and Paulus, 2005)]. A recent meta-analysis showed a strong association between poor DM capacities using the Iowa Gambling Task (IGT), a tool widely accepted as a direct assessment method for measuring affective DM, and Alcohol Use Disorders (AUD) (Kovács et al., 2017). Furthermore, it has been shown that affective DM moderates the effects of associations on alcohol (Cappelli et al., 2017). Much less is known regarding BD, and the current results from the scientific literature are scarce. Previous studies have associated high and stable BD in college students with less advantageous choices in the IGT, hypersensitivity to reward and impaired reversal learning, without correlation to impulsivity or working memory capacities and academic school performances (Goudriaan et al., 2007; Johnson et al., 2008; Yoo and Kim, 2016). Impaired DM performances and response inhibition have also been reported as a predictor of future problematic use of alcohol (Goudriaan et al., 2011). Other studies have however found no relationship between BD and DM, suggesting that impairments of this cognitive function are associated with more severe forms of alcohol consumption (Bø et al., 2016; Carbia et al., 2017). Secondly, higher impulsivity scores have been associated with the maintenance and intensity of BD (Leeman et al., 2015; Adan et al., 2017), and correlated with drinking episode frequency and the number of drinks per episode (Doumas et al., 2017) (Ashenhurst et al., 2016). Overall, most previously cited studies have shown that BD is associated with impaired impulse control and DM abilities, but the link between them is poorly understood. Weak DM capacities could play a role in the vulnerability to BD, which in turn would lead to DM impairments and thus perpetuate BD. Most studies are cross-sectional and there is a clear need for further longitudinal studies. In a cross-sectional study we previously showed using a Rat Gambling Task (RGT), a protocol inspired from the IGT and described as an animal model of affective decision-making (de Visser et al., 2011), that a history of voluntary BD is associated with impairments of DM abilities in male rats (Jeanblanc et al., 2019). Longitudinal preclinical studies are lacking in the BD research field with the possibility to better control for various factors than in clinical studies (Jeanblanc et al., 2018).

Both DM and BD behaviors are influenced by sex. For instance, findings supported the subdivision of binge drinkers according to gender and personality dimensions (Gierski et al., 2017). Sex differences in IGT performances are however poorly understood, some human studies highlighting males outperforming females in gain (Evans and Hampson, 2015), while others found no difference (Hooper et al., 2004). It has been non-etheless suggested that women may use a different choice strategy, and are more sensitive than men to punishment frequency and occasional losses in the IGT long-term advantageous decks (van den Bos et al., 2013). Sex differences in DM may be attributable in part to interactions between gonadal hormones and dopamine signaling (Becker and Hu, 2008). Previous work have also shown that males and females differ in their responses to dopamine manipulations that could involve basal differences in extracellular levels of dopamine, dopamine receptor levels, and/or dopamine D2/3 autoreceptors control, all of which are modulated by estradiol (Becker and Hu, 2008).

Alteration of dopamine signaling in the ventral striatum is involved in the effects of BD and DM processes. Acute alcohol intake increases tonic dopamine concentrations in the NAc (Imperato and Di Chiara, 1986; Di Chiara and Imperato, 1988) and is involved in alcohol rewarding effects (for review, (Spanagel, 2009)). Alcohol displays biphasic effects on evoked phasic dopamine release in the NAc *in vivo* (Budygin et al., 2001; Robinson et al., 2005; Jones et al., 2006; Pelkonen et al., 2010) and *ex-vivo* (Budygin et al., 2001; Mathews et al., 2006) as well as an increase in the frequency of phasic dopamine transients (Robinson et al., 2009). Effects of chronic alcohol exposure and especially BD are much less investigated. Only a handful of studies assessed the consequences of a binge-like exposure on the dopamine mesolimbic system, but reveals possible impairments of the mesolimbic dopaminergic system, both at baseline and in response to alcohol, depending on age, dose and the withdrawal time (Pascual et al., 2009; Philpot et al., 2009; Shnitko et al., 2016; Zandy et al., 2016). Dopamine D2/3 receptors play a crucial role in both DM and alcohol reinforcing effects. Increasing dopamine release by either ventral tegmental area stimulation, or blockade of the D2/3 autoreceptors is associated with increased risky choices (Stopper and Floresco, 2015). In the same vein, the administration of a D2 receptor antagonist in pathological gamblers increased the rewarding effect of gambling and the desire to gamble (Zack and Poulos, 2007). Regarding addiction, numerous studies have shown that a low D2/3 receptor binding is associated with AUD in both animals and humans (Trifilieff and Martinez, 2014). Overall, phasic dopamine signaling in the NAc is involved in many central processes of reward and DM, and its alteration by alcohol could possibly constitute one of the main factors underlying its effects on both BD and DM capacities.

We posited that BD would decrease DM capacities associated with alterations in ventral striatum dopamine signaling and we therefore used the RGT with a longitudinal approach to investigate changes in DM capacities after a history of BD. We also explored whether BD could impact memory and anxiety-like behavior, since both could potentially interfere with DM capacities. We hypothesized that DM deficits induced by BD may be associated with changes in dopamine release potentially due to alteration in D2/3 receptors. In brain slices from the same animals, we tested the sensitivity of dopamine transmission to quinpirole (D2/3 agonist), due to the involvement of D2/3 receptors in DM. We decided to focus on the core part of the NAc due to its involvement in both DM (Sugam et al., 2012) and the approach and treatment of motivational stimuli (Dreyer et al., 2016). The NAc core plays a more significant role than the shell in behaviors regulated by cues, such as lever pressing for a reward or a cue-induced reinstatement of reward seeking (McFarland et al., 2003; Di Ciano et al., 2008). Different procedures to study BD behavior in animals are used mainly consisting in repeated passive exposures to alcohol and during adolescence (Pascual et al., 2009). More relevant models exist such as the one we recently developed based on the "happy hour" session in which the animal can freely self-administer a 20% ethanol solution during daily sessions of only 15 min (Jeanblanc et al., 2018). We used males and females with an operant self-administration procedure to evaluate inter-individual vulnerability (Jacobs et al., 2003; Jeanblanc et al., 2019).

2 Methods and materials

2.1 Reagents

Ethanol (96%) was purchased from WWR (Prolabo, Fontenay-sous-Bois, France) and diluted into tap water at a 20% concentration (v/v). NaCl, KCl, NaH_2PO_4, $MgCl_2$, $CaCl_2$, $NaHCO_3$, glucose, ascorbic

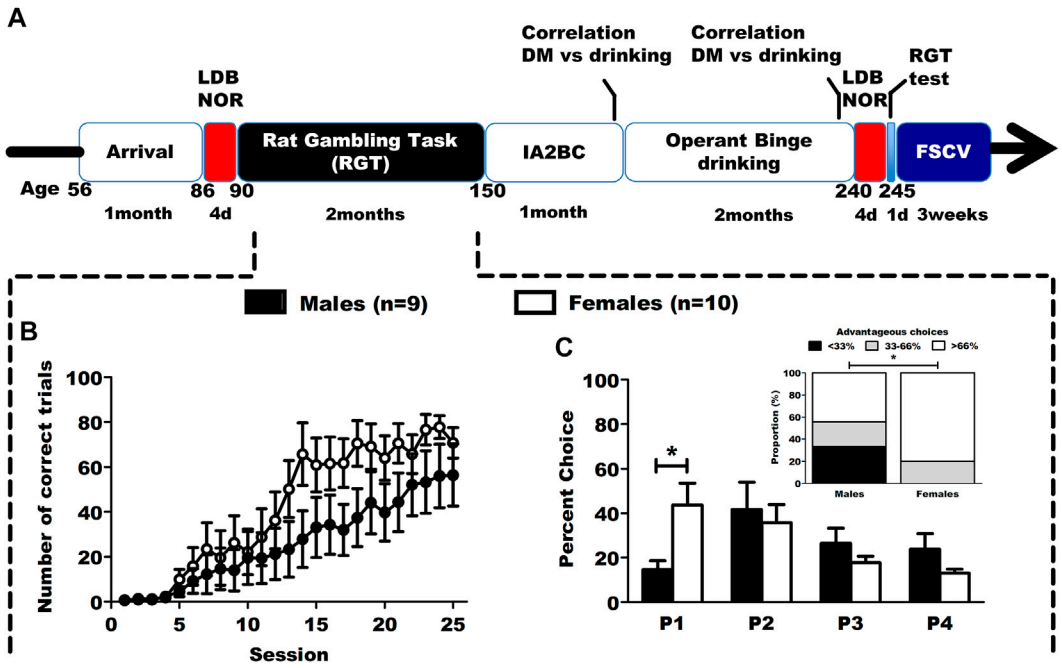

FIGURE 1
Timeline of the study and baseline results in the RGT. **(A)** Timeline of the longitudinal study. Animals were tested in DM capacities, anxiety (LDB) and learning (NOR) both before and after an operant binge drinking procedure. At the end of the behavioral experiments, the animals (as well as a control group without behavioral training) were sacrificed to assess mesolimbic phasic dopamine transmission in the core of the NAc, using *ex vivo* FSCV. **(B)** Correct trials during the first phase of RGT training. Results are expressed as mean ± SEM of the proportion of correct trials over the total number of trials during training sessions. **(C)** Choice behavior in the baseline session of RGT, and distribution of the DM level in categories (poor < 33%, neutral 33%–66% and good > 66%). The male rats favored the optimal P2 option, while the female rats favored both P1 and P2. The male group had significantly more individuals with a poor DM level than the female group. Results are expressed as mean ± SEM of the percent choice for each option, and as number of rats in each categories of decision makers. $^{\#}p < 0.01$, $^{*}p < 0.05$.

acid and quinpirole were purchased from Sigma-Aldrich (Saint Quentin Fallavier, France).

2.2 Animals

32 Long Evans rats (16 males and 16 females) were purchased from Janvier Laboratories (Le genest-Saint-Isle, France) at the age of 8 weeks. The animals were single housed in individually ventilated cage (IVC) with food and water *ad libitum* and no enrichment. The light phase started at 7:00 a.m. for 12 h. The experiments started 1 month after their arrival. Prior to all experiments, 20 of the animals were randomly assigned to a group of voluntary alcohol administration (10 males and 10 females), and the remaining 12 rats (6 males and 6 females) were used as a control group for the FSCV experiments, without any exposure or behavioral training. Experiments were carried out in accordance with the guidelines of the E.C. regulations for animal use in research (CEE no. 86/609) and our local ethics committee (CREMEAP; no. APAFIS#2145).

2.3 Anxiety-like behavior: Light-dark box test (LDB)

Anxiety-like behavior was performed using the light dark box (LDB). The test was carried out before and after voluntary BD exposure (see Figure 1 timeline). Behavioral testing took place in a calm room inside two opaque plexiglass boxes (45 × 45 × 45 cm), divided into two equal compartments by a central partition (15 × 15 cm): an open lit compartment (30 lux), and a closed dark compartment (two Lux). The rats were habituated daily to the room for 1 hour during 1 week (5 consecutive days), inside their home cage, and the test sessions happened the day following the last habituation session. The animals were transferred to the room 30 min prior to every behavioral test. The test consisted in a single 5 min session where the animals were positioned in the lit compartment, back to the central door, and were allowed to freely move inside the box. All test sessions were performed during the same day, with an approximate time of 2 min between rats. The entry latency, the time spent inside the lit compartment and the number of transitions between compartments were recorded. A transition was recorded when all four limbs of the animal passed the central partition. The boxes were cleaned after each trial to prevent a bias based on olfactory cues.

2.4 Learning and memory: Novel object recognition task (NOR)

Learning abilities were assessed using the Novel Object Recognition test (NOR). The test was carried out before and after voluntary BD exposure (see Figure 1 timeline). Behavioral testing took place the day following the LDB test in the same calm room, inside two brightly illuminated (30 lux) opaque Plexiglas boxes (45 × 45 × 45 cm).

The task consisted in three phases, one each consecutive day, for a total of 3 days: habituation, acquisition and test. The animals were transferred to the room 30 min prior to every behavioral test. The rats were first habituated to the boxes during a single 10 min session where they were allowed to move freely. During the acquisition phase, two objects (A and B) of distinct height, form and structure, were placed equidistant to the wall in each corner of the boxes. The rats were allowed to freely explore them for a single 10 min session. During the test phase, one object (counterbalanced for each box) was replaced with a new object (C) of different height, form and structure. The rats were allowed to once again freely explore them for a single 10 min session. There was an approximate time of 2 min between rats testing. Exploration time was recorded for each object, with any behavior of sniffing, licking or touching considered as interaction. The boxes and objects were cleaned after each trial to prevent a bias based on olfactory cues. A new set of different objects was used for the NOR test after ethanol exposure to limit retest effects.

2.5 Decision-making: Rat gambling task (RGT)

2.5.1 Apparatus

Behavioral testing took place in four identical operant chambers (Imetronic, Pessac, France, 28 × 30 × 34 cm) in a calm room. Each chamber was standing in a dark, ventilated and sound-proof conditioning box. The chambers were divided into two equal compartments by a central plexiglass partition (0.5 × 29.5 × 30 cm), parallel to the wall and opened in its center (7 × 7 cm). They were also equipped on one side of the box with four nose-poke holes on a curved wall (dimly illuminated within with a white LED), equidistant from the food magazine at the opposite side. The nose-poke holes were equipped with an infrared detector connected to an external dispenser for the delivery of food pellets (45 mg, Test Diet, Cambridge Univ., United Kingdom). The apparatus and data collection were controlled using the POLY software (Imetronic, Pessac, France). The animals were moderately food restricted during the procedure (95% of their normal bodyweight).

DM was assessed using a rat gambling protocol inspired from the IGT in humans and developed by Zeeb et al. (2009), better suited for longitudinal studies than other available options [see (de Visser et al., 2011)]. The rats were alcohol naïve during the whole training phase of the RGT and the first test phase before the operant self-administration procedure (see Figure 1 timeline). Briefly, rats had to nose poke in four holes with different magnitude and probability of rewards and punishments. The rats were first habituated to the chamber during two 30 min sessions, during which food pellets were placed inside the nose-poke holes and the food magazine. During daily training, trials started with the animal visiting the food magazine, triggering the start of a 5 s Inter-Trial-Interval (ITI). Rats were first required to nose-poke into a briefly illuminated hole (0.5 s, randomly varying between each trial) within 10 s to earn a reward (one sugar pellet). A lack of response was recorded as an omission, while a response during the ITI was recorded as premature, both ending the ongoing trial and not giving a reward. Each session lasted for a maximum of 30 min and 100 trials. Training was pursued 5 days a week until a performance criterion of more than 80% correct trials and less than 20% omissions was achieved. To ensure equal experience with all future contingencies, the rats were then trained on a forced-choice version of the RGT for 7 sessions, where each nose-poke was associated with a different reward and punishment probability. The contingencies were such that the more rewarding options were associated with higher punishment in the form of timeouts (P1: 1 pellet $p = 0.9$, 5 s timeout $p = 0.1$; P2: 2 pellets $p = 0.8$, 10 s timeout $p = 0.2$; P3: 3 pellets $p = 0.5$, 30 s timeout $p = 0.5$; P4: 4 pellets $p = 0.4$, 6 0 s timeout $p = 0.5$; see Supplementary Table S1). One hole was illuminated per trial following a chronological order, and a rewarded trial consisted in the delivery of the pre-set number of pellets and signaled by onset of the tray light until collection of the food. Punishment consisted in a time-out window of the pre-set amount of time and signaled by the tray light remaining off and flashing of the stimulus light within the selected hole (frequency of 0.5 Hz). Training phase lasted between 3 weeks and more than a month.

2.5.2 Test phase

Test phase consisted in daily 30 min free-choice RGT sessions. The trial design and their contingencies were the same, except that they started with the stimulus lights being turned on in all of the active holes. P1 and P2 options are considered as the advantageous choices, while P3 and P4 are considered as disadvantageous choices. If a rat chooses only one option, then the greatest number of pellets possible would be with P2 (411, most optimal option), then P1 (295), P3 (135) and P4 (99, least optimal option) (Zeeb et al., 2009). The animals were split in 2 groups receiving a different configuration of response outcomes in the holes (left-right counterbalance) to ensure no spatial or bias preference. All procedures were performed as previously described (Zeeb et al., 2009; Georgiou et al., 2018), with the exception of test sessions being limited (5 to 7 sessions) to the animals only displaying a stable preference for one of the options (3 consecutive sessions with the same option preferred), in order to avoid the development of an inflexible choice behavior. Here, we purposely limited the amount of test sessions, as it has been suggested that a prolonged training can lead to a highly robust choice behavior that is difficult to pharmacologically modulate (Spoelder et al., 2015). Reducing familiarity with the task also provide more face validity regarding the IGT, and is closer to a design supposed to involve both an exploratory and an exploitative phase (Buelow and Suhr, 2009).

2.6 Voluntary ethanol administration using an operant self-administration procedure

BD behavior was generated after the first RGT test (see Figure 1 timeline), with a protocol combining intermittent access to 20% ethanol in a two-bottle choice procedure (IA2BC) followed by an operant self-administration procedure in skinner cages. All the procedures have been previously described in one of our previous works (Jeanblanc et al., 2019). First, the rats had access to two bottles in their home cage, one containing tap water and the other a solution of 20% ethanol (v/v), every other day for 3 weeks. The bottles were placed and removed at 2:00 p.m., and weighed at the end of each drinking session. Two bottles were placed in an empty cage to control for the spillage of liquid. The rats were then trained daily to self-administer ethanol (0.1 mL of a 20% ethanol solution w/v per delivery) during the operant self-administration procedure. They were first submitted to two overnight sessions of 16 h (fixed ratio 1, FR1, between 5:00 p.m. and 9:00 a.m.) followed by shorter sessions 5 days a week (between 2:00 p.m. and 5:00 p.m.) with the following schedule: FR1—1 h for 5–7 days, FR3—1 h for 5–7 days and finally FR3—30 min until reaching a stable baseline of drinking (less than

20% of variation for three consecutive sessions. 8 days on average for males, 9 days on average for females). The sessions were then reduced to 15 min until leading to a stable BD phenotype with intoxicating levels of self-administration. Both male and female rats underwent 37 days of FR3-15 min sessions during this experiment. The number of active, inactive lever presses and rewards were recorded. Behavioral experiments were conducted 24 h after the end of the procedure.

2.7 Mesolimbic phasic dopamine transmission: Fast-scan cyclic voltammetry (FSCV)

2.7.1 Surgery

Rats were anesthetized with isoflurane (IsoVet, 5%) before being decapitated, and their brain were extracted and immersed in ice-cold artificial cerebrospinal fluid (aCSF) (NaCl 126 mM, KCl 2.5 mM, NaH_2PO_4 1.1 mM, $MgCl_2$ 1.4 mM, $CaCl_2$ 0.5 mM, $NaHCO_3$ 18 mM, Glucose 11 mM, ascorbic acid 0.4 mM, pH 7.2–7.4) and glued into a vibratome (Leica, VT 1200S). Coronal slices (250 µm thick) of the NAc were selected and stored in a 31°C aCSF (NaCl 126 mM, KCl 2.5 mM, NaH_2PO_4 1.1 mM, $MgCl_2$ 1.4 mM, $CaCl_2$ 2.4 mM, $NaHCO_3$ 18 mM, Glucose 11 mM, pH 7.2–7.4) reservoir gassed with carbogen (95% O_2, 5% CO_2) for at least 1 hour. After rest, the slices were transferred to a recording chamber and perfused with aCSF (3 mL/min, 31°C).

2.7.2 Recordings

DA measurements were conducted in the NAc core using FSCV and carbon-fiber microelectrodes (7 µm diameter, cut to 100–150 µm long, GoodFellow, Huntington, England). Those electrodes were calibrated prior to the recordings using a 1 µM dopamine solution in aCSF. A triangular waveform potential ramping from −0.4 V to +1.3 V was applied to the microelectrodes at 10 Hz during the recordings. A bipolar stimulating electrode (Stimulus Isolator A360, WPI, England) was placed on the afferent fibers coming from the VTA, around 100 µm near the working carbon-fiber microelectrode. Phasic DA release was evoked every 5 minutes using a monophasic stimulation (0.5 s long, 24 pulses, square-wave pulses, 2 m/phase, 300 µA, 60 Hz). The electric signal was amplified, filtered and transmitted to the Tarheel CV software (Scott Ng-Evans, Electronics and Materials Engineering Shop, Seattle, WA, United States). Using color plots, changes in current were plotted as a function of applied potential over time, and the oxidation current converted to DA concentration. A baseline of three consecutive stable signals was obtained for each slice. For the pharmacology, quinpirole 100 nM was applied for at least 30 min and until achieving three consecutive stable signals.

After performing the behavioral experiments (48 h to 1 week), rats were euthanized and coronal slices containing the NAc were collected to measure electrically evoked dopamine transmission in the core of the NAc. Rats from the control group (6 males and 6 females) were euthanized and their coronal slices collected 1 week after their arrival (57 weeks). The sensitivity to the D2/D3 receptor agonist quinpirole (100 nM) was tested.

2.7.3 Data analysis

All analysis of release and uptake were conducted on the concentration-versus-time traces. These traces were fit to a model describing dopamine signaling as a balance between release and uptake, using the Michaelis-Menten equation (see, (Wu et al., 2001)), with the Lvit software (Scott Ng-Evans, Electronics and Materials Engineering Shop, Seattle, WA, United States). The equation is as follow:

$$\frac{d[DA]}{dt} = f[\mathrm{DA}]_p - \frac{Vmax}{\left(\frac{Km}{[DA]}\right) + 1}$$

where $[DA]$ is the instant extracellular concentration of *DA* released, f is the frequency of stimulation, $[\mathrm{DA}]_p$ is dopamine concentration released per pulse, and Vmax and Km are respectively the velocity and affinity constants of the dopamine transporter (DAT). Km was fixed at a constant value of 200 nM (Wu et al., 2001). $[\mathrm{DA}]_p$ is the reflect of the presynaptic mechanisms regulating release as those of the auto-receptors (D2/D3 activity) (Kennedy et al., 1992). Peak dopamine concentration was extracted for each trace before fitting to the model in order to obtain a $[\mathrm{DA}]_{max}$ value, reflecting maximum extracellular dopamine concentration, and was used as a parameter of dopamine release. $[\mathrm{DA}]_p$ and V_{max} values were modulated until fitting the traces to the model, with a correlation coefficient of 0.8 or more with our experimental data, using the Lvit software.

2.8 Statistical analysis

Data were analyzed using SigmaPlot 11.0 (SysStat Software, Inc.) with an analysis of variance test (2-way ANOVA or 1-way ANOVA, with repeated measures when appropriate) followed by a Tukey multiple comparison test, when a significant effect was observed for the data following a normal distribution and an equality of variances. When the data did not follow these criteria, a non-parametric analysis was performed (Friedman's test or Kruskal-Wallis test and Dunn's *post hoc* test). For single comparison, we used a Student's t-test (2-tailed) for the data following a normal distribution and an equality of variances, and a Mann-Whitney rank sum test otherwise. For proportions, we used a χ^2 test. For the correlation analysis, we used a Pearson correlation test. All data were presented as Means ± standard error means (SEM). The significance threshold was fixed at $p < 0.05$.

3 Results

A time line of the study is presented on Figure 1.
All the statistical analyses are provided in Supplementary Table S2.

3.1 Sex differences observed in baseline training and testing in the RGT

The animals underwent 8 weeks of daily training in the RGT, and had to learn to nose-poke in the operant holes to earn a reward. During the first 25 sessions of training (Figure 1B; Supplementary Table S1), females rats seemed to increase their percentage of correct trials quicker than males although no statistically significant differences were found (2way-RM ANOVA: session $F_{(24,191)} = 20.306$, $p < 0.001$; sex $F_{(1,191)} = 2.899$, $p = 0.127$; interaction $F_{(24,191)} = 1.180$, $p = 0.264$). Thereafter, we evaluated their baseline choice behavior in the RGT on

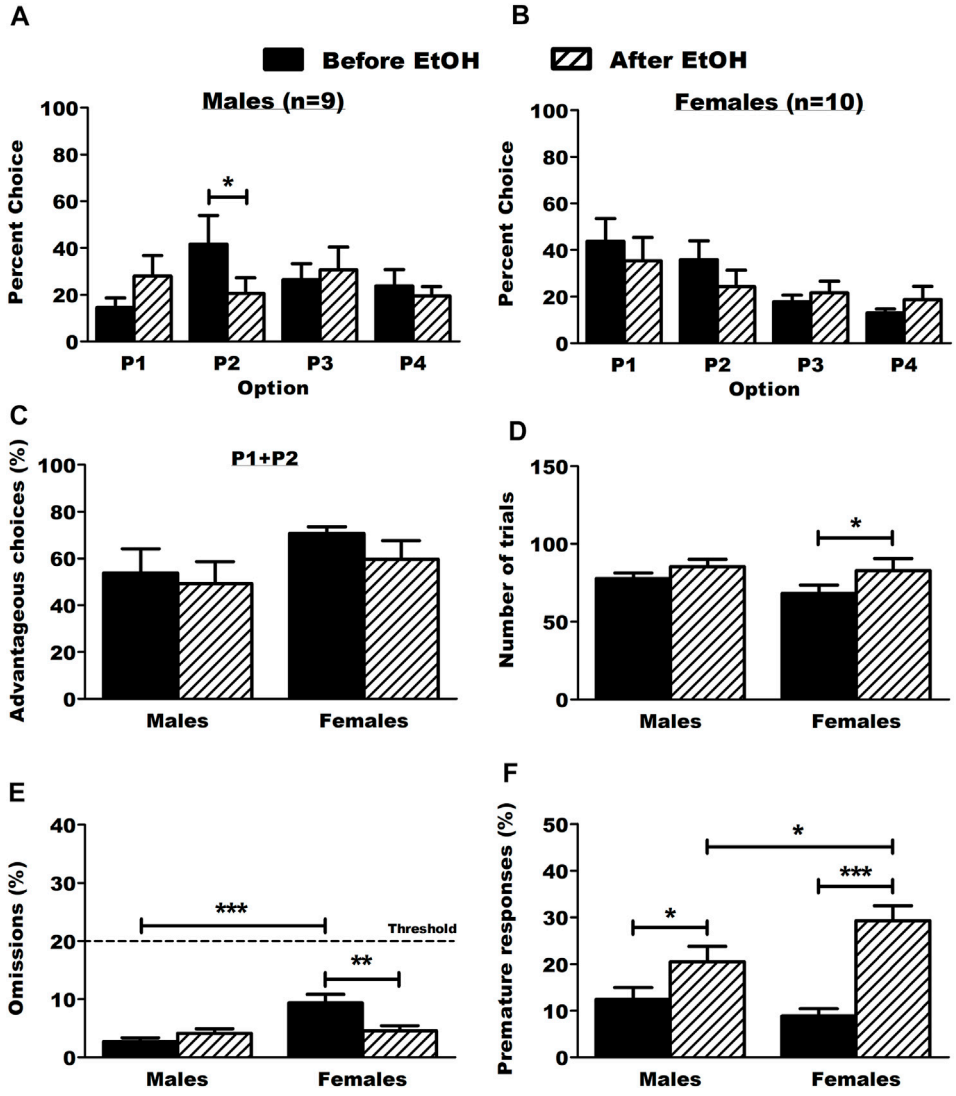

FIGURE 2
Choice behavior and other parameters in the RGT before and after ethanol. **(A)** Male rats chose the optimal option P2 significantly less after ethanol. Results are expressed as mean ± SEM of the percent choice of each option. **(B)** Ethanol did not affect choice behavior in female rats. Results are expressed as mean ± SEM of the percent choice of each option. **(C)** Ethanol did not affect the proportion of advantageous choices (P1 + P2) in both males and female rats. Results are expressed as mean ± SEM of the proportion of advantageous choices over the total number of choices. **(D)** Ethanol increased the number of trials in female rats. Results are expressed as mean ± SEM of the total number of trials made. **(E)** Ethanol decreased omissions in female rats. The dot line represents the threshold of allowed omitted responses for the animals during baseline test sessions. The male rats omitted more trials than the female rats before ethanol. Results are expressed as mean ± SEM of the proportion of omitted trials over the total number of trials. **(F)** Ethanol increased the proportion of premature responses in both male and female rats. The female rats made more premature responses than the male rats after ethanol. Results are expressed as mean ± SEM of the proportion of premature responses over the total number of trials. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

the last 3 sessions. Male rats favored the most advantageous option (P2) and female rats favored both advantageous options (P1 and P2) (Figure 1C; Supplementary Table S1, 2way-RM ANOVA: sex $F_{(1,24)} = 0.346$, $p = 0.573$; option $F_{(3,24)} = 0.1436$, $p = 0.257$; interaction $F_{(3,24)} = 5.740$, $p = 0.004$). Female rats chose the P1 option significantly more than male rats (Tukey, $p < 0.001$). Distribution of poor (<33% good choices), neutral (≥33–≤66%) and good (>66% good choices) decision makers was different depending on sex (Figure 1C, $\chi^2_{(2)} = 6.14$, $p < 0.05$). Regarding the other RGT parameters, no sex differences were observed for advantageous choices, number of trials and premature responses, but there were more omitted trials in females (Supplementary Figure S1).

3.2 BD impaired DM in males but not females

After the self-administration procedure, one male rat was excluded from the group due to sickness. Results from the operant BD procedure are detailed in Supplementary Figure S2. Briefly, Escalation in both ethanol intake and preference was observed in both sexes and there were no sex differences in ethanol intake during the operant self-administration, thus ruling out the potential bias of differential ethanol intake during the 3 months of BD history. Although we did not assess blood ethanol concentrations in our rats, we expect mean concentrations between 40 and 50 mg/dL, according to our previous work showing an almost linear positive

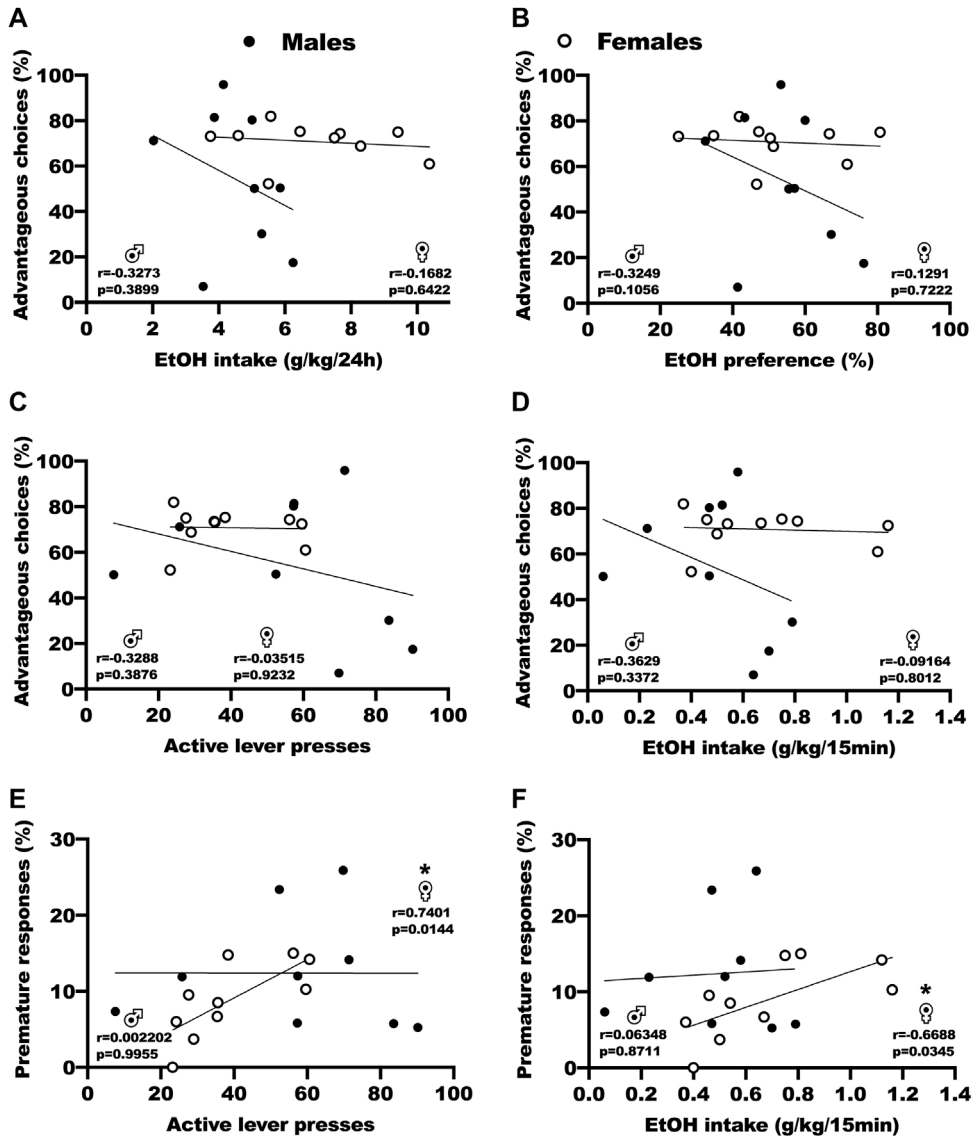

FIGURE 3
Correlation analysis of the relation between baseline DM abilities and ethanol consumption. **(A)** No correlation between advantageous choices (P1 + P2) during baseline RGT sessions and ethanol intake by weight during the last IA2BC session. Results are expressed as the percent of choices in the P1 and P2 options versus the ethanol intake by weight during the 24 h sessions (g/kg/24 h). **(B)** No correlation between advantageous choices (P1 + P2) during baseline RGT sessions and ethanol preference during the last IA2BC session. Results are expressed as the percent of choices in the P1 and P2 options versus the proportion of ethanol consumed over total fluid consumed. **(C)** No correlation between advantageous choices (P1 + P2) during baseline RGT sessions and active lever presses during the last 5 stable operant self-administration FR3 15 min sessions. Results are expressed as the percent of choices in the P1 and P2 options versus the number of presses on the active lever during the 15 min sessions. **(D)** No correlation between advantageous choices (P1 + P2) during baseline RGT sessions and ethanol intake by weight during the last 5 stable operant self-administration FR3 15 min sessions. Results are expressed as the percent of choices in the P1 and P2 options versus the ethanol intake by weight during the 15 min sessions (g/kg/15 min). **(E)** Positive correlation in females, but not males, between premature responses during baseline RGT sessions and the number of presses on the active lever during the last 5 stable operant self-administration FR3 15 min sessions. Results are expressed as the percent of premature responses versus the number of presses on the active lever during the 15 min sessions. **(F)** Positive correlation in females, but not males, between premature responses during baseline RGT sessions and ethanol intake by weight during the last 5 stable operant self-administration FR3 15 min sessions. Results are expressed as the percent of premature responses versus the ethanol intake by weight during the 15 min sessions (g/kg/15 min). *$p < 0.05$.

correlation between ethanol intake in the BD procedure and blood ethanol concentrations (Jeanblanc et al., 2018). The RGT test was done 24 h after the last operant session (BD sessions were maintained in between behavioral experiments). The BD history changed DM capacities with a decrease in P2 choices specifically in males (Figure 2A, 2way RM-ANOVA: treatment $F_{(1,18)} = 26.761$, $p < 0.001$; option $F_{(3,18)} = 0.390$, $p = 0.761$; interaction $F_{(3,18)} = 2.694$, $p = 0.069$; Tukey $p < 0.05$) but not in females (Figure 2B, 2way RM-ANOVA: treatment $F_{(1,24)} = 3.006$, $p = 0.117$; option $F_{(3,24)} = 2.363$, $p = 0.093$; interaction $F_{(3,24)} = 1.314$, $p = 0.290$). There were no effects on advantageous choices (P1+P2, Figure 2C, 2way RM-ANOVA: sex $F_{(1,6)} = 1.902$, $p = 0.186$; treatment $F_{(1,6)} = 2.170$, $p = 0.159$; interaction $F_{(1,6)} = 0.380$, $p = 0.546$) and only females displayed a small increase in their number of trials (Figure 2D, 2way RM-ANOVA: sex $F_{(1,6)} =$

0.725, $p = 0.406$; treatment $F_{(1,6)} = 6.484$, $p = 0.021$; interaction $F_{(1,6)} = 0.643$, $p = 0.434$; Tukey $p < 0.05$). Females made significantly more omissions than male rats before BD onset and they reduced their number of omissions after a voluntary BD history (Figure 2E, 2way RM-ANOVA: sex $F_{(1,6)} = 9.378$, $p = 0.007$; treatment $F_{(1,6)} = 3.722$, $p = 0.071$; interaction $F_{(1,6)} = 12.657$, $p = 0.002$; Tukey $p < 0.001$ vs. males, $p < 0.01$ vs. after EtOH). Both males and females made significantly more premature responses after voluntary BD history and this effect was more pronounced in females (Figure 2F, 2way RM-ANOVA: sex $F_{(1,6)} = 0.824$, $p = 0.377$; treatment $F_{(1,6)} = 30.164$, $p < 0.001$; interaction $F_{(1,6)} = 5.697$, $p = 0.029$; Tukey $p < 0.05$ males vs. females after EtOH, $p < 0.05$ in males before EtOH vs. after EtOH, $p < 0.001$ in females before EtOH vs. after EtOH). An additional analysis including the sex factor for choice behavior in each option of the RGT is provided in the supplementary material (Supplementary Figure S3).

3.3 Correlations between DM abilities at baseline, ethanol intake and FSCV parameters

We used correlation analysis to assess the relation between baseline DM performances in the RGT, the following voluntary ethanol consumption in the IA2BC and operant self-administration procedures, and the FSCV parameters (Figure 3; Supplementary Table S3). For both sexes, Pearson correlation tests revealed no significant correlation between advantageous choices (P1+P2) during baseline RGT test sessions and ethanol intake by weight during the last session of IA2BC (Figure 3A, r = −0.33 and $p = 0.389$ for males, r = −0.17 and $p = 0.642$ for females), ethanol preference during the last session of IA2BC (Figure 3B, r = 0.32 and $p = 0.106$ for males, r = 0.13 and $p = 0.722$ for females), active lever presses during the last 5 stable FR3 15 min operant self-administration sessions (Figure 3C, r = −0.33 and $p = 0.388$ for males, r = −0.01 and 0.923 for females), and ethanol intake during the last 5 stable FR3 15 min operant self-administration sessions (Figure 3D, r = 0.36 and $p = 0.337$ for males, r = −0.09 and $p = 0.801$ for females). Pearson correlation tests however revealed a positive correlation in female rats between premature responses and active lever presses (Figure 3E, r = 0.7401 and $p = 0.144$)/ ethanol intake (Figure 3F, r = −0.6688 and $p = 0.0345$) during the last 5 stable FR3 15 min operant self-administration sessions, but not in male rats (r = −0.3288 and $p = 0.3876$ for active lever presses, r = −0.3629 and $p = 0.3372$ for ethanol intake). Outside of the ones we are showing in this manuscript, we found no correlation between the other parameters from the RGT, the BD procedure and the FSCV (Supplementary Table S3).

3.4 BD history has no effects on memory and anxiety-like behavior

3.4.1 Learning and memory

In the NOR test, the rats were presented with 2 objects and tested with retention in presence of a new object again 24 h later (Figure 4A). We evaluated the time spent on the familiar and the novel object, before and after voluntary ethanol. The male rats explored the novel object significantly more than the familiar object before (Tukey $p < 0.001$) and after (Tukey $p < 0.001$) BD (Figure 4B, 2way RM-ANOVA: object $F_{(1,34)} = 211.05$, $p < 0.001$; treatment $F_{(1,34)} = 0.01$, $p = 1.000$; interaction $F_{(1,34)} = 0.20$, $p = 0.655$). The female rats explored the novel object significantly more than the familiar object, both before (Tukey $p < 0.001$) and after (Tukey $p = 0.002$) BD (Figure 4C, 2way RM-ANOVA: object $F_{(1,9)} = 38.12$, $p < 0.001$; treatment $F_{(1,9)} = 0.01$, $p = 1.000$; interaction $F_{(1,9)} = 0.35$, $p = 0.569$).

3.4.2 Anxiety

In the DLB test (Figure 4D), the rats were left for 5 min to explore the box. We evaluated the time spent in the lit compartment. The male rats spent significantly less time in the lit compartment than female rats, both before (Tukey $p = 0.021$) and after (Tukey $p = 0.02$) BD (Figure 4E, 2way RM-ANOVA: sex $F_{(1,17)} = 8.38$, $p = 0.010$; treatment $F_{(1,17)} = 3.38$, $p = 0.084$, interaction $F_{(1,17)} = 0.01$, $p = 0.988$).

3.5 Effects of BD history on baseline phasic dopamine signaling 48 h after the last ethanol exposure

We evaluated the phasic dopamine signaling induced by electrical stimulation in the core of the NAc using FSCV on brain slices, in both male and female rats, after behavioral experiments. Thus, both DM capacities and dopaminergic signaling were assessed in the same animals. We tested a 100 nM dose of quinpirole on the slices to unravel potential changes in the sensitivity of the D2/3 receptors (Figure 5; Supplementary Table S2 for all statistical analyses).

At baseline, we did not observe any changes in the dopamine signaling parameters between control and rats with an history of BD. In general, and as expected, quinpirole decreased dopamine signaling and all parameters of the different groups of males. Strikingly, this effect is lacking in the control group of females but observed after a history of exposure to BD.

In males, quinpirole decreased [DA]max in control (Tukey $p = 0.002$) and binger rats (Tukey $p = 0.036$) (Figure 5B top left panel, 2way RM-ANOVA: treatment $F_{(2,10)} = 24.715$, $p < 0.001$; group $F_{(1,10)} = 0.00594$, $p = 0.442$; interaction $F_{(2,10)} = 1.007$, $p = 0.399$) [DA]p in control (Tukey $p < 0.001$) and binger rats (Tukey $p = 0.002$) (Figure 5B middle left panel, 2way RM-ANOVA: treatment $F_{(2,10)} = 33.906$, $p < 0.001$; group $F_{(1,10)} = 0.116$, $p = 0.747$; interaction $F_{(2,10)} = 1.328$, $p = 0.308$), and Vmax in control (Tukey $p = 0.002$) and binger rats (Tukey $p = 0.009$) (Figure 5B bottom left panel, 2way RM-ANOVA: treatment $F_{(2,10)} = 12.283$ $p = 0.002$; group $F_{(1,10)} = 3.787$, $p = 0.109$; interaction $F_{(2,10)} = 1.156$, $p = 0.354$).

In females, quinpirole decreased [DA]max in binger (Tukey $p = 0.01$) but not control rats (Figure 5B top right panel, 2way RM-ANOVA: treatment $F_{(2,10)} = 8.231$, $p = 0.008$; group $F_{(1,10)} = 0.605$, $p = 0.472$; interaction $F_{(2,10)} = 1.780$, $p = 0.218$), [DA]p in binger (Tukey $p = 0.011$) but not control rats (Figure 5B middle right panel, 2way RM-ANOVA: treatment $F_{(2,10)} = 10.346$ $p = 0.004$; group $F_{(1,10)} = 1.828$, $p = 0.234$; interaction $F_{(2,10)} = 1.387$ $p = 0.294$), and had no effect on Vmax (Figure 5B bottom right panel, 2way RM-ANOVA: treatment $F_{(2,10)} = 1.394$ $p = 0.292$; group $F_{(1,10)} = 0.949$, $p = 0.375$; interaction $F_{(2,10)} = 0.0214$, $p = 0.979$).

4 Discussion

The present study outlines that a chronic voluntary BD exposure impairs DM capacities specifically in male rats. Those DM impairments were not associated with an increase in cognitive

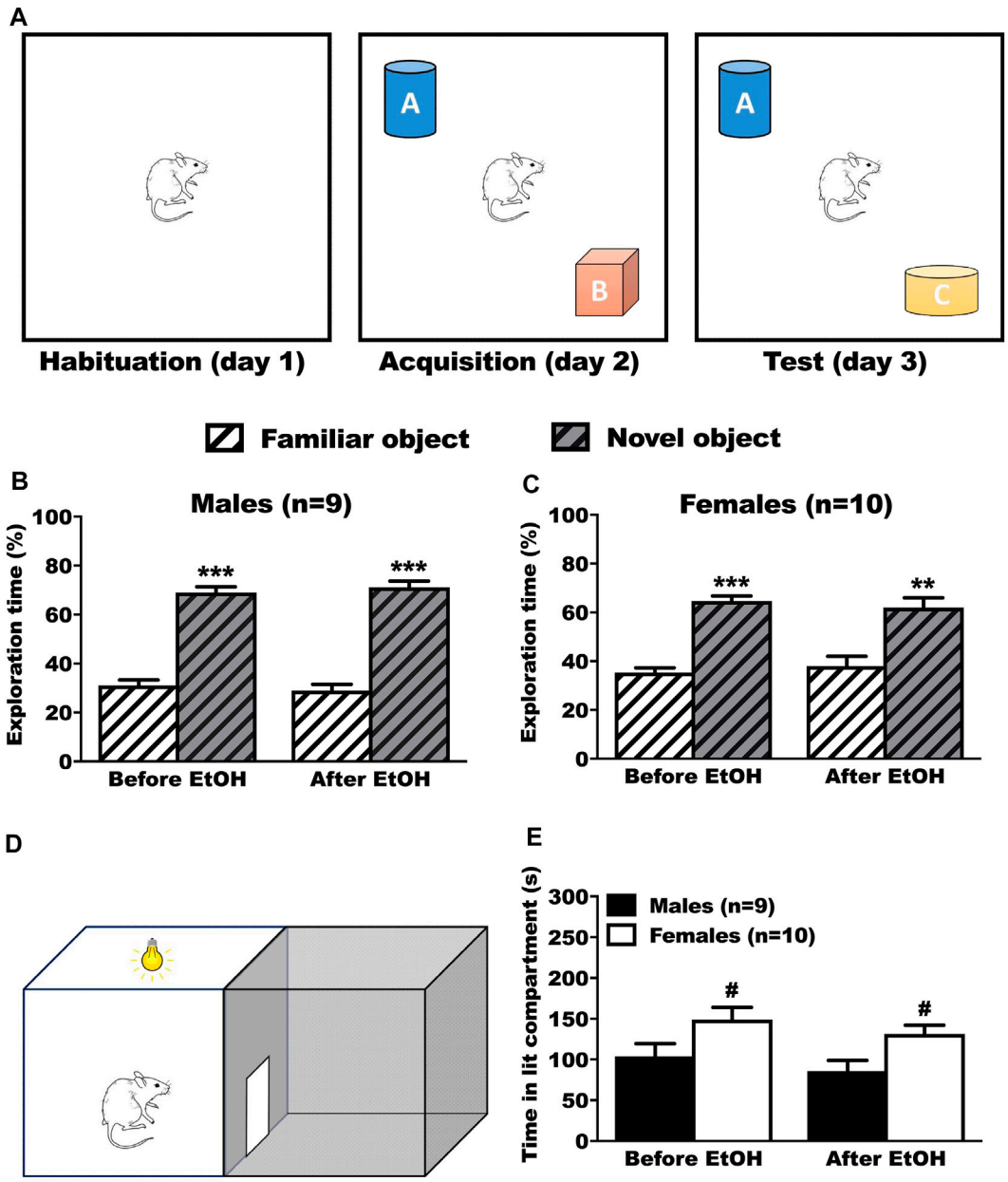

FIGURE 4
Results of the anxiety (LDB) and learning/memory test (NOR) before and after ethanol. **(A)** Timeline of the NOR test. After exploring the box during the habituation phase, animals had the chance to explore 2 different objects (A and B) or during the acquisition phase. During the test phase, one of the objects was switched with a new different one (Novel Object, C), while the other remained (Familiar Object, A). **(B,C)** No differences in performances were observed before and after ethanol. Male **(B)** and female **(C)** rats spent significantly more time on the novel object, showing that they memorized the familiar object, both before and after ethanol. Results are expressed as mean ± SEM of the proportion of time spent exploring each object over the total time spent exploring. **(D)** Schematic representation of the DLB test. The animal was positioned in the lit compartment, back to the central door, and allowed to freely move inside the box. **(E)** No effect of ethanol on the time spent inside the lit compartment during the LDB test. Female rats spent significantly more time inside the lit compartment than the male rats, both before and after ethanol. Results are expressed as mean ± SEM of the time in seconds spent inside the lit compartment during the test. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs. familiar object. $^{\#}p < 0.05$ vs. males.

deficits or in anxiety-like behavior. They were also not associated with impairments in dopaminergic transmission in the core of the NAc. In females, despite no effects on choice behavior, BD history altered impulsive control and increased sensitivity to the inhibitory effect of quinpirole on dopamine release thus suggesting adaptation in D2/3 receptor functioning.

Sex differences in DM capacities were seen before the onset of BD. Although we found no significant statistical differences, it seemed like most females were faster in acquiring the task which may be explained by better attention skills, despite making more omissions. As expected, sex differences were obvious regarding preferences for options: i) no poor decision makers in females; ii) males significantly preferred the optimal P2 option and iii) females preferred both P1 and P2 options. The P1 option, preferred by females, can be seen as a "risk-averse" phenotype, as it is associated with the lowest probability of punishment, as previously suggested (Georgiou et al., 2018). This

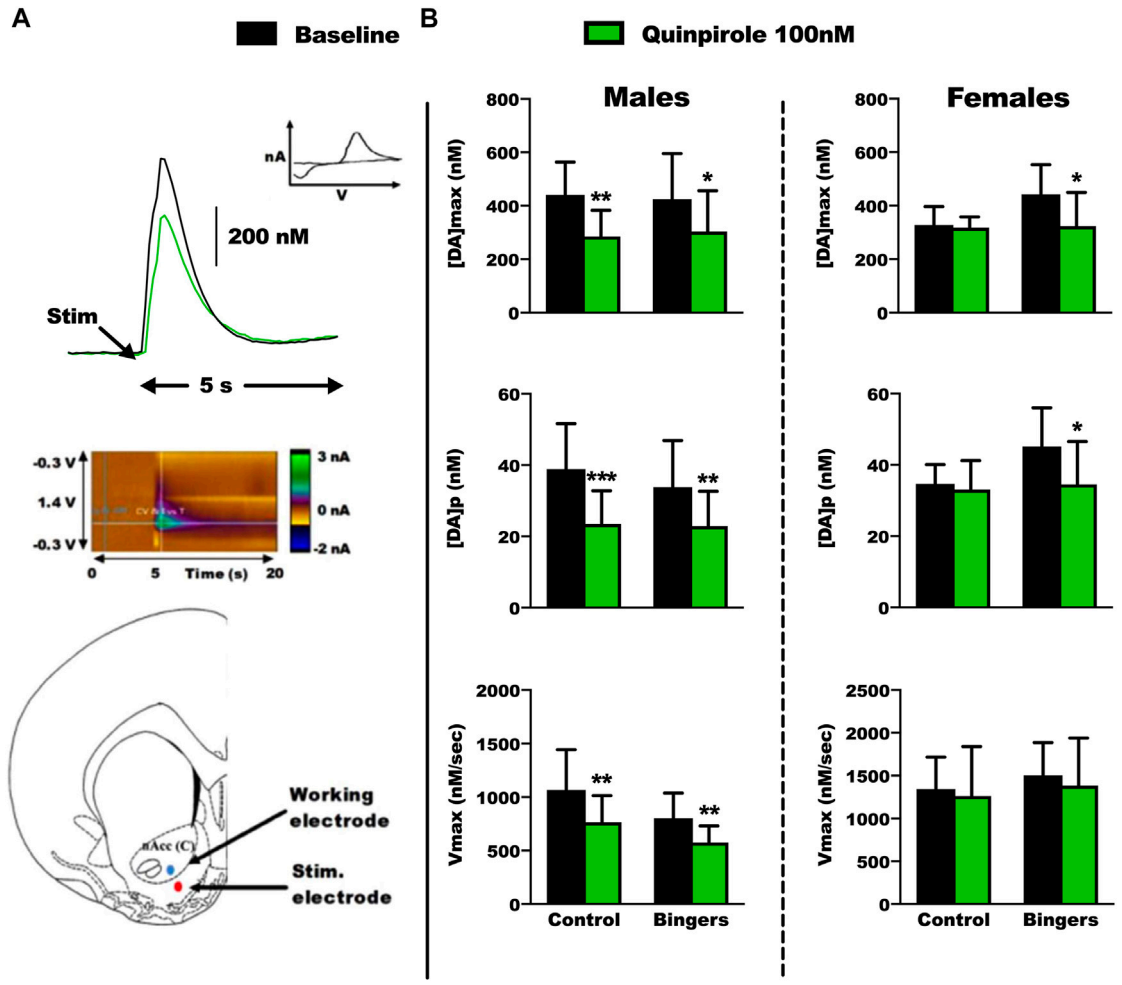

FIGURE 5
Ex-vivo FSCV results in male and female rats. Control: n = 6 males and n = 6 females, Bingers: n = 8 males and n = 7 females. **(A)** Top panel: Example of a FSCV trace from a control male rat, and characteristic voltamogramm of dopamine. Middle panel: Example of color plot from a control male rat during the FSCV recordings. Bottom panel: Electrode placements for the FSCV recordings in the core of the NAc. **(B)** Top panel: results for $[DA]_{max}$ in male and female rats. Results are expressed as mean ± SEM of the maximum extracellular [DA], in nM. Middle panel: results for $[DA]_p$ in male and female rats. Results are expressed as mean ± SEM of the [DA] per pulse of stimulation, in nM. Bottom panel: results for V_{max} in male and female rats. Results are expressed as mean ± SEM of the dopamine transporter velocity, in nM/sec. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. respective baseline.

observation is in line with human studies in which women use a different choice strategy than men, displaying more sensitivity to punishment frequency and occasional losses in the IGT (van den Bos et al., 2013).

Voluntary BD impaired choice behavior specifically in males, with a decrease of the optimal P2 option choice (50% decrease), although without effects on the overall advantageous choices made. BD history in males made their choice behavior become "random" (around 25% choice for each option), as they could not effectively select the advantageous options in the task anymore. Our results are in line with those showing impaired DM in conflictual and risky situations after both forced (Nasrallah et al., 2011; Boutros et al., 2015) and voluntary (McMurray et al., 2014; 2016) binge-like procedures in male rodents. Clinical studies have also shown impairment of DM abilities in adolescent bingers (Goudriaan et al., 2007; 2011; Johnson et al., 2008). Male rats did not significantly increase the less advantageous choices (more immediate reward with more punishment), suggesting that they did not display a state or trait of hypersensitivity to reward or increased risk-taking as previously suggested in humans (Johnson et al., 2008). Instead, rats were unable to discern options for their value and adapt from feedback, as described in alcohol addiction (for review, (Verdejo-Garcia et al., 2018)), but not yet in the case of BD. A previous preclinical study using low dose i.p. ethanol during the acquisition of the task found similar results (Spoelder et al., 2015). Our results show that DM impairments were not linked to changes in anxiety-like behavior in the LDB or cognitive deficits in the NOR. BD also notably increased motor impulsivity in both sexes (increased premature responses) in line with heightened motor impulsivity previously described in humans (Sanchez-Roige et al., 2014). It is also important to note that the second RGT measurements were performed during acute ethanol withdrawal, but we did not notice any acute withdrawal symptoms that may have affected behavior in the task.

One of the most striking result of our study is that BD history had no effect on DM capacities in female rats. Many human studies have

shown that women are more sensitive to the effects of alcohol than men, but sex differences regarding BD remain poorly investigated (for review, (Wilsnack et al., 2017)). Some studies have found worse performances in global executive functioning and DM in male bingers (Parada et al., 2012), while others have found similar impairments in both sexes (Goudriaan et al., 2007; Carbia et al., 2017). In the present study, it is noteworthy that before BD onset, the female group displayed more good decision makers than the male group, and no poor decision makers. In addition, the males also displayed a higher level of anxiety than females, a trait that has already been associated with poor DM (Miu et al., 2008). Those results could suggest that good baseline DM performances are less sensitive to the effects of alcohol as shown in well-trained animals (Spoelder et al., 2015). In agreement with this observation, we showed in a previous study (Jeanblanc et al., 2019) using a different RGT procedure [as described in (Rivalan et al., 2009)], that alcohol could preferentially impair individuals with neutral or poor performances, while not affecting those with good performances. On the contrary, individuals with poor DM abilities could be more vulnerable. For instance, it has been shown that rats with poor DM abilities in the RGT display extreme scores in risk taking, reward seeking, behavioral inflexibility and motor impulsivity (Rivalan et al., 2013). Working on female rats also raises the question of the role of the hormonal cycle. However, our females were housed individually in ventilated racks and therefore did not synchronize their hormonal cycle. As such, there is little risk of a statistically significant effect of the phase of the cycle on our results. Moreover, we have previously confirmed in our laboratory that the hormonal cycle does not affect ethanol consumption in our BD procedure (data not shown), and previous studies have shown that it has no effect on the IGT in humans (van den Bos et al., 2013), and the RGT (Georgiou et al., 2018) in rats.

No study has yet analyzed whether DM abilities can predict the vulnerability to consume ethanol in individuals who have never used ethanol before. The use of a longitudinal design allowed us to assess the vulnerability to consume ethanol in the BD procedure, but the analysis revealed no correlation between baseline DM abilities (advantageous choices: P1 + P2) and ethanol consumption in the IA2BC and operant self-administration procedures (Figure 3). Interestingly, we found a positive correlation in females (but not males) between premature responses and active lever presses/ethanol intake during the FR3 15 min self-administration sessions. As premature responses in the task reflect motor impulsivity, this could mean that female animals with a high base level of impulsivity could end up drinking more in our task. We did not find any correlation between the other parameters in the RGT, the BD procedure and the FSCV data (Supplementary Table S3). It is however important to note that our sample size was not optimal for such analysis, and would probably require more animals. Thus, our results overall do not support the widespread intuition that poor DM abilities may increase vulnerability to drink ethanol, but rather that chronic ethanol intake is responsible for DM impairments in a sex specific manner. Some results in the literature indicate that cognitive deviations and personality traits (impulsivity, sensation seeking, risk taking. . .) accompanying addiction, rather than drug consumption in itself, may explain DM impairments (Kovács et al., 2017). The relation between drug consumption and preexisting impulsivity, risk taking or DM impairments has however been shown in a very mild and inconstant manner for alcohol and other drugs, with a remaining uncertain causality (Ahmed, 2018).

Our results on dopamine transmission demonstrate that BD does not affect basal dopamine signaling in the NAc core, regardless of sex, but reveal sex-dependent changes in the sensitivity to the inhibitory effects of quinpirole. Baseline dopamine signaling (release and uptake) was similar in both sexes in control groups. Our results are in line with those of a recent meta-analysis on 39 microdialysis studies showing that there are no sex-dependent differences in basal dopamine levels within the NAc (Egenrieder et al., 2020). It is noteworthy that other studies have however suggested sex-dependent differences in dopamine signaling (Walker et al., 1999; Walker et al., 2006). Thus, our results on basal dopamine signaling cannot explain our behavioral results showing sex-differences in baseline training and testing in the RGT, as we initially hypothesized. Using a bigger sample size, it would however be interesting to compare baseline dopamine signaling between different DM groups. In a previous work, we indeed found a significant difference in DA release between male rats with good and poor DM levels (although using a different RGT protocol and having a possible confounding effect of ethanol) (Jeanblanc et al., 2019).

Baseline dopamine signaling was not altered in both sexes after a history of BD exposure. Our result is in line with those of a recent study that used a forced BD exposure, although in adolescent male rats, and showed no changes in baseline dopamine signaling using *in vivo* FSCV at adulthood (Shnitko et al., 2016). To the best of our knowledge, no studies have analyzed the effects of a BD protocol on striatal dopaminergic signaling using *ex vivo* FSCV. It may be that basal phasic dopamine signaling is only impaired using protocols to induce alcohol dependence, but not BD (Karkhanis et al., 2015). While quinpirole reduced dopaminergic signaling in males and the history of BD had no effect, in females, we found that the history of BD may have induced neuro-adaptations making the dopaminergic transmission (release but not the transporter since the V_{max} is unchanged) sensitive to the inhibitory effect of quinpirole. It seems that autoreceptors are less sensitive to quinpirole in females with no BD history. A previous study using FSCV in female rhesus macaques showed that 1 year of daily ethanol self-administration induced greater dopamine uptake rates and sensitivity to D2 autoreceptors in the core of the NAc, thus driving a hypodopaminergic state (Siciliano et al., 2016). Altogether, these results suggest sex differences in striatal dopamine signaling and that alcohol exposure history may also differently affect release mechanisms depending upon sex-related factors. Previous findings indicate that dopamine neurotransmission is differently regulated in male and female rats (Walker et al., 2006; Georgiou et al., 2018). Contrary to what we would expect from our results, preclinical studies supporting sex differences in D2 receptors expression show that females have a higher D2 density in the striatum (Williams et al., 2021). Age could also be a factor in our results, especially the lack of effect of our quinpirole dose in female controls, as our animals were far into adulthood and it has been shown that D2 receptor density is declining in the striatum, although seemingly with a greater exponential decline in males than females (Williams et al., 2021). Finally, it is important to note that the fact that our control group did not undergo any behavioral procedure could influence our dopamine recordings and the responses to pharmacology. Phasic DA release in the NAc is involved with associative learning during operant conditioning (Roitman et al., 2004; Owesson-White et al., 2008), and active administration of

drugs is associated with neuroadaptations in specific cognitive processes (Jacobs et al., 2003).

It is interesting to note that our behavioural results cannot be clearly explained by our FSCV data. As only male rats showed DM impairments with BD, we expected to observe phasic signaling impairments specifically in them, but only female rats were affected by BD in their sensitivity to quinpirole. It seems like impairments in DM processes are not explained by modifications in basal dopamine signaling or pre-synaptic D2 activity. The effects of D2 modulation on DM using the same RGT protocol than we did remains inconclusive. It has been shown that the selective D2 dopamine receptor antagonist eticlopride increased advantageous choices specifically in males, while quinpirole increased advantageous choices specifically in females (Zeeb et al., 2009). Other studies have found no effect at all on DM (Di Ciano et al., 2015) or only with a concomitant serotoninergic modulation (Di Ciano et al., 2018). Although the NAc core is important in value-based reward, being limited to it in *ex vivo* FSCV may explain the lack of a causality link between behavioral and neurobiological data. It will be important to use whole brain setups such as *in vivo* FSCV in the future to better understand how DM processes are affected by chronic ethanol.

5 Conclusion

Overall, our study emphasize that BD exposure impairs both DM processes and dopamine signaling in the core of the NAc in a sex-related manner, further suggesting that these effects may play a role in the vicious cycle leading to BD perpetuation and the early onset of AUD and dependence. We further advocate for the use of our operant model of BD, which shows better face validity and leads to changes in behavior without negative effects (behavioral suppression, inflammation, stress. . .) compared to classic passive exposures (injection, gavage. . .). So far, clinical results on the sex differences in the BD field of research looking at brain and cognitive deficits are still inconclusive and need more investigation. Thus, the overall difference in BD exposure raises the important question about the BD history that is also often matter of debate in human studies because it is difficult to have homogeneous population of binge drinkers with the same BD history.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author: MN, mickael.naassila@u-picardie.fr.

Ethics statement

The animal study was reviewed and approved by the Comité Régional d'Ethique en Matière d'Expérimentation Animale de Picardie (no. APAFIS#2145).

Author contributions

JJ and MN designed research; PS performed research; PS and JJ analyzed data; PS, JJ, FB, FG, and MN wrote and edited the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1076465/full#supplementary-material

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Adolescent brain maturation and the neuropathological effects of binge drinking: A critical review

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Adolescence is a transitional stage marked by continued brain development. This period is accompanied by physical and neurochemical modifications in the shape and function of the hippocampus, prefrontal cortex, and other limbic system structures. Brain maturation during adolescence, which is typically governed by intrinsic factors, can be dramatically altered by environmental influences such as drugs and alcohol. Unlike many other addictive substances, binge drinking is very common and normative among teenagers and young adults. This repeated pattern of excessive alcohol consumption in adolescents has been shown to cause behavioral changes and neurocognitive impairments that include increased anxiety, risky decision-making, and learning deficits, which could lead to the development of alcohol use disorder (AUD). This manuscript highlights factors that lead to adolescent binge drinking, discusses maturational changes that occur in an adolescent's brain, and then evaluates the effect of adolescent alcohol consumption on brain structure, function, and neurocognitive abilities in both human studies and animal models. The impact of gender/sex and COVID-19 are briefly discussed. Understanding the factors that promote the onset of adolescent binge drinking and its undesirable consequences could serve as a catalyst for developing therapeutic agents that would decrease or eradicate the damaging effects of alcohol on an adolescent brain.

KEYWORDS

alcohol, binge drinking, adolescence, maturation, neurocognitive

1. Introduction

Adolescence is a developmental period, evidenced by distinct physical, structural, and behavioral changes (Spear, 2016). This transitional period is usually split into early, intermediate, and late stages in both humans and rodents (Salmanzadeh et al., 2020). Even though characterizing the exact start and end of adolescence is challenging, there are distinct developmental and behavioral qualities seen during each stage (Spear, 2000).

Adolescence is also a time of increased incidences of psychological disorders such as depression, and anxiety which occur during early to mid-adolescence, and schizophrenia which can emerge during late adolescence to adulthood (Paus et al., 2008). Substances of abuse such as alcohol and drugs are also frequently initiated at this age, with reports showing that cases of alcohol misuse and addiction are high during the middle and latter stages of adolescence and the transition into young adulthood (Anderson et al., 2010).

Alcohol, a widely used recreational drug, is consumed during adolescence and young adulthood by many Americans. It is estimated that excessive alcohol use accounts for close to 95,000 deaths in the United States every year (Centers for Disease Control and Prevention, 2020). This makes alcohol the third leading cause of preventable deaths in the United States, behind tobacco- and obesity-induced deaths (Mokdad et al., 2004). In a national survey conducted by Sacks et al. (2015), it was reported that in 2010 alone, excessive drinking cost the U.S. about $250 billion, or $2.05 per drink. One of the major reasons for the high death toll and economic impact is the alarming rate of alcohol use among American adolescents that has the potential to escalate over time. For example, reports from the 2020 National Survey on Drug Use and Health (NSDUH) showed that about 8.2% of adolescents between the ages of 12 to 17, and about 52% of adolescents between the ages of 18 to 25 indicated that they had used alcohol in the past 30 days (SAMHSA, 2020). This rate of alcohol consumption was anticipated to increase exponentially following the COVID-19 pandemic. However, recent findings demonstrate that the pandemic had mixed results on alcohol consumption. For instance, in a study that surveyed Swiss university students (i.e., mean age = 27.0 years) between April 2020 and June 2021, 20% of the sampled population reported an increased in alcohol consumption, with 26% indicating that they engaged in binge alcohol consumption (Zysset et al., 2022). Conversely, in two separate studies conducted by Bonar et al. (2021) in adolescents with a mean age of 18.05 years, and Bollen et al. (2021) in adolescents with a mean age of 22.10 years, the authors reported reduced alcohol consumption. The discrepancy in these findings could be due to the different age groups analyzed in these studies and increased parental monitoring in the younger cohorts. Further data from longitudinal studies are continuing to be analyzed and will provide valuable information regarding the local and global impact of the COVID-19 pandemic and the potential impact that variations on regulatory lock-down procedures has had on drinking outcomes. For further review on the impact of COVID-19 on adolescent binge drinking see (White et al., 2020; Charles et al., 2021; Rogés et al., 2021; Vasconcelos et al., 2021).

Binge drinking is defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), as consuming a significant amount of alcohol such that blood alcohol concentration rises to 0.08 g/dL or at least 0.08% (NIAAA, 2004). In rodent studies, binge-like drinking is modeled by repeated intermittent episodes of alcohol exposure either through intragastric gavage, self-administration, or vapor inhalation exposure, followed by withdrawal (Becker and Lopez, 2004; Hiller-Sturmhöfel and Swartzwelder, 2004; Vargas et al., 2014). This form of alcohol consumption has been linked to acute loss of motor coordination and poor cognitive performance (Fillmore, 2007; Lees et al., 2020). However, it is worth noting that the quantity of drinks that constitute binge drinking differs between men and women. Hence, the definition of binge drinking for women constitutes ingesting four or more standard alcoholic drinks, while for men it constitutes ingesting five or more standard drinks within a 2-hour interval (Chung et al., 2018). Additionally, the frequency and amount of alcohol consumed by adolescents and adults differ per occasion. The quantity of alcohol consumed per occasion is higher in adolescents than in adults, even though, they do so less frequently (Chung et al., 2018). Results from longitudinal studies show that underage drinkers normally drink 4 to 5 standard drinks (i.e., one standard drink contains 14 grams of alcohol) at a sitting. Compared to adults, this number is almost twice what adults consumed on average (Chung et al., 2018). Even though the rate at which alcohol use is initiated is comparable in boys and girls, the rate at which drinking becomes a problem, possibly leading to AUD during adulthood is more prevalent in males than in females (Young et al., 2002; Smith et al., 2021). Binge alcohol consumption during adolescence is a major public health concern that is associated with unintended injuries, suicidal thoughts, severe AUD, and neurocognitive deficits (Crego et al., 2009; Parada et al., 2012; Mota et al., 2013; White and Hingson, 2013; López-Caneda et al., 2014; Carbia et al., 2017; Kanny et al., 2018; Lees et al., 2019). The high prevalence of binge drinking and the increasing evidence of binge alcohol-induced cognitive dysfunction has led studies to examine whether adolescents are more vulnerable to the neurotoxic effects of alcohol because of the structural and functions changes that occur during adolescence (Jones et al., 2018). Therefore, the central thesis of this critical review is to highlight factors that contribute to adolescent binge drinking, discuss maturational changes that occur in an adolescent brain, and evaluate the effect of adolescent alcohol exposure on neurocognitive abilities in humans and animal models with a focus on prefrontal cortex and hippocampus.

To present a balanced review of both human and rodent models on a topic that has received considerable attention, the following criteria influence the inclusion and exclusion of studies in this review. Firstly, studies were included to the introduction if they provided broad overview on binge drinking and its potential impact on adolescent health. Due to the lack of recent studies on social factors that influence adolescent binge drinking, studies included in section "Social factors that influence adolescent binge drinking: peers, parents/guardians, and society" were mainly review articles and observational

studies published in the last 30 years. However, given the huge interest in alcohol research and the appreciable work done over the years, pre-clinical and longitudinal/cross-sectional studies were included in sections "Brain maturation during adolescence, Effect of adolescent binge drinking on brain structure and function, Effect of adolescent binge drinking on higher cognitive abilities" if they highlighted brain maturation during adolescence and provided extensive review and/or empirical data on the effect of binge alcohol exposure on neurocognitive abilities in humans and animal models. Finally, studies that had major flaws in their experimental designs, unclear research aim, conference presentations, and unpublished manuscripts were excluded from this review. Again, this decision was influenced by the tremendous progress made in the field of study over the last decade.

2. Social factors that influence adolescent binge drinking: peers, parents/guardians, and society

Physiologically, adolescence marks a period of physiological and psychosocial change which raises one's desire to make their own decisions. In addition to the physiological changes that occur during this stage, adolescents also turn to their peers for support and guidance instead of their parents (Brown et al., 2008). This is because it has been shown that peer-directed interactions are rewarding especially during adolescence (Douglas et al., 2004). These interactions are important for developing new social skills and support networks (Harris, 1995) which may ease the transition to adulthood, especially when an adolescent is away from the family (Spear, 2010). During this transitional period in the life of an adolescent, there is an increased focus on peer-directed social relationships, along with rising conflicts with parents, and elevations in risk-taking and sensation-seeking behaviors (Spear, 2010). In humans, however, the shift from parental dependence to peer approval or independence could also promote daring behaviors, such as engaging in binge alcohol consumption (Steinberg, 2008; Schriber and Guyer, 2016). For instance, data from the National Center for Statistics and Analysis, showed that in 2020 binge drinking contributed to a higher incidence of unintended injuries through alcohol-induced increase in risky behavior and alcohol-impaired driving which resulted in about 12,000 deaths–a 14% increase from 2019 (NCSA, 2020). Therefore, factors influencing risky behaviors in adolescents warrant thorough investigation. Among these, peer pressure has been identified as one of the key factors that compel adolescents to engage in various risky behaviors such as binge drinking.

Peers, examples of social facilitators, can invoke risk-taking behaviors such as alcohol consumption which usually occurs during peer gatherings (Mayer et al., 1998; Sieving et al., 2000; Friese et al., 2013). These social contexts create the platform for adolescents to engage in binge drinking because under such settings adolescents may be under the impression that accepting alcohol offered by peers or drinking more with peers would help them gain social approval and acceptance (Hallett et al., 2014). In addition to peers providing access to alcohol, factors such as parental influence and places where alcohol consumption occurs are also possible contributors to adolescent binge drinking. For example, it is more likely for adolescents to engage in binge drinking at pubs or places where there is no parental supervision. These factors have been proposed as possible contributors to the high incidences of alcohol-related violence in adolescents (Mair et al., 2015).

Parents, on the other hand, have a commanding influence on how adolescents develop or behave, as well as whether they misuse alcohol or not (Lamborn et al., 1991; Kaynak et al., 2014). Parental monitoring and involvement in an adolescent's life is important because children who feel loved and supported most often are less likely to exhibit risky behaviors such as binge drinking. By studying the influence of parents on adolescent development, it has been determined that adolescents whose behaviors are well-monitored by their parents are less likely to engage in alcohol and other drug use (Dishion and Loeber, 1985; Borawski et al., 2003; Habib et al., 2010). Conversely, it is reported that parents who depend on alcohol tend to offer little or no parental guidance–an act that increases the chances that an adolescent may start using alcohol (Windle, 1996). In scenarios where parents drink excessively and fail to provide the much-needed parental guidance, adolescents may be compelled to associate with friends who engage in activities such as binge drinking. Additionally, parents who are fond of drinking alcohol tend to be lenient and tolerate adolescents who drink more or misuse other substances thus normalizing this behavior (Windle, 1996; Gilligan et al., 2012).

Normalizing and perceiving alcohol as a hallmark of adulthood in today's society has unintended consequences on adolescents and hence, could serve as a contributing factor to adolescent binge drinking. Even though western societies have experienced massive changes in the laws and regulations surrounding alcohol advertisement, it is hard to argue against the overshadowing influence of alcohol advertisements on different platforms as contributing factors to adolescent alcohol exposure (Bonnie and O'connell, 2004; Anderson et al., 2009). The lack of universal policies and regulations governing alcohol advertisement make it is easy for curious adolescents to fall prey to some of these overshadowing alcohol commercials on a tv set or as portrayed in music videos. These limitations have raised concerns about the alcohol industry in general and the type of information they disseminate to the public, especially to adolescents. For example, in a study that examined the transparency and accuracy of the information propagated by 27 alcohol industries on the association between alcohol and cancer, Petticrew et al. (2018) found a significant misrepresentation of evidence on the risk

of developing cancer following alcohol consumption. This is particularly troubling, since most of these industry players are key stakeholders in developing alcohol-related policies in some countries. Given these shortcomings, it is important to implement public health policies that would regulate alcohol advertisement and/or restrict underage teens from entering public events where alcohol is easily accessible, as well as scrutinize the information disseminated by the alcohol industry. Another major obstacle that hinders the effort to mitigate adolescent binge drinking is the level at which alcohol is accepted and regarded as a norm in today's society. This notion certainly influences underage alcohol consumption. It comes as no surprise that in communities where policies on underage drinking are strictly enforced and youths receive proper parental guidance, incidences of underage drinking are scarce (Bonnie and O'connell, 2004). In addition to these environmental factors, college and university campuses are ideal environments where the use of alcohol tends to be tolerated and encouraged by students. For example, the development of new peer networks in colleges, the low cost of alcohol on or around campuses, and the rate at which campus events involve alcohol are all factors that can increase the tendency of a university student to engage in alcohol consumption (Borsari and Carey, 2001; Weitzman et al., 2003; Hallett et al., 2014; Roberson et al., 2018). Even though others argue that pragmatic steps and strict policies have been enacted by some colleges and universities, these environments remain ideal for alcohol use by adolescents (Bonnie and O'connell, 2004). This is evident in a nationwide survey of college students (i.e., between the ages of 18 to 22 years), where about 53% of the students surveyed indicated that they had consumed alcohol within the past month, and 33% reported to have been involved in binge drinking during that same time frame (SAMHSA, 2019). As stated previously, this level of drinking often leads to an increased prevalence of alcohol-related accidents such as motor and vehicle crashes (Hingson et al., 2017), and behavioral problems such as fighting (Swahn et al., 2004), and unsafe sexual practices (Hingson et al., 2003; Moure-Rodríguez et al., 2016) including unintentional sex with and without protection (Rehm et al., 2012; Chaney et al., 2016). NIAAA estimates that close to 700,000 adolescent students are assaulted by their colleagues who engage in excessive drinking (Hingson et al., 2005). With more recent data showing that for every five college women, one is likely to be sexually assaulted while in college (Muehlenhard et al., 2017). Unfortunately, most of these cases are alcohol or other substance of abuse-related (Lawyer et al., 2010; Carey et al., 2015).

Risk-taking behaviors in adolescents, driven by these contextual factors, have been hypothesized to provide adaptive functions, such as providing opportunities to explore adult behaviors which include alcohol consumption. Taken together, it is evident that the social factors highlighted here increase peer-directed interactions and the seeking of novel and exciting stimuli (Spear, 2010), such as alcohol, which may enhance incidences of binge alcohol consumption (Weitzman et al., 2003) and alcohol-induced injuries in adolescents (Swahn et al., 2004). Here, we briefly explore maturational changes that take place in human and rodent adolescents and how these processes are impacted by binge drinking.

3. Brain maturation during adolescence

As stated previously, adolescence is a transitional period that results in many neurobiological and physiological changes in the brain (Spear, 2016). During this period, there are also neurodevelopmental changes in synaptic plasticity and neural connectivity, that are ongoing and important for brain refinement and specialization (Giedd, 2004; Carbia et al., 2018; Lees et al., 2019; Squeglia, 2020). These processes are critical because maturing connections among brain regions enhance brain network integration and complexity (Pascual et al., 2018). Tremendous progress has been made in the field of neuroscience and addiction to understand how the brain functions and how insults such as alcohol affect specific regions of the brain, especially during adolescence (Arain et al., 2013; Chwedorowicz et al., 2017; El Marroun et al., 2021; Walker et al., 2021). Two of the major maturational changes that happen during adolescence that have received considerable attention are alterations in both white and gray matter. Physiologically, it has been determined that gray matter volume decreases during adolescence–a maturational phenomenon that enhances synaptic pruning and myelination in the cortex (Giedd, 2004; Gogtay and Thompson, 2010; Pfefferbaum et al., 2016; Dow-Edwards et al., 2019; Sakai, 2020; El Marroun et al., 2021). It has also been shown that during adolescence, there is a continuous growth of white matter fibers–a process that enhances communication between different brain regions (Giedd, 2004; Lebel and Beaulieu, 2011; Yap et al., 2013; Dow-Edwards et al., 2019). These changes have been reported in different brain regions. For example, the prefrontal cortex, an area that mediates critical, complex cognitive abilities has been shown to have decreasing gray matter volume during the transition from adolescence to adulthood (Giedd, 2004). Similarly, changes in subcortical brain structures have also been identified. For instance, through magnetic resonance imaging study it has been shown that the size of subcortical regions such as the putamen and caudate decreases throughout adolescence. Inversely, subcortical regions such as the hippocampus and amygdala are shown to first increase in size during puberty, with slowing but continual growth observed into adolescence (Østby et al., 2009).

In addition to structural remodeling, reports indicate that neurochemical maturation also occurs during these formative years. For example, it has been determined that during adolescence, there is reorganization in the dopaminergic system involved in reward and incentive

processing (Wahlstrom et al., 2010). Specifically, during adolescence, it has been demonstrated that dopamine fibers continue to increase in density in the medial prefrontal cortex (Naneix et al., 2012; Willing et al., 2017). The continual increase of these fibers potentially makes adolescents vulnerable to positive and negative influences (Hoops and Flores, 2017). This finding supports a previous report by Andersen et al. (2000) that shows that dopamine receptor expression increases maximally during adolescence in cortical and subcortical regions. Another brain region that has been heavily explored because of its involvement with reward and sensation-seeking is the nucleus accumbens (NAcc). Neuroimaging studies have also shown that NAcc is very sensitive during the formative years. It has been discovered that changes in reward sensitivity during adolescence are partly due to decreasing dopamine signaling; possibly explaining why adolescents may engage in sensation-seeking and risky behaviors (Arain et al., 2013). Even though the exact molecular mechanisms driving sensation-seeking and the onset of early alcohol use are not clearly understood, a recent study by Morales et al. (2019) shows that NAcc possibly mediates individual differences in sensation-seeking during adolescence.

As stated previously, during adolescence there are ongoing and significant changes to the projecting neuronal circuitry between brain regions geared toward improving cognition. For example, it has been shown that the continuous growth and development of these circuits enhances cognitive abilities such as multitasking, problem-solving, and the ability to process complex information (Arain et al., 2013). Developing these higher cognitive abilities as one transitions from childhood to adolescence requires a healthy and functioning brain, but since an adolescent brain is still undergoing maturation, they are more vulnerable to many insults such as alcohol. Based on this assertion, it is obvious that even subtle alterations in structure, thickness of the cerebral cortex, and demyelination due to binge drinking in adolescents could lead to psychological and social consequences (Nagy et al., 2004; Casey et al., 2008). Therefore, to understand how adolescent binge alcohol consumption negatively affects cognition, there is a need for a holistic review of the morphology and function of the hippocampus, prefrontal cortex, and cerebellum. The ensuing section provides a brief overview of human and rodent experiments that examine the effects of binge drinking on brain structure and function during adolescence.

4. Effect of adolescent binge drinking on brain structure and function

Brain maturation during adolescence is influenced by inherent factors such as heredity, prenatal and post-natal insults, and extrinsic and environmental factors such as substance abuse (Bolton et al., 2012; Arain et al., 2013; Miguel et al., 2019; Tooley et al., 2021). Among the extrinsic factors, alcohol is highlighted in this review. This is because alcohol binge drinking poses a great challenge to adolescent brain maturation due to how normative it has become among most youths in the United States. This has led to extensive studies on maturational changes and how alcohol alters their development during the formative years (**Figure 1**).

Changes in brain structure and function following binge drinking in adolescents have been well-examined in human studies using electrophysiology and neuroimaging principles (**Table 1**). For example, to determine the effect of binge drinking on brain volume and microstructure, a magnetic resonance imaging (MRI) technique was used and demonstrated that adolescents who use alcohol and those with marginal alcohol exposure have different gray matter microstructure volumes (Jacobus and Tapert, 2013). The reduction of gray matter volume observed by Jacobus, aligns with current longitudinal studies that shows that binge alcohol consumption reduces cortical and subcortical gray matter volumes in adolescents (Infante et al., 2022). Cross-sectional human studies reveal that adolescents who engage in binge drinking have different volumes of gray matter in distinct brain areas when compared to non-binge drinking adolescents (Howell et al., 2013; Doallo et al., 2014; Pfefferbaum et al., 2016; Sousa et al., 2019). For example, in their study of adolescent binge drinkers, Pfefferbaum et al. (2016) observed a decrease in the volume of both frontal and temporal lobes in subjects who drank minimal to high volumes of alcohol compared to those who do not consume alcohol. Through the compilation of cross-sectional and longitudinal studies of adolescent binge drinkers (Cservenka and Brumback, 2017; Lees et al., 2020; Almeida-Antunes et al., 2021) it has been demonstrated that adolescents who engage in binge drinking show abnormalities in gray matter volume and deficits in neural activity in distinct brain regions during working memory, verbal learning, and tasks that involve inhibitory control (Cservenka and Brumback, 2017). This evidence stems from magnetic resonance imaging and event-related potentials data from both cross-sectional and longitudinal studies that focus on structural and functional changes in frontal brain regions following binge alcohol consumption. Through these experimental designs, the effects of binge drinking on frontal areas such as the insular cortex, the inferior frontal gyrus (IFG), and the anterior cingulate cortex (ACC) in adolescents during cognitive processes have been investigated (López-Caneda et al., 2012; Xiao et al., 2013; Mashhoon et al., 2014; Suárez-Suárez et al., 2020; Pérez-García et al., 2022). For example, by comparing cortical thickness between binge drinking females and their light drinking counterparts, Mashhoon et al. (2014) found a significant reduction in cortical thickness in the mid-ACC of binge drinkers. Further analysis from their study demonstrated a positive correlation between ACC thinness and alcohol use patterns in the binge drinking group. These findings are

further supported by empirical data obtained from event-related potentials studies (López-Caneda et al., 2012). For example, by measuring event-related potentials, López-Caneda et al. (2012) aimed to determine the effect of alcohol on frontal brain areas in young binge drinkers. As part of a longitudinal study that is focused on the prefrontal cortex, López-Caneda et al. (2012) recorded an abnormal brain activity (i.e., hyperactivation of the right inferior cortex) in binge drinkers compared to the control group. This finding aligns with previous experiments conducted by Crego et al. (2010) in which binge drinking university students showed altered prefrontal cortex function during an identical pairs performance task. Specifically, in their experiment, anterior prefrontal cortex activity was significantly reduced in binge drinkers when compared to the control group (Crego et al., 2010). In another study where Kvamme et al. (2016) examined T1-weighted magnetic resonance imaging (MRI) images of college-age binge drinkers and matched healthy volunteers using voxel-based morphometry and covarying the anatomical scans with AUD identification test (AUDIT) scores, Kvamme and colleagues found volumetric changes in the frontal lobe of college-age drinkers. Furthermore, in a recent analysis of data from the National Consortium on Alcohol and NeuroDevelopment, it was demonstrated that cortical gray matter volume was significantly decreased in adolescent binge-drinkers compared to non-binge drinkers (Infante et al., 2022). A complementary study by Pérez-García et al. (2022) examined differences in gray matter morphology between young university stable binge drinkers and a stable control group *via* a cross-sectionally and longitudinally analysis. From their cross-sectional studies, which compared baseline parameters to follow-up, there were no structural abnormalities observed between the two groups at baseline. However, during the follow-up period, Pérez-García and colleagues observed a larger surface area in the left insular in the stable binge drinkers when compared to the stable control group (Pérez-García et al., 2022). While there were no sex-specific differences recorded for the insular cortex, region of interest analysis on structural thickness showed a sex-specific effect where binge drinking males appeared to have smaller right rostral middle frontal gyrus thickness than either the control males or binge drinking females. Similarly, it was evident in their longitudinal study that continuous binge drinking significantly decreased the volume of NAcc. These findings are important because the presence of gray matter enhances learning, motor control, and attention, among others. These findings align with previous data from De Bellis et al. (2005) which aimed to determine how alcohol affects adolescents who have early-onset AUD. Through MRI studies, they reported a decrease in prefrontal cortex volume and smaller volumes of prefrontal cortex white matter in adolescents who had AUD (De Bellis et al., 2005). In a parallel human study, McQueeny et al. (2009) assessed the integrity of white matter in binge-drinking adolescents who had no record of AUD. Similar to the aforementioned study,

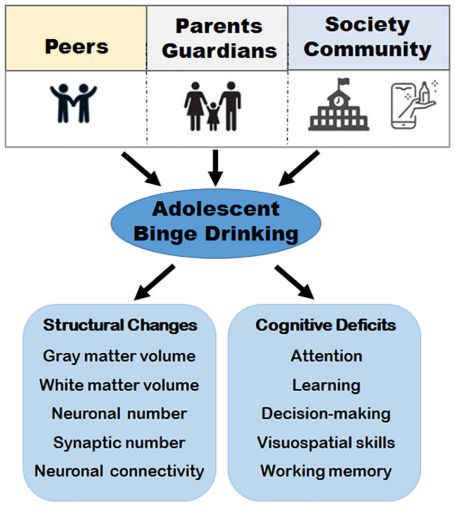

FIGURE 1
A schematic representation of major factors that contribute to binge drinking and the downstream consequences. Social factors such as peers and social acceptance, family and parental guidance, and the community, combined with internal factors, such as, age, sex hormones, and psychological status can influence binge drinking during adolescence. Binge drinking (i.e., consuming 4 ≥ standard drinks for women and 5 ≥ standard drinks for men in a brief period of time) usually within 2 h, contributes to structural changes such as decreased gray matter volume and white matter density, changes in synaptic number, neuronal loss, and disruption of brain connectivity. These structural changes have been implicated in cognitive deficits such as altered working memory, attention, visuospatial skills, decision-making, and learning deficits in adolescent binge drinkers and young adults.

McQueeny and colleagues found a widespread reduction in fractional anisotropy in major white matter regions–indicating compromise of the integrity of white matter in the sampled population (McQueeny et al., 2009). Even though longitudinal and cross-sectional studies exploring binge drinking-induced hippocampal impairments are not extensively covered in this review, the effect of alcohol on the structure and function of the hippocampus has been identified in adolescents who engage in heavy alcohol consumption. For example, by analyzing MRI brain scans of college freshmen, Meda et al. (2018) found a positive correlation between heavy alcohol consumption and increased hippocampal gray matter volume decline. The finding from this study aligns with previous report showing smaller left hippocampal gray and white matter volumes in adolescents who have AUD compared to their non-alcohol using counterparts (Nagel et al., 2005). Although these two experiments used non-binge drinking patterns, the empirical data support the notion that a variety of alcohol intake models can result in similar outcomes.

It is important to state that it cannot be explicitly determined whether these brain volume reductions in the subjects are due to binge drinking or if the brain volume reduction is a driving

factor for high drinking in adolescents and development of AUD. However, the use of rodent models can assist with this obstacle. It has been well-established that effective information processing requires well-structured and functional myelinated nerve fibers (Simons and Trotter, 2007). A study by Montesinos et al. (2015) demonstrated that binge-like alcohol consumption in adolescent mice causes white matter disruption, specifically, ultrastructural myelin sheath disarrangement in the prefrontal cortex and down-regulation of proteins involved in myelination. This finding aligns with previous experiments conducted by Vargas et al. (2014), where reduced myelin density was found in the medial prefrontal cortex of alcohol-exposed adolescent rats (Vargas et al., 2014). These data demonstrate that binge drinking disrupts myelin sheath development. More importantly, since the formation and development of myelin sheaths is important for motor activity and learning (McKenzie et al., 2014; Wang et al., 2020), its disruption due to adolescent binge drinking could contribute to subsequent behavioral deficits in adulthood. In addition to the microstructural changes in gray and white matter volumes induced by binge drinking in adolescents, rodent model experiments have also found structural alterations in the cortex (Vetreno et al., 2017), hippocampus (Risher et al., 2015c), and cerebellum (Vetreno et al., 2016) in adolescent rodents that are exposed to binge ethanol. Vetreno et al. (2017) exposed female adolescent Wistar rats to the adolescent intermittent ethanol (AIE) paradigm from P25 to P55 and found that P80 rats who underwent the drinking paradigm had reduced cerebellar and hippocampal volumes when compared to the controls (Vetreno et al., 2017). These results support previous work conducted with rats that underwent similar adolescent alcohol paradigms and showed neuronal loss within the hippocampus (Crews et al., 2006; Hansson et al., 2010; Risher et al., 2015a,c), and reduced glia number in the medial prefrontal cortex (Koss et al., 2012). Evidence from Broadwater et al. (2014) and Hiller-Sturmhofel and Spear (2018), have demonstrated that alcohol exposure in adolescent rats not only enhances cell death in select brain areas but also decreases neurogenesis, while Morris et al. (2010) demonstrated that adolescent alcohol exposure disrupts the growth of neural stem cells in the dentate gyrus of male Sprague-Dawley rats. Additional rodent studies focusing on the hippocampus support the finding that binge alcohol consumption during adolescence impairs neurogenesis in the dentate gyrus (Lacaille et al., 2015; Vetreno and Crews, 2015; Nwachukwu et al., 2022). This is an important finding because neurogenesis is necessary for developmental processes in select brain regions throughout life, and is important for functions such as learning, memory (Costa et al., 2015), and cognitive flexibility (Toda et al., 2019). Thus, its disruption by alcohol exposure may be a contributing factor to the cognitive decline observed in binge drinkers.

It is possible that disruption of neurogenesis and cell death occurs due to changes in neuroimmune gene expression, potentially leading to alcohol-induced brain damage (Crews et al., 2000; Pascual et al., 2007, 2017; Sanchez-Alavez et al., 2019; Barney et al., 2022). For example, to determine the effects of adolescent ethanol exposure on the regulation of inflammatory markers, Pascual et al. (2007) measured the levels of COX-2 and iNOS (examples of cytokines and inflammatory mediators) in the brain of adolescent rats. They demonstrated that expression of cytokine and inflammatory mediators were significantly increased in the neocortex, hippocampus, and cerebellum of ethanol-exposed rats. In their experiment, the elevations of these mediators correlated with neural cell death and induced neurobehavioral deficits in the rats (Pascual et al., 2007). Interestingly, recent work by Nwachukwu et al. (2022) revealed a sex-specific effect of adolescent ethanol exposure on hippocampal neurogenesis and cytokine release. In their experiment, pro-inflammatory markers such as IL-1β and TNFα were only increased in alcohol-exposed male rats suggesting a sex-dependent differential immune-responsivity to alcohol in adolescence. There are a growing number of pre-clinical studies emerging that support a role for alcohol-induced astrocyte and microglia activation, imbalance of reactive oxygen species, and pro-inflammatory signaling (Crews and Nixon, 2009; Alfonso-Loeches et al., 2012; Risher et al., 2015b; Vetreno and Crews, 2015; McClintick et al., 2018; Melbourne et al., 2021; Peng and Nixon, 2021). Based on these findings, it would be interesting to determine if targeting these non-neuronal cells and related pro-inflammatory signaling pathways is an effective approach to preventing alcohol-induced neuronal cell death. Given that hippocampal integrity is critical for cognitive functions such as learning and memory formation, results from these studies show that alcohol-induced alterations to neurogenesis, cell death, and neuroinflammation could have unintended consequences on brain function (**Table 2**). For further reading see (Vilpoux et al., 2022).

Binge-like alcohol exposure results in deficits in learning and memory in rodent models (Tapia-Rojas et al., 2018). Therefore, it should be of no surprise that in addition to neuronal loss, synaptic function in many of these adolescent binge alcohol models, is also impaired. As previously stated, during adolescence, there are constant modifications of synapses and neuronal activities geared toward optimizing higher cognitive abilities (Glantz et al., 2007; Dow-Edwards et al., 2019; Sakai, 2020). Binge-like alcohol consumption during adolescence has been shown to cause aberrant synaptic transmission (Mulholland et al., 2018; Amodeo et al., 2021), in part due to changes in synaptic protein expression and localization of glutamate receptor subunit 2B (GluN2B) in rodent models (Swartzwelder et al., 2016; Wills et al., 2017). For example, by exposing male Sprague-Dawley rats (beginning P30) *via* intragastric gavage to 5 g/kg ethanol during adolescence, Risher et al. (2015c) found that alcohol-exposed rats displayed enhanced synaptic efficacy in the CA1 region of the hippocampus. In their study, the change in long-term potentiation (LTP) was

TABLE 1 Summary of studies exploring structural and functional anomalies in adolescent binge drinkers.

Model	Parameters	Effects	References
Adolescents (N = 28; mean age = 16–19 years)	Diffusion tensor imaging analysis of Fractional Anisotropy (FA)	Binge drinking resulted in a widespread reduction of FA in major white matter pathways	McQueeny et al., 2009
Adolescents (N=59; men age = 16–19 years)	MRI analysis of brain morphometry	Binge drinking females showed thicker cortices in the frontal pole, pars orbitalis, medial orbital frontal, and rostral anterior cingulate	Squeglia et al., 2012
Adolescents (N = 38; mean age = 22–24)	MRI analysis of voxel-based morphometry	Binge drinkers showed larger ventral striatal gray matter volume	Howell et al., 2013
Adolescents (N = 54; mean age = 18–22 years)	High-resolution MRI analysis	Binge drinkers showed a significant reduction in cortical thickness in the mid-ACC	Mashhoon et al., 2014
Adolescents (N = 32; mean age = 21–23 years)	Structural MRI analysis of voxel-based morphometry	Binge drinkers showed larger gray matter volume in the left mid-dorsolateral PFC	Doallo et al., 2014
Adolescents (N = 674; mean age = 12–21.9 years)	T1-weighted MRI analysis	Binge drinking decreased the volume of both frontal and temporal lobes of the cortex	Pfefferbaum et al., 2016
Adolescents (N = 36; mean age = 18–23 years)	T1-weighted MRI analysis	Binge drinkers showed increase nucleus accumbens volume	Sousa et al., 2019
Adolescents (N = 166; mean age = 12–21 years)	High-resolution structural MRI analysis	Binge drinkers showed decrease cortical gray matter volume	Infante et al., 2022
Adolescents (N = 44; mean age: baseline = 18–19 years; follow-up 20–21 years)	Magnetic resonance imaging analysis	Binge drinkers showed larger insular surface area, and a sex-specific decrease in the right rostral middle frontal gyrus thickness, and in NAcc volume	Pérez-García et al., 2022

associated with an increase in immature spines that are known to have increased plasticity when compared to more mature dendritic spines. More recent work has demonstrated similar shifts in dendritic spine phenotype within select sub-regions of the prefrontal cortex that are suggested to be associated with a loss of astrocyte support (Walker et al., 2022). Physiologically, the mechanisms modulating alcohol-induced synaptic alterations warrant further study. However, given the findings shown here, it is evident that adolescent intermittent alcohol exposure alters synaptic protein expression and synaptic function, likely contributing to changes in synaptic excitation and subsequent cognitive changes.

Quantification of the measures discussed in the manuscript is rather straightforward in rodent models, however, this becomes more challenging in patient populations. This could be in part due to the unpredictability of the reliance on memory recall and estimation of drink number following intoxication that some retrospective studies employ. Unlike rodent studies where binge drinking, environment, and environmental stressors can be carefully controlled, in longitudinal and cross-sectional studies, it is difficult to truly characterize the true extent of binge drinking in adolescents along with the variety of drivers of such behaviors, thus potentially increasing data variability. Additionally, since most of these retrospective studies rely on answers provided by binge drinkers in surveys, there could be variations in the data collected, especially when adolescents are asked whether they indulge in polysubstance use. These limitations could contribute to the lack of clear parallels between rodent and human studies concerning hippocampal impairment following binge alcohol consumption. Nonetheless, it is worth noting that these retrospective studies have contributed significantly to the field of study and are incredibly valuable to the field of adolescent alcohol in understanding how additional variables contribute to the onset and emergence of AUD. Altogether, the experimental evidence highlighted here suggests that binge drinking during adolescence could modify select brain regions, alter microstructure volume, decrease neurogenesis, affect synaptic integrity, and enhance cell damage and/or cell death, resulting in neuropathological consequences during adulthood. In addition to the structural modifications and consequences highlighted above, the ensuing section reviews how binge alcohol-induced structural modifications can impact higher cognitive abilities in adolescents.

5. Effect of adolescent binge drinking on higher cognitive abilities

Research topics focusing on insult to the adolescent brain are of great interest because of the critical transformations that occur during this time-period and clear evidence of adolescent susceptibility to the effects of alcohol. Higher cognitive abilities or executive functions are sets of behaviors that emerge during the early ages of childhood and continue to develop during

TABLE 2 Summary of studies exploring the effect of adolescent binge-like ethanol intake in rodent models.

Model	Parameters	Effects	References
Male Sprague-Dawley rats (beginning PND35)	Intragastric gavage of single dose ethanol (1.0, 2.5, or 5.0 g/kg, 25% v/v in saline)	Acute ethanol exposure inhibited neural progenitor cell proliferation in the dentate gyrus, forebrain regions, and subventricular zones	Crews et al., 2006
Wister rats (Beginning PND25)	Intraperitoneal administration of ethanol (3.0 g/kg; 25% w/vol), 2-days on/2-days off	Binge-like ethanol administration increased inflammatory cytokine expression, enhanced cell death in the neocortex, hippocampus, and cerebellum	Pascual et al., 2007
Sprague-Dawley rats (Beginning PND28)	Intragastric gavage of ethanol (1.5, 3.0, or 5.0 g/kg; 25% w/vol), 4-day binge model	Repeated binge-like ethanol administration during adolescence enhanced ethanol consumption during adulthood	Maldonado-Devincci et al., 2010
Long-Evans rats (Beginning PND35)	Intraperitoneal administration of ethanol (3.0 g/kg; 25% w/vol), 2-days on/2-days off	Binge-like ethanol administration caused sex-specific decrease in the number of glia cells in the mPFC	Koss et al., 2012
Male Sprague-Dawley rats (beginning PND30)	Intraperitoneal administration of ethanol (3.0 g/kg; 25% w/vol) for 2 consecutive days at 48 h-intervals; followed by operant drinking task	Bine-like ethanol administration during adolescence enhanced motivation for ethanol self-administration during adulthood	Alaux-Cantin et al., 2013
Male Wister rats (Beginning PND 28)	Operant self-administration of sweetened alcohol (8–10% w/v ethanol)	Binge-like ethanol consumption reduced myelin density in the mPFC of adolescent rats	Vargas et al., 2014
Female C57BL/6 Mice (Beginning PND30)	Intraperitoneal administration of ethanol (3.0 g/kg; 25% w/vol), 2-days on/2-days off	Binge-like ethanol exposure increased cytokines and pro-inflammatory mediators levels, resulting in ultrastructural myelin sheath disarrangement in the PFC	Montesinos et al., 2015
Male Sprague-Dawley rats (Beginning PND30)	Intragastric gavage of ethanol (5.0 g/kg, 35% w/v), 2-days on/1-day off, 2-days on/2-days off	Binge-like ethanol exposure decreased the number of mature dendritic spines, and reduced post-synaptic proteins in the hippocampus	Risher et al., 2015c
Male C57BL/6 mice (Beginning PND30)	Intraperitoneal administration of single (2.5 g/kg, twice plus 2 g/kg 2-h apart) or multiple dose ethanol	Multiple binge-like ethanol exposure decreased the number of progenitor cells in the hippocampus with deficits in short-term memory	Lacaille et al., 2015
Male Sprague-Dawley rats (beginning PND35)	2 Intraperitoneal administrations of ethanol (3 g/kg; 20% vol/vol) 9 h apart	Ethanol-treated rats failed to recognize a novel object, an indication of alcohol-induced cognitive deficit	De Ferron et al., 2015
Female Wister rats (Beginning PND25)	Intragastric administration of ethanol (5.0 g/kg; 20% w/vol), 2-days on/2-days off	Binge-like ethanol consumption reduced axial diffusivity (PND80-220) in the cerebellum, hippocampus, and neocortex	Vetreno et al., 2016
Male Wister rats (Beginning PND26)	Two-bottle choice paradigm of ethanol (20%) and water; followed by an operant drinking task (fixed ratio)	Rats exposed to ethanol during adolescence recorded fewer fixed ratio failed response, and consumed more alcohol during adulthood	Amodeo et al., 2017
Wister rats (Beginning PND25)	Intragastric administration of ethanol (5.0 g/kg; 20% w/vol), 2-days on/2-days off	Binge-like ethanol exposed rats showed bilateral thinning of the PFC, with reduced hippocampal and cerebellar volumes	Vetreno et al., 2017
Male Sprague-Dawley rats (Beginning PND25)	Intraperitoneal administration of ethanol (3.0 g/kg; 25% w/vol), 2-days on/-day off	Binge-like ethanol administered rats showed impaired synaptic plasticity with alterations in learning and memory tests	Tapia-Rojas et al., 2018
Male Sprague-Dawley rats (beginning P30)	Intragastric gavage of ethanol (5.0 g/kg, 35% w/v), following AAV microinjection of green fluorescent protein tag	Binge-like ethanol administration induced PFC subregion-specific changes in dendritic spine maturity with changes in astrocyte-neuronal interactions	Walker et al., 2022

TABLE 3 Summary of behavioral studies exploring the effect of binge drinking in adolescents during cognitive tasks.

Model	Task	Effects	References
Memory			
Adolescents (N = 27; mean age = 18–23 years)	Neuropsychological assessment of sustained attention and long-term memory (recall tasks)	Binge drinkers performed poorly on the sustained attention and recall tasks	Hartley et al., 2004
Adolescents (N = 95; mean age = 18–20 years)	ERP analysis of visual task	Binge drinking affects the execution of a visual task with a high working memory load	Crego et al., 2009
Adolescents (N = 24; men age = 16–18 years)	fMRI analysis of verbal encoding task	Binge drinkers showed no hippocampal activation during novel encoding and performed poorly during word pair recall	Schweinsburg et al., 2010
Adolescents (N = 95; mean age = 18–20 years)	ERP analysis of identical pair continuous performance task	Binge drinkers showed hypoactivation of the right anterior PFC for matching stimuli during the performance task	Crego et al., 2010
Adolescents (N = 95; mean age = 16–19 years)	fMRI analysis of spatial working memory task	Binge drinking females showed less frontal, temporal, and cerebellar brain activation which correlated with poor working memory performances	Squeglia et al., 2011
Adolescents (N = 122; mean age = 18–20 years)	Neuropsychological assessment of spatial and verbal working memory	Binge drinkers recorded lower scores during the verbal working memory test	Parada et al., 2012
Adolescents (N = 89; mean age: baseline = 18–19 years; follow-up 20–21 years)	Neuropsychological assessment of episodic memory and executive functions	Persistent binge drinkers performed poorly on episodic memory task	Mota et al., 2013
Adolescents (N = 32; mean age = 19–24 years)	fMRI analysis of working memory task	Binge drinkers showed higher working memory-related brain activation in the dorsomedial PFC	Campanella et al., 2013
Adolescents (N = 155; mean age baseline: 18–19 years; follow-up 24–25 years)	Neuropsychological assessment of verbal episodic memory task	Stable binge drinkers during the follow-up demonstrated verbal episodic memory deficits	Carbia et al., 2017
Inhibition			
Adolescents (N = 48; mean age: baseline = 18–19 years; follow-up 20–21 years)	ERP analysis of go/no-go task	Binge drinkers showed hyperactivation of the right inferior cortex during response execution and inhibition response	López-Caneda et al., 2012
Adolescents (N = 23; mean age = 18–20 years)	fMRI analysis of go/no-go task	Recent binge drinkers showed decreased activation of both dorsolateral and dorsomedial PFC, and ACC during negative inhibitory trials	Cohen-Gilbert et al., 2017
Adolescents (N = 67; mean age = 18–19 years)	fMRI analysis of alcohol-cued go/no-go task	Binge drinkers showed increase neural activity in the bilateral inferior frontal gyrus and insula during response inhibition	Suárez-Suárez et al., 2020
Reward and decision-making			
Adolescents (N = 200; mean age = 16–18 years)	Neuropsychological assessment of Iowa Gambling task	Stable high binge drinkers made less advantageous choices on the IG task which is associated with poor decision-making	Goudriaan et al., 2007
Adolescents (N = 28; mean age = 16–18 years)	fMRI analysis of Iowa Gambling task	Binge drinkers perform worse on the IG task and showed higher neural activity in the left amygdala and insula	Xiao et al., 2013
Adolescents (N = 48; mean age: baseline = 14–16 years; revisit 16–18 years)	fMRI analysis of Wheel of Fortune (reward processing) task	Binge drinkers showed reduced cerebellar brain activity at revisit during the reward processing task	Cservenka et al., 2015
Emerging adults (N = 50; mean age = 21–29 years)	fMRI analysis of a reward-guessing game (the Doors' task)	Binge drinkers showed enhanced activation in the right and left NAcc during reward processing relative to loss	Crane et al., 2017
Adolescents (N = 50; mean age = 21–22 years)	ERP analysis of Iowa Gambling task	Binge drinkers recorded lower total net score which correlates with poor decision-making	Na et al., 2019

adolescence and the early twenties (Crone, 2009; Gil-Hernandez et al., 2017), and are important for appropriate integration and adaptation to society (Jurado and Rosselli, 2007). The development of working memory, learning, attention, decision-making, effective planning, cognitive flexibility, inhibition, and self-control are important during maturation. However, binge alcohol consumption during adolescent brain development has been shown to affect these cognitive functions in both rodent and human studies (Goudriaan et al., 2007; Schweinsburg et al., 2010; De Ferron et al., 2015; Carbia et al., 2017; Patte et al., 2017; Tong et al., 2021).

To fully understand how binge alcohol consumption affects these core functions in adolescents (**Table 3**), studies are currently using encoding cues and different learning tasks to assess human behavior following binge alcohol exposure. In a preliminary human study comparing the performance of verbal encoding tasks in adolescent binge drinkers vs. non-drinkers, Schweinsburg et al. (2010) report that those with a history of binge drinking performed poorly on the task. This finding supports the notion that alcohol can impair the learning or processing of new word pairs. Working memory is another important feature of executive functioning and information processing system that maintains information over a brief period (Tapert et al., 2004). However, adolescents and young adults who engage in binge drinking have been shown to have altered neuronal activity during working memory (Crego et al., 2009, 2010; Squeglia et al., 2011; Campanella et al., 2013; López-Caneda et al., 2013a). For example, in their study involving human subjects, Tapert et al. (2004) identified a negative relationship between brain activity for a task involving visual working memory and alcohol response. In their experiment, healthy adolescents with different drinking habits were recruited and the consequences of acute alcohol were measured through neuropsychological testing. The data collected from this study revealed that adolescents who needed to drink an increased volume of alcohol to achieve intoxication had enhanced stimulation in select brain regions (Tapert et al., 2004). Similarly, by measuring event-related potentials in college freshmen, Crego et al. (2009) found functional differences in a visual task involving a high working memory load. In their experiment, college freshmen who engage in binge drinking required higher attentional effort to carry out the assigned visual task compared to the control group. In another experiment, increased stimulation in the superior frontal gyrus (SFG), inferior parietal lobule (IPL), and supramarginal gyrus was recorded in adolescents who engaged in binge drinking compared to their non-drinking peers under baseline conditions (Squeglia et al., 2012). Given the role of the prefrontal cortex in executive functions, it is important that studies highlight the impact of binge drinking on functions subserved by the prefrontal cortex. For example, by examining the effect of binge drinking on the dorsolateral prefrontal cortex, Parada et al. (2012) report that binge drinking impacts executive control of working memory in college students. A more recent study by Carbia et al. (2017) investigating the effect of binge drinking on verbal episodic memory, demonstrated that adolescents who binge drink showed episodic memory deficits compared to non-binge drinkers. These studies further highlight the vulnerability of the brain to the neurotoxic effects of alcohol.

In addition to working memory, the association between binge drinking and poor performance in attention, learning, and visuospatial abilities has been examined (Hartley et al., 2004; Squeglia et al., 2011; Mota et al., 2013). For example, Squeglia et al. (2011) found binge-drinking females performed poorly in visuospatial, inhibition, and attention tasks when compared to their non-drinking females. These sex-specific cognitive deficits were attributed to alterations in the cortical thickness of gray matter. The relationship between adolescent alcohol consumption and inhibitory control has also been extensively studied in the last decade. The central hypothesis of these studies is that the inability to inhibit a response (i.e., alcohol use) during adolescence, could promote excessive alcohol consumption (López-Caneda et al., 2013b). To test this hypothesis, Norman et al. (2011) used a go/no-go task to examine response inhibition in relation to alcohol and other substance use in middle schoolers. In their experiment, decreased neural activity in brain regions such as the cingulate gyrus, and left dorsal and medial frontal areas during response inhibition predicted later alcohol use. It has also been determined that college students who engaged in a higher incidence of binge drinking in the last 3 months have altered neural activity in distinct frontal brain regions that are involved in inhibition response (Cohen-Gilbert et al., 2017). Specifically, in this experiment, reduced activation of brain regions such as the ACC, dorsolateral prefrontal cortex, and dorsomedial prefrontal cortex was evident in students with higher recent incidence of binge drinking during the go/no-go inhibitory control task (Cohen-Gilbert et al., 2017). In a more recent study that explored the impact of binge alcohol consumption on brain regions implicated in inhibition response, Suárez-Suárez et al. (2020) recorded enhanced neural activity in brain regions such as the inferior frontal gyrus, and the anterior insula when binge drinking college students were asked to perform alcohol-cued go/no-go task. Given that impairment in response inhibition has been suggested to contribute to substance use disorder (Zilverstand et al., 2018), several studies are investigating the effect of binge drinking on other frontal brain regions. For an extensive review of how alcohol consumption alters inhibitory control during adolescence see (Loeber and Duka, 2009; López-Caneda et al., 2012; Wetherill et al., 2013; Campanella et al., 2017; Blanco-Ramos et al., 2019). It is well-established that during adolescence risky behaviors such as alcohol and drug use increase (Eaton et al., 2012). Physiologically, these risk-taking behaviors have been attributed to the development and remodeling of reward-related neurocircuitry that continues to

mature during adolescence (Galvan, 2010). Similarly, it has been determined that exposure to alcohol during the formative years enhances the motivation for alcohol through novelty-seeking with unintended consequences on motor function (White et al., 2000; Stansfield and Kirstein, 2007), due to alcohol-induced alterations in neurochemical markers in the prefrontal cortex. In attempts to establish the relationship between novelty seeking and motivation through human studies, Van Dyke and Fillmore (2015) used a cue reactivity paradigm that involves exposing drinkers to either images of beer or a series of non-drink images (i.e., food items), and then measuring motivation for operant response task. Reports from their experiment showed that alcohol-related cues increased operant response behavior in drinkers. The impact of adolescent binge drinking on reward and decision-making processes has also been reported in the literature. For example, by using the Iowa Gambling Task (IGT) as a decision-making parameter, a longitudinal study by Goudriaan et al. (2007) found an association between binge drinking and poor decision-making. Specifically, in their experiment, college students who were identified as stable high binge-drinkers made less advantageous choices on the gambling task than their low binge-drinking peers. In a recent study that used event-related potential (ERPs) and IGT to assess the impact of binge drinking on decision-making in female college students, Na et al. (2019) found a strong correlation between binge drinking and decision-making deficits. As shown previously, alterations to brain regions that mediate the decision-making process following binge alcohol consumption offer potential explanations to the deficits in decision-making observed in these two studies. Given the change in brain structure and neurocircuitry during adolescence, it is important to understand the impact of binge drinking on reward-driven behaviors. In a study that aimed to determine the potential impact of alcohol on reward processing in college binge drinkers, Cservenka et al. (2015) used a modified version of the Wheel of Fortune (WOF) coupled with functional magnetic resonance imaging. In their longitudinal study, Cservenka et al. (2015) found reduced cerebellar brain activity during reward processing in binge drinkers compared with the control group. The reduction in cerebellar brain activity in binge drinkers negatively correlated with the amount of alcohol consumed in the last 90 days (Cservenka et al., 2015). In another study that examines brain reactivity *via* a reward-guessing game (i.e., Win vs. Loss), Crane et al. (2017) found enhanced NAcc activation in their healthy binge drinking sample compared to the non-binge drinking group during reward processing relative to loss. As stated previously, the NAcc is critical for reward and sensation-seeking in adolescence (Morales et al., 2019), hence its enhanced activation in binge drinkers could be a risk factor for developing AUD later in life. Taken together, these results further support the hypothesis that binge alcohol consumption could cause structural and functional changes to frontal brain regions such as the superior frontal gyrus (SFG), inferior parietal lobule (IPL), and supramarginal gyrus (Squeglia et al., 2012), anterior cingulate cortex (Mashhoon et al., 2014; Cohen-Gilbert et al., 2017), cingulate gyrus (Norman et al., 2011), inferior frontal gyrus, and anterior insula (Suárez-Suárez et al., 2020), and other areas such as the cerebellum (Cservenka et al., 2015), and NAcc (Crane et al., 2017), potentially contributing to deficits in abilities such as decision making (Goudriaan et al., 2007), working memory (Campanella et al., 2013), verbal encoding (Schweinsburg et al., 2010), and inhibition response (Suárez-Suárez et al., 2020).

As stated previously, adolescent binge alcohol consumption leads to undesired neurobiological changes and exacerbates the risk of developing AUD during adulthood. Since many of the affected brain regions are involved in the modulation of reward and response to negative emotions, some studies are currently examining whether adolescent binge drinking reinforces further consumption and contributes to the development of AUD later in life. Experimentally, it has been determined that binge drinking at an early age enhances alcohol consumption in rodent models. For example, by using a four-day binge model, and analyzing dose and sex-related changes that occur when adolescent (PND 28) male and female Sprague Dawley rats are continuously administered different concentrations of ethanol, Maldonado-Devincci et al. (2010) observed that exposure to ethanol during adolescence pre-disposed the rats to consume more ethanol in adulthood. Currently, the use of operant tasks is being explored to enhance our understanding of the impact of adolescent binge drinking and alcohol use later in life. Alaux-Cantin et al. (2013) using Sprague-Dawley rats administered binge-like ethanol concentrations and demonstrated an association between early ethanol consumption and increased motivation to self-administer ethanol in young adults. Similar positive relationships between adolescent alcohol exposure in rats and increased alcohol consumption during adulthood have been reported in a recent experiment by Amodeo et al. (2017). In addition to increasing alcohol consumption later in life, it has also been shown that administering binge-like ethanol concentration (i.e., 3 g/kg) to adolescent rats by intraperitoneal injection can lead to cognitive deficits as demonstrated in the novel object recognition test (De Ferron et al., 2015). In a more recent study, Van Hees et al. (2022) demonstrated that adolescent mice that voluntarily binge drink alcohol *via* a modified drinking in the dark paradigm performed poorly on a novel object recognition test. In another study investigating the relationship between alcohol intermittent exposure and risk-seeking behaviors in rodents, Boutros et al. (2014) recorded a negative relationship between risky choices and the levels of dopamine, norepinephrine, and choline in alcohol-exposed rats. These experiments further support the premise that adolescent binge drinking reinforces further consumption and could contribute to the development of AUD later in life. In summary, through the human data

and rodent adolescence models outlined here, there is enough evidence to demonstrate that binge alcohol consumption impairs cognitive functions such as visuospatial processing, working memory, learning, attention, inhibition response, and decision-making.

6. Discussion and future directions

Adolescence is a transitional period that is marked by biological changes that include brain maturation. Due to continued brain development during this stage, it is vulnerable to the effects of illicit drugs and alcohol which can lead to cognitive deficits later in life. The rate and amount of alcohol consumed by adolescents can be excessive (Adan et al., 2016; Hermens and Lagopoulos, 2018) and has been linked to cognitive dysfunction, behavioral conflict, unsafe sexual practices, vehicular accidents, and increased likelihood of developing AUD later in life (Hansson et al., 2010, Hong et al., 2013; Moure-Rodríguez et al., 2016; Hingson et al., 2017). Based on these concerns, many studies are currently exploring the impact of binge drinking on specific regions of the brain, especially areas that mediate higher cognitive functions (Crego et al., 2010; López-Caneda et al., 2012; Mashhoon et al., 2014). Through extensive research, it has been determined in both human and rodent models that binge alcohol consumption during adolescence disrupts white and gray matter development and normal function of cortical and hippocampal areas. Neuronal death and impaired adult neurogenesis appear to be consistently impacted across studies and likely involve the activation of non-neuronal cells and pro-inflammatory signaling. All of these factors likely contribute to alcohol-induced cognitive impairment that can persist into adulthood and can include the disruption of learning, attention, working memory, impulsivity, decision-making, and inhibition response. Even though significant steps have been taken to understand the impact of adolescent binge alcohol on neurocognitive function, future studies need to build on the knowledge gained from different fields of study. For example, using sequencing techniques to help understand the temporal changes that occur at the gene level during normal adolescent development and under the influence of chronic intermittent ethanol exposure is needed. These studies should be compared to GWAS data collected from patients and families with a history of AUD. Combined approaches to understand the fundamental changes in non-neuronal and neuronal cell interactions and responses to adolescent alcohol need to be rigorously addressed to further understand the cell-to-cell signaling mechanisms involved in the pro-inflammatory responses that occur acutely and during abstinence. Further work is needed to understand the drivers of alcohol-induced gray and white matter loss and how these changes impact the ongoing development of projecting neuronal circuitry, critical for higher cognitive function and reward-related behavior. Not surprisingly, comparative studies to further our understanding of sex differences need to be employed with the consideration of whether male optimized behavioral assays are also appropriately optimized for female rodent models of cognition. The development of new technologies, employing integrative methodologies, designing translationally relevant binge drinking paradigms in animal models that augment human studies, and examining cellular markers in a sex-specific manner would enhance our understanding of how binge drinking affects brain maturation during the formative years and leads to unintended neurocognitive complications.

7. Conclusion

The aim of this review is to discuss the maturational changes that occur in the adolescent brain and evaluate the effects of adolescent alcohol consumption on brain structure, function, and neurocognitive abilities in both human and animal models. As shown here, the adolescent brain undergoes important maturational changes necessary for effective brain development. However, at the same time, the brain also becomes susceptible to the neurotoxic effects of alcohol. During adolescence, negative impacts can emerge from peers, parents, and the environment, and contribute to increased binge alcohol consumption resulting in undesirable neurocognitive consequences. There is a need for more temporal, neuropathological studies on adolescent brain maturation across cell types with brain sub-region specificity that consider the impact of sex with and without binge alcohol exposure. There is no doubt that the knowledge gathered from both cross-sectional and translational studies will continue to provide a further understanding of the mechanisms that underlie the cognitive deficits that persist and/or emerge during abstinence. Continued investigation into this area of research will help create useful policies and clinical interventions to treat complications related to adolescent binge drinking across the lifespan.

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Longitudinal change of inhibitory control functional connectivity associated with the development of heavy alcohol drinking

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Introduction: Heavy drinking (HD) prevalent pattern of alcohol consumption among adolescents, particularly concerning because of their critical vulnerability to the neurotoxic effects of ethanol. Adolescent neurodevelopment is characterized by critical neurobiological changes of the prefrontal, temporal and parietal regions, important for the development of executive control processes, such as inhibitory control (IC). In the present Magnetoencephalography (MEG) study, we aimed to describe the relationship between electrophysiological Functional Connectivity (FC) during an IC task and HD development, as well as its impact on functional neuromaturation.

Methods: We performed a two-year longitudinal protocol with two stages. In the first stage, before the onset of HD, we recorded brain electrophysiological activity from a sample of 67 adolescents (mean age=14.6±0.7) during an IC task. Alcohol consumption was measured using the AUDIT test and a semi-structured interview. Two years later, in the second stage, 32 of the 67 participants (mean age 16.7±0.7) completed a similar protocol. As for the analysis in the first stage, the source-space FC matrix was calculated, and then, using a cluster-based permutation test (CBPT) based on Spearman's correlation, we calculated the correlation between the FC of each cortical source and the number of standard alcohol units consumed two years later. For the analysis of longitudinal change, we followed a similar approach. We calculated the symmetrized percentage change (SPC) between FC at both stages and performed a CBPT analysis, analyzing the correlation between FC change and the level of alcohol consumed in a regular session.

Results: The results revealed an association between higher beta-band FC in the prefrontal and temporal regions and higher consumption years later. Longitudinal results showed that greater future alcohol consumption was associated with an exacerbated reduction in the FC of the same areas.

Discussion: These results underline the existence of several brain functional differences prior to alcohol misuse and their impact on functional neuromaturation.

KEYWORDS

binge drinking, functional connectivity, MEG, inhibitory control, adolescence, heavy drinking

Introduction

Heavy Drinking (HD) is a prevalent pattern of alcohol consumption among adolescents, which has become a major social and health concern. In adolescent population, such pattern of HD behaviors is characterized by the so-called Binge Drinking (BD) pattern, which consist in the ingest of at least four standard alcohol units (SAUs-10 mg ethanol-) in women, or five in men, within 2 h, followed by short abstinence periods (Courtney and Polich, 2009). It drives the organism into an ethylic intoxication state, with harmful neurobiological and neuropsychological consequences (Squeglia et al., 2014; Carbia et al., 2018; Almeida-Antunes et al., 2021). During adolescent neurodevelopment, the nervous system is engaged in a series of critical neurobiological changes, involving important high-order brain regions, making teenagers especially vulnerable to the outcomes of HD consumption (Blakemore and Choudhury, 2006; Crews et al., 2007). The development of the prefrontal, temporal, and parietal regions is particularly prominent during this period, characterized by delayed and progressive cortical thinning, and increasing structural connectivity (Spear, 2013). At the functional level, the adolescent brain shows a progressive reduction of electrophysiological local activation during cognitive tasks (Segalowitz et al., 2010). Along with this neurobiological maturation comes the improvement of higher-order executive functions. Despite the multiple definitions of executive functions, they can be understood as cognitive skills oriented to the planning, control, and supervision of complex thoughts and behavior (Jurado and Rosselli, 2007). Among other executive processes, inhibitory control (IC) is crucial in the behavioral regulation and proposed as a core function affected by and involved in the development of HD consumption (López-Caneda et al., 2014).

Some studies have evidenced the electrophysiological consequences of HD regarding IC, featured by a greater activation of supplementary motor areas, the right inferior frontal cortex (López-Caneda et al., 2012; Suárez-Suárez et al., 2020), as well as increased frontoparietal synchronization during the inhibition of alcoholic stimuli (Blanco-Ramos et al., 2022). Overall, these studies show altered neurofunctional activity during IC processes, despite not detecting differences in behavioral performance (see Almeida-Antunes et al., 2021) for a systematic review of electrophysiological signatures associated with BD consumption).

Nevertheless, despite the valuable evidence provided by those studies, their cross-sectional nature has some limitations when drawing causal inferences. Over the last decade, there has been raising concern about the existence of potential factors which predispose some individuals to engage in hazardous behaviors such as HD. In this scenario, albeit scarce, some longitudinal studies have provided evidence regarding neurobiological and neurocognitive differences predating HD. Focusing on IC, neuropsychological prospective works have highlighted poorer IC as predictive of future heavy drinking episodes (Squeglia et al., 2014; Peeters et al., 2015). Regarding neuroimaging studies, fMRI works reported reduced BOLD signal during IC tasks in frontal, parietal, and temporal regions predating HD, joint to an increase of BOLD response after HD initiation (Wetherill et al., 2013). Concerning electrophysiological evidence, previous MEG study evidence increased synchronization between frontotemporal regions during successful inhibitory responses before HD initiation, being associated with worse dysexecutive and impulsive symptomatology (Antón-Toro et al., 2021). However, electrophysiological studies exploring this important question from a prospective design, and even more so, studies from the perspective of functional connectivity, are still lacking.

Electrophysiological techniques, like magnetoencephalography (MEG), provide a direct measure of neural oscillatory activity with an excellent temporal resolution and good spatial resolution. These measures are optimal to explore fast oscillatory dynamics as those associated with IC processes (Cohen, 2011). Functional connectivity (FC), defined as the statistical dependence between the activity of two or more brain regions (Friston, 1994), discloses important information regarding dynamic neural synchronization. This allows studying the integrity of neural networks associated with relevant cognitive processes, and neuropsychiatric conditions (Baillet, 2017). Among the different FC metrics, the phase locking value (PLV) (Bruña et al., 2018), based on phase coupling theories, has shown the highest consistency and robustness applied to electrophysiological data (Garcés et al., 2016).

The current work aims to explore the relationship between the electrophysiological FC signatures during an IC task and heavy alcohol consumption, before and after its initiation. For this purpose, we conducted a two-year longitudinal study over a cohort of initially alcohol naïve adolescents. We recorded their electrophysiological activity by means of MEG during an IC task (go/no-go). We analyzed the relationship between their IC functional connectivity and the intensity of future alcohol consumption. Two years later, we studied the longitudinal change in FC between pre-and post-alcohol initiation stages, exploring its relationship with the intensity of alcohol consumption. According to previous reports, we expect an increased FC of fast oscillatory bands in core IC regions associated with higher consumption rates years later. After HD initiation, we hypothesize a switch in that pattern, with a greater decrease in FC in those adolescents who show greater consumption rates.

Materials and methods

Participants

We recruited an initial sample formed of 611 adolescents from different secondary education schools in the community of Madrid. All subjects reported no previous alcohol intake, familiar history of alcohol misuse, and no psychiatric or neurological disorders. All participants fulfilled the *Alcohol Use Disorder Identification Test* (AUDIT), and those who reported previous alcohol use episodes were discarded from the experiment. From this initial sample, 67 right-handed adolescents accepted to participate in the neuroimaging study. In the first stage ("Stage pre"), all participants completed again the AUDIT test and a personal semi-structured interview, in order to ensure that they had no previous alcohol use. Brain electrophysiological activity of each participant was recorded by MEG during the performance of an inhibitory control task go/no-go. Two years later, in the second stage ("Stage post"), 32 participants fully completed the experimental protocol. All 32 participants (mean age "stage pre" 14.6 ± 0.7; mean age "stage post" 16.7 ± 0.7) went through a similar protocol; they fulfilled the AUDIT test and a semi-structured interview to measure their alcohol consumption habits. Also, they completed a MEG recording during the go/no-go task. Based on the information from the AUDIT and the interview, for each participant, we calculated the number of SAUs ingested in a regular consumption episode. We took into consideration the number of drinks within 2–3 h and the type of beverage. Tobacco and cannabis consumption was controlled by means of self-reported tests and personal interview. Only four participants showed tobacco consumption in very low doses (less than 5 cigarettes per day), and three

of those four participants had ever consumed cannabis (between one and eight joints in total). All participants were asked not to consume alcohol or other psychoactive drugs in the 48 h prior to the MEG recording (96 h in the case of cannabis use). All participants and their parents or legal guardians signed informed consent for each stage of the study, following the guidelines in the declaration of Helsinki. The ethical committee of the Universidad Complutense de Madrid approved the study.

MEG recordings and data processing

MEG data were acquired using a 306-channel Elekta Neuromag system located in the Center for Biomedical Technology (Madrid, Spain), using an online anti-alias filter between 0.1 and 330 Hz and a 1,000 Hz sampling rate. Environmental noise was reduced using an offline signal space separation method (Taulu and Simola, 2006), and subject movements were compensated using the same algorithm. The acquired data were segmented into event-related epochs, and artifacted epochs were discarded from subsequent analyses. Only successful inhibitory trials were considered for further analysis. Additionally, only those participants with a performance accuracy (correct inhibitions) higher than 60% were considered for the final sample.

MRI recording

A structural MRI was obtained from each participant using a General Electric Optima MR450w 1.5 T machine. Imaging protocol consisted in 3D T1-weighted high-resolution images with the following parameters: TE = 4.2, TR = 11,2 and TI = 450 ms, Flip angle = 12°, FoV = 100, acquisition matrix = 256 × 256, and slice thickness = 1 mm.

Inhibitory task

An equiprobable go/no-go task measured the performance of inhibitory networks in the subjects (Lavric et al., 2004; López-Caneda et al., 2012). A total of 225 "go" trials and 225 "no-go" trials were presented randomly in two different blocks. Figure 1 shows structure and time parameters of task presentation. All participants responded in the first block with their right hand. In the second block, they were commanded to respond with the left hand.

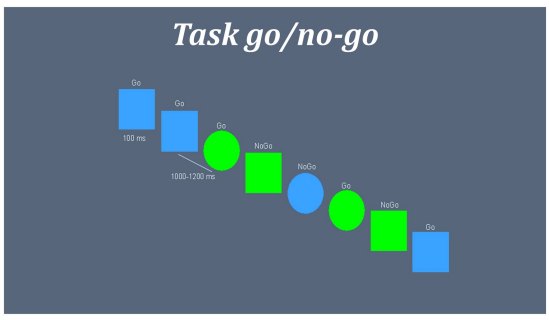

FIGURE 1
Representation inhibitory task go/no-go. Blue squares and green circles were set as "GO" targets, while green squares and blue circles were set as "NO-GO" targets. Inter stimuli interval were a random time between 1,000 and 1,200 ms. Stimulus were presented in screen during 100 ms followed by a fixation cross "+." GO and NO-GO trials were presented randomly.

Source-space reconstruction and functional connectivity analysis

We converted MEG signal into source-space using the subject's native T1 and a single shell approach as forward model (Nolte, 2003). As inverse model, we used a linearly constrained, minimum variance (LCMV) beamformer in three classical bands: Alpha (8–12 Hz), Beta (12–30 Hz), and Low Gamma (30–45 Hz). The source model consisted of 1,204 cortical sources, labeled according to the automatic anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Once calculated the spatial filter, we calculated the source-space functional connectivity matrix of successful inhibitory trials under the hypothesis of phase synchronization, using the PLV analysis (Lachaux et al., 1999; Bruña et al., 2018) in the time window of 250 to 350 ms after stimulus onset. We choose this time window based on previous literature, which highlights this temporal window as crucial in the inhibitory dynamics, and according to results of previous works (Antón-Toro et al., 2021), which evidence predominant differences in this time window. This metric is based on the study of the distribution of the instantaneous phase difference of two time-depending signals. If $\varphi_1(t,n)$ and $\varphi_2(t,n)$ are the instantaneous phase for instant t and trial n for signals 1 and 2, respectively, the value of PLV is given by:

$$PLV = \frac{1}{N}\sum_{n=1}^{N}\left|\frac{1}{T}\sum_{t=1}^{T}e^{i\left(\varphi_1(t,n)-\varphi_2(t,n)\right)}\right|$$

PLV value was calculated for each pair of cortical positions, obtaining a matrix of 1,204 × 1,204 for each frequency band and subject. From these matrices, we calculated the global FC for each cortical source, or "*nodal-strength,*" defined as the averaged FC of each cortical source with each other's, obtaining a FC of 1×1,204 sources for each subject and frequency band. This analysis protocol was replicated in pre-and post-stages. In a second step, in order to assess the change of FC between "*Stage-pre*" and "*Stage-post,*" we calculated the symmetrized percent of change (SPC). This approach offers an index of the bidirectional rate of change between two-time points considering the time variance within the sample. An SPC value equal to zero means the absence of change in FC between stages, while positive values reflect an increase, and negative values a decrease. The higher the absolute values, the higher the change in that direction. This calculation resulted in an SPC matrix of 1,204 × 1,204 for each frequency band and subject, reflecting the corrected differences in terms of PLV between "*Stage-pre*" and "*Stage-post.*"

Quality assessment for the source reconstruction

The beamformer is a spatial filter mapping the activity measured at the sensor level to the cortical space. Applying the beamformer spatial filter results on creating a single time series per source position, allowing to identify the brain activity related to a given cortical region. The correctness of this spatial filter is paramount in order to generate a

trustworthy representation of the cortical activity, and with it a correct representation of the FC patters in brain space.

As the task used in this work was a visual go/no-go task, a related activity should appear in posterior regions of the brain, mainly calcarine fissure and occipital pole, approximately 100 ms after the presentation of the stimulus. In order to evaluate the quality of the spatial filter, we performed a source reconstruction of this response. For each participant, we reconstructed the source-space time series and calculated the average power of each source position between 80 and 120 ms after the presentation of the stimulus. This average value was normalized to the average power during the baseline, defined between 300 and 1 ms before the presentation of the stimulus. This gives us a value of activation for each source position.

Figure 2 shows the result for this verification for the beta band in pre-and post-stages. The activity in the selected window maps correctly into visual areas, confirming the validity of the spatial filter. The rest of the bands are not displayed here but showed a similar behavior.

Statistical analysis

Initially, we explored in out sample the relationship between demographic variables (sex and age) with alcohol consumption habits. We conducted a between-group *t*-test analysis using sex (male or female) as the independent variable (IV), and the number of SAUs as the dependent variable (DV). To study the influence of age on alcohol consumption, we performed three Spearman's correlation analyses between age (pre-stage, post-stage, and age difference between pre-post stages) and the number of SAUs.

After, our main objective was to assess the relationship between the inhibitory control FC before alcohol use initiation, and the intensity of alcohol intake years later, as well as its relationship with the longitudinal changes of FC between both stages. First, using the "*Stage-pre*" FC matrix for each frequency band, we conducted a cluster based permutation test (CBPT) (Maris and Oostenveld, 2007) based on Spearman's correlation analysis. This analysis allows identifying a cluster of cortical sources with significant correlations between FC and the level of future consumption in non-parametric datasets. Secondly, we used a similar approach using the SPC matrix for each frequency band. We conducted an unconstrained CBPT analysis using the whole SPC matrix (without cortical restrictions based on "*Stage-pre*" results). All results were corrected for multiple comparisons by a Bonferroni stepwise method. Only the clusters which survived this correction were reported as significant. PLV metrics are known to be affected by source leakage effects. This issue was controlled by the direct estimation of main source leakage confounders and by verifying its independence from our results. This analysis is shown in the Supplementary material; Supplementary Table S3.

Besides, in some analysis toolboxes (like Fieldtrip), permutation analyses such CBPT have some limitations controlling the interaction of multiple variables. The permutations of the data are not designed to maintain any data as belonging to the participant (covariables), so the result would be a random re-assignation of all the variables. For this reason, to study the association of FC measures and alcohol consumption with factors of sex, age, and task performance-related variables, we conducted two *post-hoc* analyses. First, we used a multivariate stepwise regression analysis, using the consumption ratio (number of SAUs) as the dependent variable. As predictors, we used FC and age in the pre-consumption stage, gender, as well as task performance variables, such as ratio of correct inhibitions (no-go trials) and responses (go trials), and response reaction time. Secondly, we applied a multivariate regression analysis using the change in FC between pre-and post-stages as the dependent variable. As predictors, we introduced sex, age pre-post change, and consumption rate.

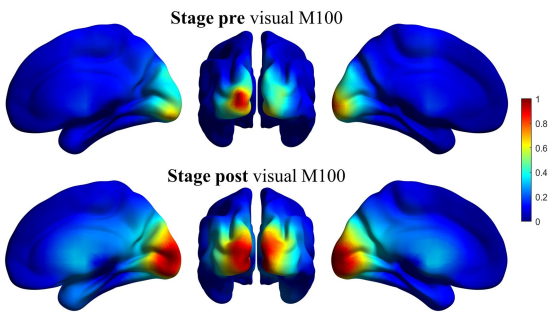

FIGURE 2
Representation of the source reconstruction of the primary visual response using the beamformer spatial filter for beta band. Grand average of the activity for all the participants. Left column: Ventral view of the right hemisphere. Middle column: Posterior view of both hemispheres. Right column: Ventral view of the left hemisphere. Superior line: pre-stage activity. Inferior line: post-stage activity. The activity is correctly reconstructed in occipital areas, mainly calcarine fissure. Similar results (not shown here) were obtained for the rest of the bands.

Results

Demographic results

We tested the relationship between sex and age with the level of alcohol consumption. Analyses did not show significant differences between sexes and SAUs level. Age correlation analysis did not show significant results with SAUs level. Table 1 shows the demographic features and the results of these analyses.

Functional connectivity results

We calculated global strength FC during an inhibitory control process both in the stage pre (before alcohol use initiation) and the stage post (2 years later, after alcohol use initiation). We analyzed the relationship of FC in the stage pre, and its change over 2 years between stages pre and post (SPC), with the level of alcohol intake in the "*Stage post*" (number of SAUs). Additionally, we studied the association of FC from each significant cluster with sex and age.

TABLE 1 Demographic alcohol consumption results.

Stage	Sex		Age	
	n (*F*, *M*)	*T* (*p*)	Mean (sd)	rho (*s*)
"Stage-pre"	11 F, 22 M	−7.34 (0.469)	14.6 (0. 7)	−0.034 (0.855)
"Stage-post"	–	–	16.7 (0.7)	0.003 (0.986)
Stage pre-post	–	–	2.09 (0.29)	0.133 (0.467)

Between-groups *t*-test analysis using Sex as IV and SAUs as DV did not show significant differences. Correlations between SAUs with Age-pre, Age-post, or Age pre-post difference did not show significant results. SAU = Standard Alcohol Unit; IV = Independent variable; DV = Dependent variable; pre = pre-consumption stage; post = post-consumption stage.

Regarding stage pre, the analysis revealed two clusters with positive correlations in the beta band with future alcohol use. The first cluster (cluster A) ($p = 0.0014$; $rho = 0.680$) was composed of 245 cortical sources mainly localized in the medial and right parts of the prefrontal cortex (superior, middle, inferior, and orbital frontal gyri), part of the left medial frontal gyrus, anterior and posterior cingulate cortices (ACC, PCC), right and medial temporal lobe (including hippocampus and parahippocampus), and parts of the right precuneus. The second cluster (cluster B) ($p = 0.0160$; $rho = 0.569$) was formed by 33 cortical sources located in the medial part of the somatosensorial and motor cortex, and the left middle cingulate cortex. Supplementary Table S1 depicts the percent of each region involved in each significant cluster. Both clusters indicate that the higher the FC in those regions, the higher the level of alcohol use 2 years later. Figure 3A shows the cortical distribution of each cluster and the graphical representation of each correlation.

Regarding stage pre-post, the analysis showed one cluster with a negative correlation in the beta band between connectivity SPC between both stages and the intensity of alcohol intake ($p = 0.004$; $rho = -0.670$). This cluster was composed of 290 cortical sources with a similar distribution to those found in both clusters of the stage pre. Additionally, this cluster encompassed a more expended part of the left prefrontal cortex (including the superior, middle, and inferior frontal gyri), the left inferior parietal gyrus, the left angular gyrus, and the left supramarginal gyrus. This cluster reflects that the higher the level of alcohol consumption, the greater decrease in FC between pre-and post-stages in those regions. Supplementary Table S1 depicts the percent of each region involved in each significant cluster. Figure 3B shows the cortical distribution of the cluster and the graphical representation of its correlation with alcohol use.

To ease the visual representation of the longitudinal relationship between FC and lower or higher alcohol intake, Supplementary Figure S1 represents the FC slopes between pre-and post-stages, subdividing the sample into low drinkers (SAUs <4) and heavy drinkers (SAUs >=4).

Post-hoc analysis results

Concerning *post-hoc* analyses, multivariate regression analysis of alcohol consumption predictors at pre-stage revealed a significant model where pre-consumption functional connectivity appears as a single and positive predictor of future alcohol consumption, explaining the 46% of the variance ($R^2_{corr} = 0.46$). This means that higher FC at pre-stage would predicts heavier alcohol intake in the future. Table 2 shows results for this analysis. Regarding regression analysis of FC change predictors, results show two significant models. In the first one, consumption rate is the

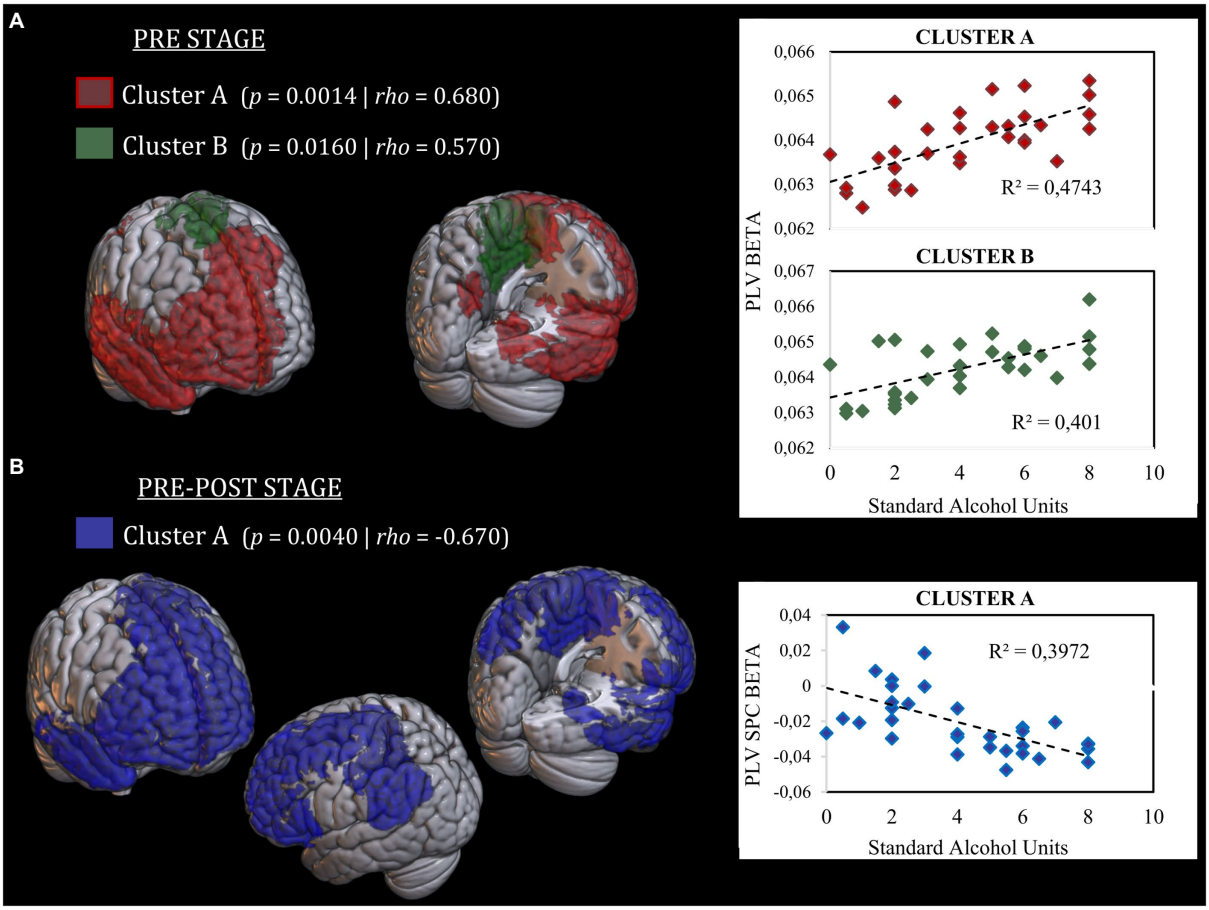

FIGURE 3
Representation of cortical distribution of significant clusters. **(A)** Significant clusters in the "*Stage-pre*" analysis. Cluster A is represented in red color. Cluster B is represented in green color. Both clusters show a positive correlation between FC and SAUs level. Scatter plots of correlation analysis are presented in the right side. **(B)** Significant clusters in the "*Stage pre-post*" analysis. Cluster A is represented in blue color. Cluster A show a negative correlation between SPC and SAUs level. Scatter plot of correlation analysis is presented in the right side. SAUs, Standard Alcohol Units; SPC, Symmetrized Percent of Change.

TABLE 2 Results of multivariate stepwise regression model at pre-stage.

Variables	*B*	E.T (*B*)	*β*	*t*	*p*	R^2_{cor}
Constant	−138,429	27,204		−5.089	0.000	0.46
FC stage-pre	2,227,452	425,186	0.691	5.239	0.000**	
Inh_acc_pre			0.208	1.614	0.117	
Resp_acc_pre			0.038	0.287	0.776	
RT_pre			0.210	1.636	0.113	
Age_pre			0.101	0.730	0.471	
Sex			0.242	1.889	0.069	

Number of SAUs were used as DV. FC cluster at pre-stage, sex, age-pre, and task performance variables (inhibition and responses accuracy, and responses RT) were used as predictors. Higher FC at pre-stage were predictor of heavy drinking development years later.
SAU = Standard Alcohol Unit; DV = Dependent variable; FC = functional connectivity; RT = reaction time; pre = pre-consumption stage; post = post-consumption stage.
**$p < 0.01$.

TABLE 3 Results of multivariate regression model between prepost-stages.

Variables	*B*	E.T (*B*)	*β*	*t*	*p*	R^2_{cor}
Constant	−0.004	0.007		0.531	0.559	0.42
SAUs	−0.005	0.001	−0.531	3.736	0.000**	
Age_diff			−0.144	−0.974	0.338	
Sex	−0.015	0.007	−0.313	−2.205	0.036*	

FC change (SPC) were used as DV. Number of SAUs, sex, and age pre-post difference were used as predictors. Higher alcohol intake was the main predictor of greater FC decrement between pre- and post-stages. Being male also predicts in a lesser degree greater FC decrement.
SAU = Standard Alcohol Unit; DV = Dependent variable; FC = functional connectivity; RT = reaction time; pre = pre-consumption stage; post = post-consumption stage; SPC = Symmetrized percent of change.
**$p < 0.01$, *$p < 0.05$.

main predictor of the change in FC between pre-post stages, explaining the 32% of the variance ($R^2_{corr\ =}$ 0.32). Heavier drinking habits would be predictive of greater decrement of FC between pre-and post-stages. In the second significant model, consumption rate is the main predictor of FC change together with sex in a lesser degree, explaining the 42% of the variance ($R^2_{cor\ =}$ 0.42). Heavier drinking habits and being male would be predictive of greater decrement of FC between pre-and post-stages, Table 3 shows results of this analysis.

Discussion

In this study, we aimed to describe the predisposing relationship between electrophysiological FC during inhibitory control (IC) task and the development of alcohol heavy drinking years later. Moreover, we analyzed the relationship between the longitudinal changes in FC and the intensity of alcohol misuse. In *Stage pre* (before alcohol use initiation), results showed that beta band FC in medial and right prefrontal regions and right temporal regions were positively associated with future alcohol consumption. This is, the higher the FC predating alcohol use initiation, the higher the intensity of future consumption. On the other hand, *Stage pre-post* analyses (FC changes between *stage pre*, and *stage post,* 2 years later) showed a negative relationship between changes in FC and the intensity of alcohol intake, in similar cortical regions (including left prefrontal and parietal cortices). Higher SAU levels were associated predominantly with negative and lower SPC values, pointing to a greater reduction of FC between pre and post stages. Conversely, lower SAU level was related predominantly to higher SPC values around zero, both positive and negative, indicating a more stable and lesser change in the FC between pre-and post-stages. Moreover, FC predating alcohol consumption and its changes along follow-up period were mainly associated with the posterior alcohol use intensity, being independent from the sex and the age of participants (both in pre-and post-stages).

Cognitive control, and especially IC, has been traditionally and predominantly associated with behavioral regulation abilities during adolescence. Several studies have linked the development of such cognitive skills with the anatomical and functional maturation of prefrontal, temporal, and parietal brain structures (Luna and Sweeney, 2004). Thus, deviances in the brain maturational course are associated with potential cognitive and behavioral dysregulation. In this vein, our results highlight the presence of an association between functional anomalies during the performance of IC processes and the development of risky behaviors, such as alcohol misuse. Similarly, these functional properties seem to show a distinctive evolution related to the intensity of alcohol consumption independently of sex or age. These results contribute to enriching the growing, albeit scarce, body of literature evidencing the existence of neurofunctional abnormalities in cognitive control processes associated with the development of HD behaviors.

At the time, there is a paucity of literature referring to electrophysiological and FC markers of predisposition to hazardous drinking in adolescents. To our knowledge, only one previous work explored this association, reporting higher beta band FC predominantly between right frontotemporal regions in those adolescents who transited into BD years later (Antón-Toro et al., 2021). In the current work, we adopted a non-group-based approach in order to explore the distribution of FC along the continuous variable of consumption, since the classification of healthy adolescents into binge drinkers may be to a certain extent artificially thresholded along this continuous variable. In line with this approach, current results seem to support likewise previous findings, highlighting a direct relationship between medial and right frontotemporal hyperconnectivity, and the development of future alcohol misuse. Interestingly, these cortical regions experience greater neuromaturation during adolescence and show important changes in their relationship with IC processes. In this vein, previous MEG studies have evidence of the maturational development of IC networks during adolescence. Vara et al. (2014) reported that adolescents show greater recruitment of right prefrontal and right temporal regions in the execution of go/no-go tasks compared with the adult population. Similar results were reported by Stevens et al. (2007) in an fMRI study, showing that adolescents, compared to adults, had a greater engagement of right ventrolateral and inferior prefrontal regions in inhibitory networks. This recruitment of core IC regions with supplemental and prolonged involvement of prefrontal and temporal areas in adolescents may be indicating an immature or deficient IC network.

Longitudinal results showed an exacerbated reduction of FC in previously hyperconnected areas as alcohol consumption becomes more intense. Compared with previous fMRI studies, current results evidence a similar pattern of brain functioning (although in opposite directions) before and after alcohol intake initiation. As reported by Wetherill et al. (2013) before BD onset, adolescents who transitioned

into BD showed reduced BOLD activation during IC tasks in similar cortical regions, increasing in BOLD activity after a follow-up period of 3 years. These divergent results may be understood taking into account the different natures of BOLD and electrophysiological signals synchronization (slow fluctuations of hemodynamic flow vs. fast changes of oscillatory electromagnetic fields) and its complex relationship (Winterer et al., 2007). To our knowledge, there is no fMRI study that explored FC profiles during IC processes associated with HD development in adolescence, making it complicated to make solid inferences between both types of studies. Nevertheless, in spite of, and taking into account, above-mentioned differences between techniques, these studies converge underlining the existence of diverse brain functional abnormalities predating alcohol misuse, as the distinctive impact of alcohol consumption in adolescent neuromaturation.

Taking a broader perspective, outside the IC processes, as neuromaturation progress the FC properties of the adolescent brain go through significant changes. However, evidence provided by electrophysiological and hemodynamic studies seems sometimes contradictory, due mentioned reasons. In general, electrophysiological FC studies reports that functional networks tend to decrease or remain almost constant during adolescence (Machinskaya et al., 2019), while hemodynamical fMRI works evidence the opposite tendency, reflecting a progressive increase of intra-network FC (Stevens, 2016). Considering an electrophysiological perspective, the hyperconnectivity patterns found before HD seem to show that the development of consumption behaviors is associated with a lower cortical maturation of inhibitory networks. During the follow-up period, we found, in general, a decrease in the FC of the same cortical regions according to the expected, but very exacerbated in those adolescents who showed higher levels of alcohol use. These results seem to parallel with those reported by neuroanatomical studies. During adolescence, there is a normative loss of cortical and subcortical gray matter volume and cortical thickness, particularly within the prefrontal cortex (Giedd et al., 2010). In a longitudinal neuroanatomical study with adolescents, Pfefferbaum et al. (2018) found that heavy drinking initiation was associated with an exacerbated reduction of gray matter in the prefrontal, cingulate, and parietal regions. In this sense, after alcohol misuse initiation, there may be an alteration of the "normal" neurodevelopmental trajectories, characterized by overexuberant neuronal pruning. During adolescence, the synaptic pruning of excitatory contacts is a crucial event in the maturation of prefrontal circuitry. This process occurs through mechanisms of long-term potentiation (LTP), stimulating the formation of new connections, and long-term depression (LTD) which inhibits the functioning of excitatory synapses promoting its elimination (Lovinger and Abrahao, 2018). These plasticity processes are mainly dependent on glutamatergic and GABAergic neurotransmission, involving NMDA and GABAa receptors, which are particularly affected by ethanol pharmacodynamics (Lovinger and Abrahao, 2018). Several studies have demonstrated that the ingestion of low doses of ethanol (common in social drinking sessions) impairs the plasticity in multiple regions of the central nervous system (including dorsolateral PFC, motor cortex, etc.), enhancing canonical LTD and suppressing LTP (Lücke et al., 2014; Fuhl et al., 2015; Loheswaran et al., 2017). In this scenario, the recurrent ingestion of alcohol, even at low doses, would alter the normal neuromaturational course by impairing LTD and LTP mechanisms and subsequently increasing dramatically the "normal" rate of synaptic pruning. This may contribute to the sharp decline of FC observed in our results concerning the intensity of alcohol consumption. However, further experiments should explore in detail the relationship between the reduction of cortical thickness and FC regarding this matter. On the other hand, such a marked decline of functional synchronization in the prefrontal, temporal and parietal cortices may underlie some of the neurocognitive deficits associated with heavy alcohol consumption. In this sense, recent work has stated the importance of the 'functional network stability' during adolescent development, where longitudinally unstable or very changeable networks are predictive of worse cognitive performances and higher dimensional psychopathology (Fu et al., 2022).

Current work is not exempt from certain limitations. First, the reduced sample size, albeit large enough to depict distinctive FC patterns, should be increased in future research. Secondly, current works only provide evidence of functional synchronization. These results should be supported and complemented with further associations with neuropsychological and neuroanatomical data to have a wider perspective of the implications of such neurofunctional differences. Additionally, future studies should consider socioeconomic variables as potential predisposing factors and explore its interaction with neurofunctional profiles. Finally, we did not find statistical differences in the post-consumption stage. Given de sharp decline in FC, we could expect this trend to continue over time, evidencing more marked differences in heavy drinkers. Further studies should explore the evolution of FC in additional time points after HD initiation. This study also has several strengths. We use high temporal and spatial resolution techniques to explore the electrophysiological signatures of IC associated to HD development. This allows for depicting more precisely functional differences in very dynamic processes such as IC. Additionally, we used source-space analysis based on native anatomical data, providing a precise cortical localization of functional differences. This also would allow us in the future to explore the association of FC with neuroanatomical variables. Finally, the longitudinal approach of the current study enables making inferences regarding the potential neurobiological factors predisposing to HD and the divergent neuromaturational course associated with alcohol misuse.

In conclusion, heavy drinking is a concerning habit of alcohol misuse among adolescents, which causes, and consequences are complex and must be explored from multiple perspectives. In this work, we detailed electrophysiological connectivity anomalies associated with the development of BD and its impact on functional neurodevelopment. However, further research is necessary to fully understand the neurobiological cause of these differences.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Universidad Complutense de Madrid. Written informed

consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

All authors of the present manuscript have made substantial contributions to its elaboration. LG-M and FM designed this research line and outlined main experimental stages, and approved the final version of this work. LA-T and LG-M recruited participants for this study and collected data and questionnaire evaluations. LA-T, RB, DS-B, AC-L, and MU performed MEG data pre-processing and analyses, while LA-T, DS-B, MU, and LG-M analyzed data from questionnaires. All authors contributed to the redaction and supervision of this manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Neurocognitive effects of binge drinking on verbal episodic memory. An ERP study in university students

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Background: Verbal memory may be affected by engagement in alcohol binge drinking during youth, according to the findings of neuropsychological studies. However, little is known about the dynamics of the neural activity underlying this cognitive process in young, heavy drinkers.

Aims: To investigate brain event-related potentials associated with cued recall from episodic memory in binge drinkers and controls.

Methods: Seventy first-year university students were classified as binge drinkers (32: 17 female) or controls (38: 18 female). The participants completed a verbal paired associates learning task during electroencephalogram (EEG) recording. ERPs elicited by old and new word pairs were extracted from the cued-recall phase of the task by using Principal Component Analysis. Subjects also performed a standardized neuropsychological verbal learning test.

Results: Two of the three event-related potentials components indicating old/new memory effects provided evidence for anomalies associated with binge drinking. The old/new effects were absent in the binge drinkers in the two subsequent posterior components, identified with the late parietal component and the late posterior negativity The late frontal component revealed similar old/new effects in both groups. Binge drinkers showed similar behavioural performance to controls in the verbal paired associates task, but performed poorly in the more demanding short-term cued-recall trial of a neuropsychological standardized test.

Conclusion: Event-related potentials elicited during a verbal cued-recall task revealed differences in brain functioning between young binge drinkers and controls that may underlie emergent deficits in episodic memory linked to alcohol abuse. The brain activity of binge drinkers suggests alterations in the hippocampal - posterior parietal cortex circuitry subserving recognition and recollection of the cue context and generation of the solution, in relation to verbal information shallowly memorised.

KEYWORDS

alcohol, binge drinking, university students, verbal episodic memory, event-related brain potentials (ERP)

Introduction

The high prevalence of alcohol binge drinking (BD) among adolescents and young adults is a public health problem worldwide. This pattern of alcohol consumption is particularly prevalent in American, European and Western Pacific countries, where more than 20% of the population between 15 and 24 years of age engage in BD or heavy episodic drinking, according to the World Health Organization (WHO) terminology (Poznyak and Rekve, 2018).

Engaging in BD at young ages is considered one of the leading risk factors for alcohol use disorder (AUD) (Hingson and Zha, 2009; Silins et al., 2018). According to both animal and human studies, it has a significant deleterious effect on neurodevelopment and neurocognitive function (Spear, 2018), particularly related to the intermittent character of BD (i.e., intoxication followed by withdrawal periods) (Crews and Nixon, 2009; Maurage et al., 2020). The prefrontal cortex and the hippocampus are particularly sensitive to the effects of alcohol abuse and dependence, and functions relying on these regions, such as inhibitory control and working memory or declarative/episodic memory, are known to be impaired in people with AUD (Sullivan, 2017).

Medial temporal lobe and prefrontal damage have been robustly associated with deficits in AUD in regard to episodic memory (White et al., 2000; Chanraud et al., 2009). In addition, the late development of these brain regions makes them particularly sensitive to the effects of BD during adolescence and young adulthood (Meda et al., 2018; Pfefferbaum et al., 2018; Walker et al., 2021).

Episodic memory refers to the conscious recollection of events, and it involves encoding, storing, consolidating and subsequently retrieving information. Carbia and others reviewed neuropsychological studies published between 2000 and 2016 and involving episodic memory in adolescent/young adult binge drinkers (BDs) (Carbia et al., 2018). These researchers observed that regarding verbal memory, studies using list learning tasks reported memory difficulties related to executive dysfunctions in BDs and that studies using story learning tasks reported poorer verbal memory (free immediate and delayed recall) in BDs than in controls. Regarding visuospatial memory, the researchers found scant evidence that BDs exhibit difficulties in performing high-demand visuospatial memory tasks. In a meta-analysis of neuropsychological studies, Lees and others (Lees et al., 2019) concluded that there were no significant effects regarding deficits in episodic memory (immediate, recent, long-term) related to BD, although they also highlighted a longitudinal study (Carbia et al., 2017) that linked BD with deficits in immediate and delayed recall that remained over a 6-year follow-up period in stable BDs. A more recent study on BDs reported poorer delayed recall of verbal and visual memory in standardized neuropsychological tests (Kang and Kim, 2022).

Measures of brain activity may be sensitive to slight neurocognitive dysfunction in non-pathological populations. The small number of studies that have used electroencephalography (EEG)/event-related potentials (ERPs) or functional magnetic resonance imaging (fMRI) to assess declarative memory in adolescent/young adult BDs is surprising, as such studies can be used in a complementary approach to neuropsychological testing and provide some insight into underlying neural activity during memory processing.

Both fMRI and ERP recording are useful techniques for studying declarative memory, although they are not without limitations. fMRI studies provide information about the neural regions involved in different memory types, systems or processes (implicit or explicit; semantic and episodic; recollection or recognition/familiarity; encoding, consolidation and retrieval) (Ranganath and Ritchey, 2012; Squire et al., 2015; Kim, 2019; Palacio and Cardenas, 2019). EEG, particularly ERPs, which have excellent temporal resolution, provide information about the dynamics of memory processing (Staresina and Wimber, 2019).

Brain activity associated with retrieval from declarative episodic memory is usually studied using tasks in which subjects are asked to recognize or recall previously studied information. Brain activity is compared between old items (previously memorised) and new items (not previously studied). Old and new items elicit differential brain activity as recorded by ERPs, referred to as old/new effects.

Regarding recognition tasks, most studies have described the FN400 effect (or midfrontal old/new effect, peaking at around 400 ms after the retrieval cue, exhibiting larger negativity for new items), identified as an index of familiarity in recognition task, and the late parietal component (LPC), or parietal old/new effect (with an onset around 400–500 ms after the cue: larger for old items and when retrieval of contextual information is required), which is considered an index of recollection (Friedman and Johnson, 2000; Rugg and Curran, 2007; Rivas-Fernández et al., 2020). Other components that appear even later, such as the right frontal old/new effect (or right frontal episodic memory effect, extending from 500 to 2000 ms) and the late posterior negativity (LPN) (which is larger for old than new items and peaks after the subject's response), have been related to action monitoring and post-retrieval processing during reconstruction of the study episode (Friedman and Johnson, 2000; Cruse and Wilding, 2009; Mecklinger et al., 2016; Rivas-Fernández et al., 2020).

In cued-recall tasks, in which subjects are asked not only to recognise the item, but also to generate the solution, the cue elicits a broad wave extending from 300–500 to several hundred milliseconds over frontal, central and parietal areas. This wave is more positive for deeply than shallowly encoded items and when contextual information is also recalled. It is composed of several overlapping subcomponents, some of which are common to recognition tasks (LPC and right frontal episodic memory effects, LPN) and others specific to cued-recall (left inferior prefrontal activity, presumably related to the need to generate a solution) (Allan and Rugg, 1998; Allan et al., 2000; Friedman and Johnson, 2000; Mecklinger et al., 2016).

Study of the brain activity associated with retrieval of episodic memory in binge drinkers is scarce, although it is considered useful both for characterising the neural activity associated with memory processes (Wilding and Ranganath, 2012) and for detecting abnormalities related to alcohol consumption (Almeida-Antunes et al., 2021). As far as we know, only one study, by Smith and cols (Smith et al., 2017) addressed this issue. These researchers recorded ERPs during retrieval in a delayed recognition trial of an adaptation of the Rey Auditory Verbal Learning Test (RAVLT), identifying two ERP components showing old/new effects: a frontal negative component (N340) and a parietal positive component (P540). Both of these showed a similar old/new effect in controls and BDs, but overall P540 was larger in BDs than in controls.

In the present study, we aimed to extend the research on possible anomalies in brain activity during memory retrieval associated with early alcohol consumption by examining the ERPs elicited during

cued-recall episodic memory retrieval in a sample of young BDs and controls. We adapted the verbal paired associates task used by Schweinsburg and others (Schweinsburg et al., 2010, 2011) for ERP recording, to measure electrical brain activity elicited by cued-recalled old (previously memorised) and new (seen only once) word pairs. This assessment was supplemented by measuring immediate cued-recall in a standardized neuropsychological test of verbal learning. Subjects were evaluated during their first year at university. A small subsample of the subjects were followed up 2 years later, and the data obtained, which were analysed for exploratory purposes, are reported in Supplementary Material S1.

We hypothesized that the demonstrated effect of alcohol binge drinking on prefrontal and medial temporal brain regions in young adults should be reflected in anomalous brain activity during retrieval of episodic memory, even in the absence of behavioural performance impairment. This hypothesis is based on previous studies showing abnormalities in brain activity during cognitive function despite normal behavioural performance in young, non-AUD binge drinkers; these results have been interpreted as a sign of a subtle deleterious effect of binge drinking on brain functioning, which may be compensated by increased brain recruitment to achieve normal performance in the early stages of abuse, and which would progress, if persistent, to impaired behavioural performance characteristic of the AUD (see, for example, Lannoy et al., 2019).

These anomalies are expected to be observed particularly in ERP components related to memory subprocesses that are most dependent on executive functions, such as recollection, action monitoring and post-retrieval processes, as executive functions have been indicated to be the cognitive functions most severely affected by early alcohol consumption (Carbia et al., 2018; Lannoy et al., 2019). We did not formulate *apriori* hypotheses about the influence of sex on the relationship between BD and brain activity during memory retrieval, because previous research does not indicate a clear role of this variable (Carbia et al., 2018; Almeida-Antunes et al., 2021). Thus, this factor will be considered in accordance with the recommendations by Joel and Fausto-Sterling, 2016.

Materials and methods

Participants

A sample of 70 first-year students (18–19 years old) from the University of Santiago de Compostela (Spain) participated in this study, which forms part of a broader research project on binge drinking among university students and has been approved by the Bioethics Committee of the University. Initially, 1,328 volunteers participating in the epidemiological phase of the research completed a classroom-administered questionnaire composed of the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993), with additional questions regarding consumption of alcohol and other substances (illegal drugs and medications) and also sociodemographic information for epidemiological purposes (such as type of household or parents' level of education).

The students were screened on the basis of their responses to the questionnaire, and 200 of the respondents, who fulfilled the initial selection criteria, and who also provided contact information, were interviewed. These students signed informed consent and received compensation (10 euros) for their participation. The semi-structured interview included the Mini International Neuropsychiatric Interview, Spanish version 5.0.0 (Ferrando et al., 2000), and the Symptom Checklist-90-R (SCL-90-R) (Derogatis, 1983) for assessing history or current psychopathological symptomatology. It also included a detailed questionnaire about substances use, based on the Cannabis Abuse Screening Test (CAST) (Cuenca-Royo et al., 2012), the Nicotine Dependence Syndrome Scale, short version (NDSS-S) (Shiffman et al., 2004) and a diary of alcohol consumption based on the revised version of the Alcohol Use Questionnaire proposed by Townshed and Ducka (Townshend and Duka, 2002).

Selection for neurocognitive assessment was based primarily on the drinking pattern. Subjects with an alcohol consumption of six or more drinks per episode at least once a month (AUDIT item 3) and a drinking rate of at least three drinks per hour in these episodes were selected as binge drinkers; this criterion was defined to approximate the level of consumption to the NIAAA definition of binge drinking (National Institute on Alcohol Abuse and Alcoholism, 2016). Subjects were included in the control group if they never partook in 6-drink episodes and never drank more than two drinks per hour. Inclusion and exclusion criteria, applied on the basis of information obtained in the interview, are summarised in Table 1.

Seventy-four subjects (100% Caucasian) who fulfilled these criteria consented to take part in the neurocognitive assessment. These participants received 20 euros for their collaboration. Four of the participants were later excluded because of the low quality of the EEG recording. Of the final 70 subjects, 32 (17 females) were included in the binge-drinking (BD) group and 38 (18 females) in the control (CN) group. Demographics and substance use characteristics are summarised in Table 2.

Procedure

Participants were asked to abstain from consuming alcohol and other drugs (including medical prescriptions) for at least 24 h before the electrophysiological assessment, and to sleep for at least 7 hours the night before testing. An alcohol breath level of 0.00% was verified by breathalysing the participants on arrival at the laboratory.

The electrophysiological assessment began with the verbal paired associates task, which was an adaptation to ERP recording of the task used in fMRI studies by Schweinsburg and others (Schweinsburg et al., 2010, 2011).

During the EEG recording, subjects were seated on an armchair inside an electrically shielded, dimly lit, sound-attenuated room. The subjects were instructed not to move during EEG recording, to use the pauses programmed in the task to adjust their position, and to fix their gaze on a small cross in the centre of the screen (a 20″CRT monitor, 1,152 × 864 pixels, refresh rate 85 Hz), located 100 cm in front of their eyes.

The subjects were asked to learn and recall a series of phonetically related pairs of two-syllable nouns, each displayed for 2 s in the centre of the screen. A total of 192 words were selected from the *BuscaPalabras* (B-Pal) base vocabulary, which includes 31,491 Spanish words (Davis and Perea, 2005).

The task involved first memorizing a list of 16 word pairs, which were presented sequentially in the centre of the screen (learning block); immediately after this series, recall was tested by presenting

TABLE 1 Inclusion and exclusion criteria for sample selection, based on interview.

Inclusion criteria	Exclusion criteria
• First-year university students (18–19 years)	• Personal or family (first-degree) history of major psychopathological disorders (DSM-IV), including alcohol or substance abuse
• **Binge drinkers:** ≥ 6 alcoholic drinks/occasion at least once a month and speed of consumption ≥3 alcoholic drinks/hour	• History of traumatic brain injury or neurological disorder
• **Control group:** < 6 alcoholic drinks/occasion and speed of consumption ≤2 drinks/hour	• Any episode of loss of consciousness >20 min
	• Use of illegal drugs (except infrequent cannabis[a])
	• Use of psychoactive medication
	• Uncorrected sensory deficits
	• AUDIT score ≥20

[a]Less than once per week.

TABLE 2 Demographic and substance use characteristics of the sample (mean ± standard deviation).

	Controls	Binge drinkers
N (females)	38 (18)	32 (17)
Age [range]	18.5 ± 0.3 [18-19]	18.4 ± 0.3 [18-19]
Age of drinking onset	16.83 ± 1.46	15.21 ± 1.21
Total grams of alcohol in a standard drinking episode[a]	10.59 ± 13.44	109.45 ± 30.14
Speed of consumption: drinks/hour[a]	0.25 ± 0.34	3.38 ± 0.75
Estimated BAC in a standard drink episode[b,a]	0.006 ± 0.01	0.23 ± 0.08
Percentage of times became drunk when drinking[a]	0.27 ± 1.64	39.69 ± 25.14
Total AUDIT score[a] [range]	0.95 ± 1.48 [0-6]	9.22 ± 2.51 [4-14]
N regular tobacco smokers[c]	0	4
SCL-90-R - GSI (percentile scores)	22.36 ± 21.76	34.19 ± 29.98

[a]Student t-test $p < 0.05$.
[b]Gr/dL (calculated using the classic Widmark formula (Widmark, 1932; see in Kelly and Mozayani, 2012).
[c]Daily (max. Five cigarettes/day); SCL-90-R - GSI: Symptom checklist-90-revised - global severity index; AUDIT: alcohol use disorders identification test.

the first noun of each pair and asking subject to verbalize the second one (or to say 'I don't remember') when a question mark appeared on the screen (recall block). The order of presentation of the words varied between the learning and the recall blocks. The series (learning and recall blocks) were presented twice, ensuring subjects correctly recalled at least 10 of the 16 pairs (none of the subjects required presentation of a third block to reach this threshold).

Participants subsequently performed a new series (old/new learning and recall blocks), composed of 32 word pairs: the 16 previously memorised pairs (old pairs, OP) intermixed with 16 novel pairs (new pairs, NP). EEGs were recorded during both the learning and the recall blocks.

This task was repeated three times, with three different lists of words, yielding a total of 48 OP and 48 NP. The complete task lasted approximately 50 min, including pauses between blocks autoregulated by the participant. The parameters of the task (stimuli duration and interstimulus intervals) are summarised in Figure 1.

In a separate session, these participants also underwent a neuropsychological assessment including the TAVEC (*Test de aprendizaje verbal España-Complutense*) (Benedet and Alejandre, 2014), a verbal episodic memory test based on the California Verbal Learning Test (CVLT) (Delis et al., 1987).

This test began with the examiner reading the learning list (List A, 16 items) and asking the participant, immediately after the reading, to remember as many words as possible. This procedure was repeated 5 times (learning trials 1–5). The examiner then read the interference list (List B, 16 items) and asked the subjects again to freely recall as many of the words on this list as possible. Free recall of List A was then requested (short-term free recall trial), followed by a cued recall test, with the semantic category of the words (tools, fruits, clothes and spices) as cues (short-term cued recall trial). Twenty minutes later, during which subject were carrying out other neuropsychological tests (none of them on declarative memory or vocabulary), the test was resumed: the participants were asked to freely recall items from List A (long-term free recall trial) and then to perform a cued-recall test of the same list (long-term cued recall trial). Finally, a recognition test was applied: a list of 44 items (16 from the List A, eight from the List B and 20 phonologically or semantically similar new words) was read to the participant, who had to say, after each word, whether it belonged to List A or not (recognition trial).

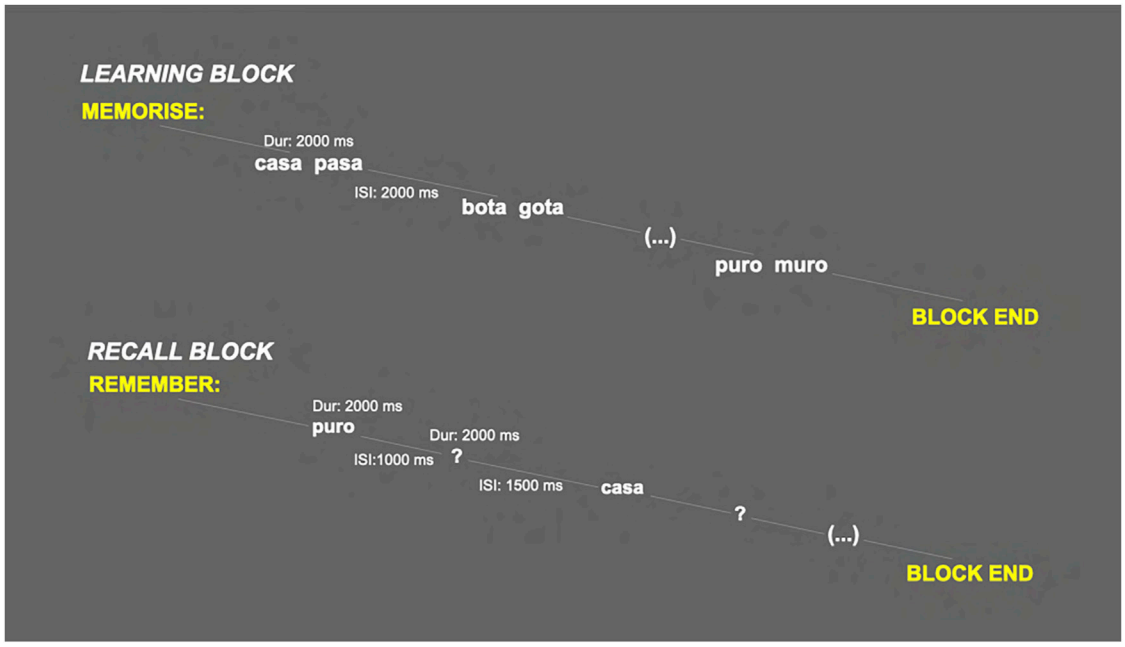

FIGURE 1
Schematic representation of the learning and recall blocks of the verbal paired associates task (Dur: stimulus duration; ISI: interstimulus interval).

EEG data acquisition and processing

The EEG was recorded during the old/new learning and recall blocks of the verbal paired associates memory task. Electrodes were located using a BrainCap with 32 positions according to the extended 10-20 International System (Nuwer et al., 1998). Active scalp electrodes were referred to the nose tip, and ground electrode was placed at Fpz. Electrooculogram was recorded from vertical and horizontal bipolar channels to control for eye movements and blinks. Electrode impedances were kept below 20 kΩ. EEG signals were continuously amplified and digitized, at a sampling rate of 500 points/s, and filtered on-line with a 0.1–100 Hz band pass filter and a 50 Hz notch filter.

EEG data were off-line processed with BrainVision Analyzer software (Version 2.0) to obtain the event-related potentials (ERP) elicited by the word pairs in the old/new recall blocks. Ocular artefacts were corrected by the procedure developed by Gratton and others (Gratton et al., 1983). The EEGs recorded during the old/new recall blocks were digitally filtered offline with a 0.1–12 Hz and segmented into epochs of 2,200 ms, from 200 ms pre-stimulus to 2000 m post-stimulus. This temporal interval was chosen for analysing effects related to memory recall reported in the literature, with latencies of 1,400 ms sometimes exceeded (Friedman and Johnson, 2000). After adjusting the pre-stimulus baseline period to 0 μV, epochs exceeding ± 80 μV were rejected.

EEG epochs were then averaged separately for old pairs (OP) and new pairs (NP). The resulting averaged ERPs comprised at least 17 epochs for each subject and type of stimulus (mean ± SD: 34.6 ± 6.8 for old pairs, 27.0 ± 6.6 for new pairs, without differences between groups); as indicated in the participants subsection, four subjects were excluded for this reason.

ERPs for each subject and type of stimulus (OP, NP) were then processed with Dien's *ERP PCA toolkit (v.2.96)* (Dien, 2010b) to isolate overlapping components of the ERPs related to memory processing. The decomposition was conducted in two-step sequential temporospatial Principal Component Analysis (PCA) (Dien, 2010a).

After reducing the sampling rate to 250 points/s, the data were subjected to a temporal Promax rotation using the voltage EEG values (550 samples) as variables, and electrode sites (32), types of stimulus (2) and subjects (70) as observations. Thirteen temporal factors were extracted using the parallel test (Horn, 1965) of the scree plot (Cattell, 1966). In a second step, these factors were then subjected to a spatial Infomax (ICA) rotation with the 32 scalp recording sites as variables and the temporal factor scores, types of stimulus and subjects as observations. Two spatial factors were extracted from each temporal factor, resulting in 26 temporospatial factors explaining 90% of the variance.

These factors were then rescaled to microvolts to facilitate interpretation, and values of amplitude at the peak channel and the peak time point were automatically extracted for each of the 16 factors accounting for a minimum of 0.5% of the variance. The characteristics of these factors (ERP components) are summarised in Table 3.

Statistical analysis

Statistical analysis of the ERP components was conducted using robust analysis of variance (ANOVA) implemented in the ERP PCA Toolkit (Keselman et al., 2003; Dien, 2010b), with Welch-James approximate degrees of freedom based on 499,999 bootstrap samples and a familywise corrected alpha of 0.05 (TWJt/c). The Dunn-Šidák correction for multiple comparisons was applied to post-hoc pairwise contrasts.

TABLE 3 Temporospatial factors (ERP components), isolated *via* two-steps temporospatial PCA, explaining at least 0.005 of the variance.

Factor	Peak latency (ms)	Peak channel (polarity)	Explained variance
TF01SF1	1,656	Oz (-)	0.392
TF01SF2	1,656	AF3 (+)	0.012
TF02SF1	812	POz (-)	0.170
TF02SF2	812	O1 (+)	0.015
TF03SF1	408	Pz (+)	0.100
TF03SF2	408	Fz (-)	0.025
TF04SF1	1,260	POz (-)	0.055
TF05SF1	624	POz (+)	0.028
TF06SF1	200	PO7 (-)	0.015
TF07SF1	280	POz (+)	0.010
TF08SF1	1976	Pz (+)	0.013
TF09SF1	1,048	PO3 (-)	0.010
TF10SF1	340	Pz (-)	0.009
TF11SF1	152	PO7 (+)	0.008
TF12SF1	96	O2 (+)	0.009
TF13SF1	1,440	PO4 (-)	0.009

The ERP components were subjected to preliminary analysis in order to determine which would be selected as indicators of old/new effects (a difference in amplitude between the previously memorised and the new word-pairs). For this purpose, the two types of stimulus (OP vs. NP) were compared in the 16 ERP components selected above.

Another preliminary analysis was carried out to decide whether to include Sex as a main factor (independent variable), following the recommendation that, in absence of *a priori* hypothesis, it must be included only when interacts with the main variables of the research (Joel and Fausto-Sterling, 2016). With this aim, a Group x Sex x Type of stimulus analysis was performed on each of the ERP components that showed old/new effects.

Given the exploratory nature of these preliminary analyses, familywise correction was not applied, and factors were considered in the main design even though the alpha level was at the borderline of the significance threshold.

The main analyses were then conducted to address the primary focus of this research (memory retrieval), taking the results of these exploratory analyses into account. The ERP components indicating a memory old/new effect were examined considering the within-subjects factor Type of stimulus (OP vs. NP) and the between-subjects factor Group (CN vs. BD), and where relevant, Sex (male vs. female). The dependent variables were the voltage of the ERP components isolated by PCA (at the peak channel and time point).

In addition, related behavioural variables were analysed using IBM-SPSS (v.25): Percentage of hits to OP and NP in the old/new recall blocks of the task were analysed using a conventional mixed-model 2 × 2 ANOVA (Group x Type of stimulus), with an alpha threshold of 0.05, and post-hoc pairwise comparisons with Bonferroni correction. The TAVEC, short-term cued-recall scores (range 0–16) from the two groups wer compared by a Student t-test; this variable was selected because it was the TAVEC measure closest to the task used with ERPs.

Results

Preliminary analysis

Preliminary analysis conducted to identify the ERP components associated with memory revealed three ERP components with significant old/new effects. One of them (TF03SF1) did not withstand the correction for multiple comparison recommended when there are *a priori* no criteria for selecting the factors. Nonetheless, it was selected for subsequent analysis because its latency and topography were consistent with previously described ERP memory components. These components are summarised in Table 4 and illustrated in Figure 2.

The earlier component (TF03SF1), peaking at 408 ms with positive polarity at a posterior location (Pz) (P408p), resembles the episodic memory effect linked to recollection (LPC or parietal old/new effect), although with earlier latency than expected. The later components, TF02SF1, with negative polarity at posterior POz (N812p), and TF01SF2, positive at the anterior AF3 (P1656a), are related to the post-retrieval processing on the cue and the generation of the completion (the second word of the pair).

Analysis of these three ERP components by considering the Sex factor revealed an influence of this variable on TF03SF1 (P408p), which showed Sex x Type of stimulus interaction (T_{WJt}/c (1.0.62.3) = 4.45, p = 0.038, mean-squared error (MSe) = 6.01) and an almost significant Sex × Group interaction (T_{WJt}/c (1.0.58.4) = 3.80, p = 0.0568, MSe = 65.90). No other ERP components showed interactions including Sex; therefore, this factor was only included in the core

TABLE 4 Temporospatial factors (ERP components) with old/new effect selected for main analysis.

Factor	Peak latency (ms)	Peak channel (polarity)	Old/new effect		Trimmed means (SE) [μV]	
			t	*p*	OP	NP
TF01SF2	1,656	AF3 (+)	16.16	0.00057	1.46 (0.03)	2.42 (0.03)
TF02SF1	812	POz (-)	15.71	0.00015	-3.53 (0.10)	-6.08 (0.10)
TF03SF1	408	Pz (+)	7.07	0.00963[a]	2.35 (0.09)	1.18 (0.09)

SE: standard error; OP: old word pair; NP: new word pair.

[a]Does not fulfil familywise corrected alpha criteria (Dunn-Šidák correction): .0032007.

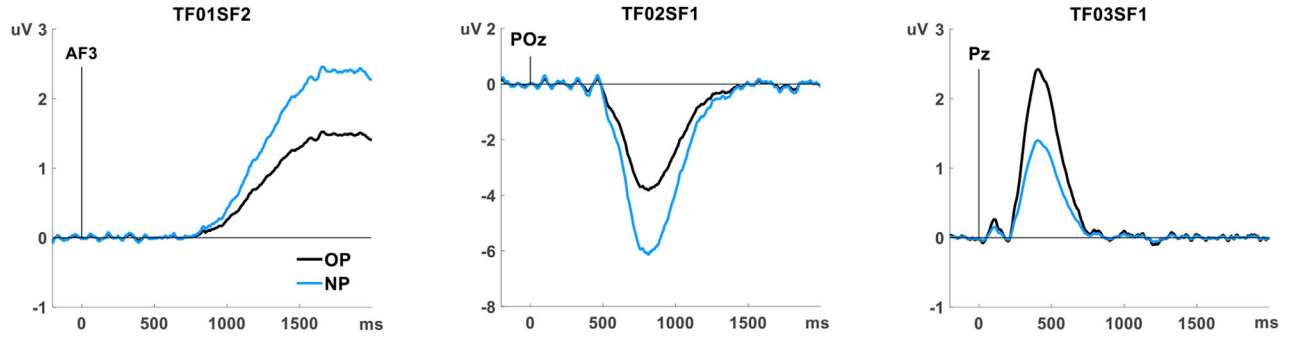

FIGURE 2
Temporospatial factors (ERP components) showing old/new memory effects, rescaled to μV at the channel with the peak amplitude. Grand average for the old word pairs (OP, black line) and the new word pairs (NP, blue line).

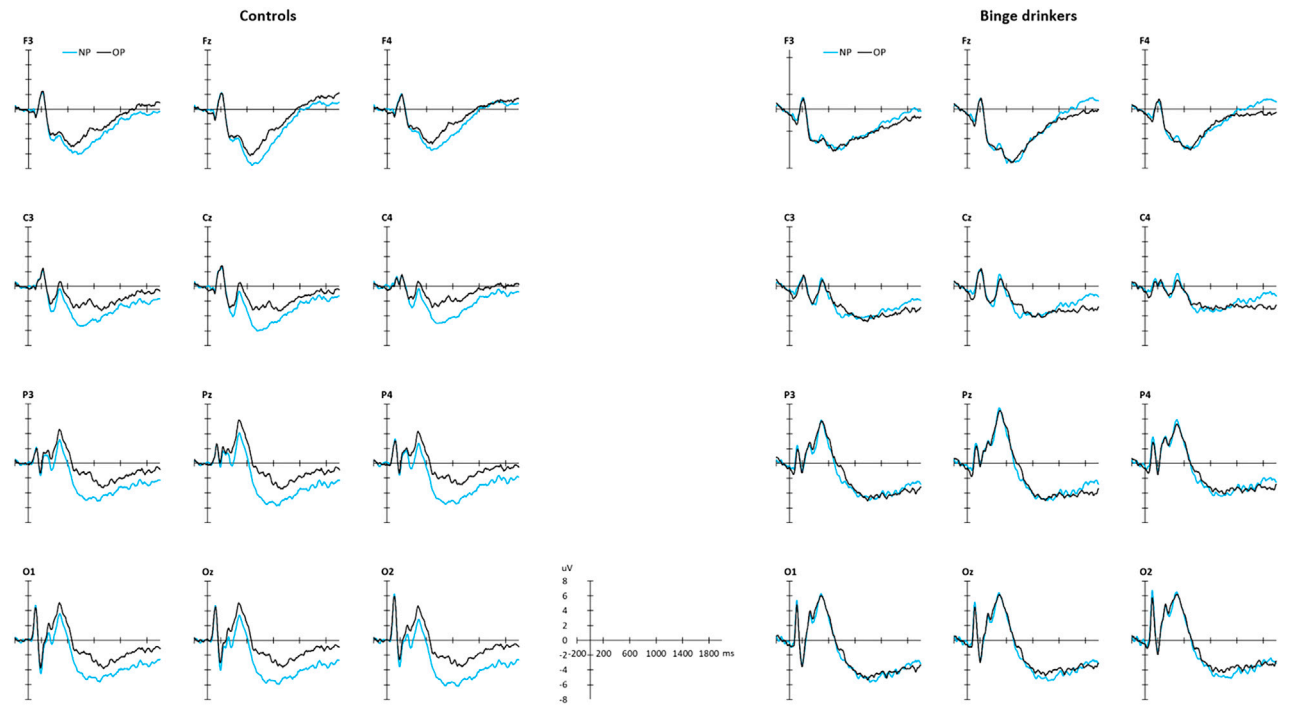

FIGURE 3
Grand average ERPs elicited by old word pairs (OP, black line) and new word pairs (NP, blue line), in a set of the recorded sites, in the control (left) and binge drinking (right) groups.

TABLE 5 Mean (standard deviation) amplitude of the selected ERP components (factors rescaled to μV at the peak latency and electrode site) for each group (binge drinkers and controls) and type of stimulus (old and new word pairs, OP/NP) (ordered by latency).

Factor/ERP component	Controls		Binge drinkers	
	OP	NP	OP	NP
TF03SF1/P408p	1.78 (5.97)	0.07 (5.51)	3.08 (6.29)	2.94 (6.20)
TF02SF1/N812p	-3.54 (7.12)	-7.04 (7.25)	-4.05 (7.10)	-4.91 (6.31)
TF01SF2/P1656a	1.38 (2.02)	2.31 (2.00)	1.60 (2.34)	2.57 (2.14)

TABLE 6 Descriptive statistics on the behavioural measures. Percentage of hits in the verbal paired associates task (old and new word pairs, OP/NP) and scores in the Short-term cued-recall measure of the TAVEC. Mean (standard deviation) for each group.

	Controls		Binge drinkers	
	OP	NP	OP	NP
Verbal memory task % hits	91.67 (8.36)	66.72 (16.80)	92.19 (6.39)	67.64 (15.55)
TAVEC	13.92 (1.78) [11-16]		12.91 (1.84) [9-16]	
Short-term cued-recall score [range 0–16]				

analysis of TF03SF1 (P408p); Sex-disaggregated data for the dependent variables are included in the Supplementary Material S1.

ERP components

The grand averaged ERP recordings are shown in Figure 3, and the descriptive statistics (mean amplitude and standard deviation) of the selected ERP components (factors rescaled to microvolts at the peak latency and electrode site), for each group (binge drinkers and controls) and type of stimulus (old and new word-pairs) are summarised in Table 5.

P408p was analysed by including the variable Sex. This analysis revealed a Type of stimulus effect (T_{WJt}/c (1.0.62.3) = 5.14, p = 0.0268, MSe = 6.01), with larger amplitudes for OP (averaged trimmed mean = 2.37 μV) than NP (1.41 μV); and a Type of stimulus x Group effect (T_{WJt}/c (1.0.62.3) = 4.30, p = 0.0418, MSe = 6.01), with the old/new effect present in controls (T_{WJt}/c (1.0.34.0) = 9.66, p = 0.00392, MSe = 6.24), but absent in BDs, and with larger amplitude (T_{WJt}/c (1.0.57.8) = 4.29, p = 0.043, MSe = 34.19) for NP in BD (2.89 μV) than CN (-0.06 μV). The Type of stimulus × Sex interaction (T_{WJt}/c (1.0.62.3) = 4.45, p = 0.039, MSe = 6.01) was also significant, with the old/new effect only emerging in females (T_{WJt}/c (1.0.32.0) = 8.56, p = 0.0068, MSe = 6.95).

N812p also presented a Type of stimulus effect (T_{WJt}/c (1.0.62.0) = 14.89, p = 0.00028, MSe = 12.46) with larger negative amplitude for NP (-5.97 μV) than OP (-3.59 μV), and a Type of stimulus × Group interaction (T_{WJt}/c (1.0.62.0) = 4.11, p = 0.0457, MSe = 12.46), showing that the old/new effect was present in controls (T_{WJt}/c (1.0.35.0) = 18.89, p = 0.000048, MSe = 12.57), but absent in BDs.

Group by Type of stimulus statistical analysis of the P1656a amplitude revealed a significant main effect of Type of stimulus (T_{WJt}/c (1.0.59.3) = 15.99, p = 0.00086, MSe = 1.92), with larger amplitude in response to NP (2.44 μV) than to OP (1.47 μV). There were no Group or Type of stimulus x Group effects.

Behavioural performance

Descriptive estatistics of the behavioural measures are summarized in Table 6. The percentage of hits to old and new word pairs showed, as expected, a Type of stimulus effect (F (1,68) = 265.947, p < 0.0001, η^2_p = 0.796), which was more accurate for OP (91.90%) than NP (67.14%), but there were no differences between groups or Type of stimulus × Group interaction.

Regarding the TAVEC measure (short-term cued-recall score), a Group effect was observed (t (68) = 2.344, p = 0.022), with poorer performance in the BD (12.91) than in the CN group (13.92). Finally, we should point out that, although the scores for free recall or long-term recall were not considered here, because they were not a direct counterpart of the verbal paired associates task, we analysed them for informative purposes, and did not find any other effects associated with alcohol consumption.

Discussion

ERPs elicited by old and new word-pairs during immediate cued-recall in young binge drinkers and controls were identified in this research by temporospatial Principal Component Analysis (Dien, 2010a; 2010b), bearing in mind the variability of the ERP components and subcomponents associated with memory retrieval across task paradigms, and the overlap between these (see Friedman and Johnson, 2000). With this approach, we found three ERP components that indicated old/new effects and resembled, in terms of latency, polarity and topography, the components already described in the relevant literature. The results showed that the old/new effects observed in the control group were absent in the binge drinkers in the two subsequent posterior components, identified as the late parietal component (LPC) and the late posterior negativity (LPN), whereas the late frontal component revealed similar old/new effects in both groups.

The literature on declarative episodic memory describes frontal (FN400) and parietal (LPC) ERP components, at latencies of between 400 and 800 m (variable across tasks), with old/new effects, which have been associated with familiarity (or priming) and recollection, respectively, in recognition tasks. Although more controversially, the LPC has also been described in cued-recall tasks (Friedman and Johnson, 2000; Fay et al., 2005). In the present study, a large parietal positive waveform resembling this LPC was observed, peaking at around 500 ms (see Figure 2). The PCA analysis allowed us to isolate the ERP component named P408p, peaking at Pz, that showed the expected old/new effect (larger positive amplitude for old than for new word pairs).

We identified two other components, of longer latency, showing old/new effects: N812p (with negative polarity, peaking at 812 ms at POz), which was less negative for old than for new word pairs, and P1654a (with positive polarity, peaking at 1,656 ms at AF3), which had more positive amplitude for new than for old word pairs.

The N812p is consistent with the late posterior negativity (LPN) described in ERP, memory-related studies. Initially reported in recognition tasks, it has also been observed in cue-recall tasks involving both episodic memory (Bai et al., 2015) and semantic memory (Hellerstedt and Johansson, 2016), with a broad latency range, from 700-800 to 1,000–1,200 m, and a possible origin in the medial posterior parietal cortex. Although described as more negative for old than for new items in recognition tasks (Mecklinger et al., 2016), some studies using cued-recall paradigms have reported less negative LPN for old items than for new ones, as well as for deeply processed than for shallowly processed items, and for more accurately than for less accurately remembered items (Fay et al., 2005; Bai et al., 2015; Hellerstedt and Johansson, 2016), as in the case of the N812p in this study.

The P1656a resembled the long-lasting frontal old/new effects in ERPs associated with postretrieval processes, such as the (right) frontal old/new effect described in recognition tasks (Wilding and Rugg, 1996) and the left inferior prefrontal activity elicited in cued-recall tasks (Johnson et al., 1998). These components vary according to the task features and the material that has to be retrieved, but share a frontal distribution, according to the role of the prefrontal cortex in postretrieval control operations, and a late latency, usually beginning after the LPC and lasting several hundreds of milliseconds, until the end of the epoch (Wilding and Ranganath, 2012).

The LPN and the late frontal old/new effects are considered indexes of postretrieval processes, both mnemonic (to generate a solution and form an integrated representation of a prior episode), and non-mnemonic (control and monitoring operations to assess the retrieved information in the context of goal-directed behaviour) (Wilding and Ranganath, 2012; Mecklinger et al., 2016).

Comparison of these ERP components in relation to alcohol consumption revealed anomalies in BDs. First, the LPC-like component (P408p) showed group-related differences, as the old/new parietal effect appeared to be influenced by alcohol consumption. The effect was present in controls but absent in BDs, in whom new word pairs elicited an equally high voltage as elicited by old word pairs. Moreover, this effect was qualified by the Sex x Type of stimulus interaction: the old/new effect only reached statistical significance in female controls.

As explained above, the LPC, or Parietal old/new effect, has been considered a correlate of recollection and described as more prominent when correctly retrieving contextual (episodic) information or when deeper processing is required on encoding (Friedman and Johnson, 2000; Rugg and Curran, 2007). The results obtained with BD subjects in this study indicated an abnormally large amplitude of the LPC for new pairs (relative to controls), which would obscure the old/new memory effect. This pattern of greater brain activity (usually referred to as hyperactivation) in BDs than controls during cognitive processing is frequently detected with both ERP and fMRI techniques (Lannoy et al., 2019; Almeida-Antunes et al., 2021), usually in the absence of behavioural impairment, and it has been interpreted as reflecting a compensatory mechanism whereby increased recruitment of neural resources is required to achieve a similar level of performance. In this study, the hyperactivation phenomenon appeared when new (seen once) word pairs are retrieved.

The study reported by Smith et al. (2017) is the most similar for comparative purposes. These researchers identified an LPC-like component that emerged during free-recall of a verbal learning task and that was referred to as P540. Overall the amplitude of this component was larger in BDs, but the old/new effect remained. In our study, although the overall amplitude was also apparently larger in BDs (2.93 ± 0.20 μV) than in controls (0.85 ± 0.17 μV), the difference was not statistically significant; however, we only observed the expected old/new effect in controls (particularly in women) and observed that the amplitude of the LPC-like component was larger for new word-pairs in BDs. Thus, some neural hyperactivation at the time of the brain index of memory recollection was observed in both studies, although our findings seem to be specific to new (once seen) word pairs.

Moreover, we can also compare the present findings with those of our previous study of memory encoding with another sample of BDs and controls, although with a task of a different nature (Folgueira-Ares et al., 2017). In the earlier study we also observed, at similar latencies (350–650 m) but during encoding, that ERPs in BDs did not indicate the memory effect (Dm effect) observed in controls at posterior electrode sites. Considering that episodic memory theories and neuroimaging studies have proposed that there is an overlap between brain activation patterns of encoding and retrieval (Persson and Nyberg, 2000), these findings call for future ERP studies of the two processes in the same samples and tasks, to assess whether these two anomalies observed in BDs can be replicated and related.

As discussed above, the two other ERP components indicating old/new effects in this study were associated with those described in literature as correlates of postretrieval processing. The N812p also indicated an absence of this old/new effect in BDs. Unlike in the case of the P408p/LPC described above, the absence of the memory effect in the N812p did not seem to indicate a hyperactivation phenomenon, as it was due to a lower (although not significant) voltage elicited by new word pairs in BDs (-4.93 ± 0.14 μV) than in controls (-7.00 ± 0.13 μV). The later, left frontal component, P1656a, did not show any differences associated with alcohol consumption. Smith et al. (2017) analysed a shorter ERP epoch than we did in the present study (ending 900 m after the stimulus onset), and therefore these late components did not appear, precluding any comparison.

Our results indicate anomalous brain activity (relative to controls) in posterior regions during the retrieval of new (shallowly memorised) word pairs. The anomalies would consist of increased neural activation during cue recognition, indicated by P408p/LPC, and decreased activity during solution generation,

indicated by N812p/LPN. Based on a recent comprehensive review on the neural basis of memory recall (Staresina and Wimber, 2019), these anomalies will depend on medial temporal lobe (MTL) and posterior parietal cortex (PPC) nodes in the episodic memory circuitry. These authors propose that episodic memory would involve a transient signal from the MTL (hippocampus), around 500 ms after the cue, at the time of the old/new parietal effect (LPC), which would initiate cortical reactivation of the memory engram. After 600 ms, the PPC would then respond to this bottom-up hippocampal signal with sustained activity during the maintenance interval (resembling the LPN), to allocate working memory and attentional resources to the retrieval of task-relevant mnemonic features. Although our ERP data do not enable us to gain insight into neural generators, they are consistent with the model derived from different sources of data (EEG, MEG, fMRI, intracranial recordings) and may indicate abnormal activity associated with BD in hippocampus/LTM and in association regions of the PPC. Whether this electrophysiological abnormality is a result of consumption or is an endophenotype that precedes it, is not discernible in the absence of data prior to the onset of BD.

Notably, no anomalies were observed in the frontal P1656a. As stated above, this component would be related to postretrieval processes associated with monitoring of the solution generated. BD has been associated with anomalous brain activity in young adults during executive functions, such as performance monitoring (Smith et al., 2016; Almeida-Antunes et al., 2021), and with impairments in executive functions involved in neuropsychological tests of verbal memory (Carbia et al., 2018). Some effects associated with alcohol consumption on this component were therefore expected.

Finally, complementing these results, the behavioural performance in the verbal paired associates task did not indicate any differences between BDs and controls; this was expected, as most ERP studies reporting anomalies in brain function in BDs have not found impairments in behavioural performance. This has usually been interpreted as a sign that ERPs are sensitive to a slightly deleterious effects of alcohol that can be compensated for (e.g., by recruiting more neural resources) to produce normal performance. Of course, replication studies are needed to confirm these results, as well as follow-up studies to assess the evolution of electrophysiological and behavioural measures with the onset and persistence of BD.

Nonetheless, the neuropyschological test results showed evidence consistent with memory impairment in BDs: In the short-term cued-recall trial of the TAVEC, in which subjects had to recall previously studied words cued by the semantic category, the BD group obtained lower scores. Previous studies with standardised neuropsychological tests consisting of word lists have reported mixed results. Consistent with our results, a study with French university students (Gierski et al., 2020), using a modified version of the Free and Cued Selective Reminding Test (FCSRT), reported that BDs showed marginally lower scores in the immediate recall cued score, which is very similar to our short-term cued-recall score. In a systematic review, Carbia et al. (2018) observed that verbal memory impairments associated with BD mainly appeared in tasks using lists of related words (such as the TAVEC), unlike in tasks using lists of unrelated words (such as the Rey Auditory Verbal Learning Test). These researchers concluded that the impairments would be associated with executive dysfunctions, such as poor semantic clustering, which is more involved in the recall of related than unrelated words. The present findings, with poor performance in the TAVEC and no differences from controls in the verbal paired associates task (where there was no semantic, but phonetic, relationship among the words), are consistent with this conclusion.

Limitations

Our study has some limitations to consider. The characteristics of the participants selected, healthy university students with high cognitive functioning may limit generalization of the results to other populations. On a technical level, the minimum number of averaged EEG epochs is below the recommended standards. The size of the sample limited a more detailed exploration of the interactions involving sex/gender detected in the P408p component. Loss of participants at follow-up, due to participants declining to participate further or no longer meeting the selection criteria, impeded completion of a robust longitudinal study. Finally, the absence of evaluation of the participants prior to beginning BD prevents any conclusions being reached about causal relationships.

Conclusion

In summary, this study provides novel information about brain activity during verbal episodic memory in relation to alcohol binge drinking. When retrieving information in a short-term cued-recall paradigm, binge drinkers showed a different pattern of activity in the posterior brain regions. At around 400 ms, the amplitude of the LPC-like component of the ERPs was larger than in controls for new (seen only once) word pairs, which led to an absence of the old/new effect observed in controls. Subsequently, at around 800 ms, the LPN-like component showed a reduced amplitude in response to the same items. No differences associated with alcohol were observed in the late frontal old/new effect. This pattern of brain activity may indicate abnormal functioning of the hippocampal–PPC circuitry responsible for the recognition and recollection of the context of the cue and the generation of the solution to shallowly processed word pairs, to achieve a normal behavioural performance. Although behavioural results were similar for the BDs and the controls in the word pair association task, the BDs showed poor execution of a more demanding test, requiring short-term recall of words cued by semantic information.

Data availability statement

The raw data supporting the conclusion of this article are available at https://osf.io/zftne/.

Ethics statement

The studies involving human participants were reviewed and approved by Bioethics Committee of the University of Santiago de Compostela. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FC and SRH obtained funding for the study. FC, SRH, MC, and SD designed the study. MC and SRH were responsible for sample selection. AC and EL-C collected the data. SRH, RF-A, and SD analysed and interpreted the data. SRH wrote the manuscript. All authors reviewed the manuscript and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1034248/full#supplementary-material

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Sex-related differences in the efficacy of Baclofen enantiomers on self-administered alcohol in a binge drinking pattern and dopamine release in the core of the nucleus accumbens

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Introduction: Clinical studies on the effectiveness of Baclofen in alcohol use disorder (AUD) yielded mixed results possibly because of differential effects of the enantiomers and sex-related differences. Here we examined the effect of the different Baclofen enantiomers on alcohol intake and on evoked dopamine release in the core of the nucleus accumbens (NAcc) in male and female Long Evans rats.

Methods: Rats were trained to chronically self-administer 20% alcohol solution in daily binge drinking sessions and were treated with the different forms of Baclofen [RS(±), R(+) and S(−)]. The effects on the evoked dopamine release within the core of the nucleus accumbens were measured in brain slices from the same animals and the alcohol naïve animals using the fast scan cyclic voltammetry technique.

Results: RS(±)-Baclofen reduced alcohol intake regardless of sex but more females were non-responders to the treatment. R(+)-Baclofen also reduced alcohol intake regardless of sex but females were less sensitive than males. S(−)-Baclofen did not have any effect on average but in some individuals, especially in the females, it did increase alcohol intake by at least 100%. There were no sex differences in Baclofen pharmacokinetic but a strong negative correlation was found in females with a paradoxical effect of increased alcohol intake with higher blood Baclofen concentration. Chronic alcohol intake reduced the sensitivity to the effect of Baclofen on evoked dopamine release and S(−)-Baclofen increased dopamine release specifically in females.

Discussion: Our results demonstrate a sex-dependent effect of the different forms of Baclofen with no or negative effects (meaning an increase in alcohol self-administration) in subgroup of females that could be linked to a differential effect on dopamine release and should warrant future clinical studies on alcohol use disorder pharmacotherapy that will deeply analyze sex difference.

KEYWORDS

binge drinking, Baclofen, enantiomers, sex, dopamine, alcohol, rat

1 Introduction

Alcohol use disorder (AUD) is a chronic disease associated with high rates of mortality and morbidity. Several AUD treatments are currently available with modest effect sizes for efficacy. For example, the numbers needed to treat (NNT) for benefit regarding the return to any drinking endpoint have been calculated to 11 and 20 for acamprosate and naltrexone, respectively (Jonas et al., 2014). The NNT estimates the number of patients that need to be treated in order to have an impact on one patient. Medications are used either to maintain abstinence [disulfiram, acamprosate, naltrexone, gamma-hydroxybutyrate, and RS(±)-Baclofen] or to reduce drinking [nalmefene and RS(±)-Baclofen].

Among the AUD pharmacotherapies, RS(±)-Baclofen [(±)-4-amino-3-(p-chlorophenyl)-butanoic acid], the racemic form, a high affinity γ-aminobutyric acid type B ($GABA_B$) receptor agonist can increase rates of abstinence and reduce alcohol craving and anxiety. The RS(±)-Baclofen (30–75 mg) has been shown to reduce both alcohol cue reactivity in prefrontal brain regions and in the percentage of heavy drinking days, but with no changes in craving (Logge et al., 2019). The RS(±)-Baclofen obtained a "Temporary Recommendations for Use" in AUD in 2014 and a Marketing Authorization Approval for doses up to 80 mg daily in 2018 (Rolland et al., 2020). Different studies on alcohol abstinence suggested that RS(±)-Baclofen is not better than placebo (Agabio et al., 2018; Minozzi et al., 2018; Rose and Jones, 2018). Other studies have reported concerns about adverse effects of RS(±)-Baclofen especially at high doses and when taken with alcohol (Rolland et al., 2014, 2015). Side effects of Baclofen also contributed to its limited clinical use and may have participated to the controversy. Preclinical studies demonstrated clear sedative effects and clinical studies reported important side effects including sedation, drowsiness and sleepiness. Controversial data about RS(±)-Baclofen efficacy in AUD may come from numerous criteria such as the optimal dose, highly variable plasma levels of RS(±)-Baclofen (Chevillard et al., 2018; Simon et al., 2018), levels of comorbid anxiety, outcomes (abstinence vs. intake reduction), lack of regarding the responder characteristics, genetics and the severity of the disease (Marsot et al., 2014; Morley et al., 2014; Durant et al., 2018; Farokhnia et al., 2018).

The RS(±)-Baclofen efficacy to decrease alcohol intake in rats has been demonstrated for a long time (Daoust et al., 1987; Colombo et al., 2000, 2005; Anstrom et al., 2003; Janak and Michael Gill, 2003; Stromberg, 2004), but at very variable doses, generally ranging from 1 to 10 mg/kg on ethanol intake or even 40 mg/kg on withdrawal signs (Colombo et al., 2000). Numerous alcohol-related behaviours (acquisition of alcohol drinking and self-administration, seeking reinstatement, relapse-like drinking) were reduced by Baclofen (Haile et al., 2021). An increase in alcohol intake has also been demonstrated after RS(±)-Baclofen treatment in two-bottle choice and operant procedures (Smith et al., 1992; Petry, 1997; Smith et al., 1999). For example, RS(±)-Baclofen reduced alcohol and sucrose responding at 5 mg/kg but increased alcohol and decreased sucrose responding at 1.25 mg/kg (Petry, 1997). The effect of Baclofen may be mediated by changes in dopamine transmission of the brain reward circuit. For example, the dopamine release in the core of the nucleus accumbens (NAcc) was inhibited by R(+)-Baclofen (Pitman et al., 2014).

It is the racemic compound that is used in patients. The racemic compound breaks down into absolute configurations of R- and S- and positive (+) and negative (−) molecular rotations. There were fewer studies on the effects of the two enantiomers S(−)-Baclofen and the R(+)-Baclofen. Enantiomers are molecules that are mirror images of each other. The biological action of the racemic compound is known to reside in the active R(+)-Baclofen (Olpe et al., 1978). The IC_{50} values for R(+)-Baclofen, S(−)-Baclofen, and racemic Baclofen for the inhibition of binding of [^{3}H]-Baclofen to GABA receptors of cat cerebellum are 15 nM, 1.77 μM, and 35 nM, respectively (Froestl et al., 1995).

R(+)-Baclofen reduced alcohol intake, motivation to consume alcohol and alcohol relapse in a relevant animal model of binge self-administration (González-Marín et al., 2018; Jeanblanc and Rolland, 2018; Jeanblanc and Sauton, 2018). In the post-dependent model of AUD R(+)-Baclofen was also more effective than RS(±)-Baclofen in reducing alcohol intake and seeking during acute withdrawal and during relapse after abstinence in male rats (Echeverry-Alzate et al., 2020). Both S(−)-Baclofen and RS(±)-Baclofen, but not R(+)-Baclofen, increased alcohol intake in a subpopulation of rats, thus highlighting a wide variability in the therapeutic responses depending on the enantiomers (Echeverry-Alzate et al., 2020). Altogether these data suggested that R(+)-Baclofen may be the most promising enantiomer; however, no data are available regarding sex-related difference in the efficacy of the different enantiomers and there are also no data regarding the effect of these enantiomers on the modulation of dopamine signaling within the NAcc, the key brain structure involved in the rewarding effects of alcohol.

Because there are no preclinical data and only one clinical study that suggested sex-related difference in RS-Baclofen response, we conducted experiments in both male and female outbred Long Evans rats. In addition, since the efficacy may be linked to pharmacokinetic factors (wide interindividual variability) (Marsot et al., 2014), we quantified plasmatic Baclofen concentrations to correlate them to the efficacy of the drugs. Finally, we used the *ex vivo* fast-scan cyclic voltammetry technique in order to measure the effects of the

different enantiomers on dopamine signaling in the core of the NAcc.

2 Materials and methods

2.1 Reagents and drug injections

Alcohol was purchased from WWR (Prolabo, Fontenay-sous-Bois, France) and diluted into tap water at a 20% concentration (v/v) for the behavioral study or in artificial cerebro-spinal fluid (aCSF) at the concentration of 100 µM for the fast-scan cyclic voltammetry experiment. NaCl, KCl, NaH_2PO_4, $MgCl_2$, $CaCl_2$, $NaHCO_3$, glucose and ascorbic acid were purchased from Sigma-Aldrich (Saint Quentin Fallavier, France). R(+)-Baclofen, S(−)-Baclofen and RS(±)-Baclofen were obtained from (Sigma Aldrich, Saint Quentin Fallavier, France). For the behavioral experiments, all drugs were dissolved in 0.9% sterile saline. Drugs were i.p. administered 30 min before the start of the operant alcohol self-administration sessions. Baclofen's enantiomers were administered at different doses, 1.5 mg/kg for the first experiment and 0.5, 1.0, 1.5, 2 or 3 mg/kg, in a volume of 1 mL/kg of body weight, subsequently. All solutions were used at room temperature, and dose and routes of administration were chosen accordingly to our previous works (González-Marín et al., 2018; Echeverry-Alzate et al., 2020). Regarding the fast-scan cyclic voltammetry experiment, Baclofen's enantiomers were used at a concentration of 100 µM in aCSF (Pitman et al., 2014).

2.2 Animals

Long Evans male ($n = 32$) and female ($n = 37$) rats were obtained from Janvier Laboratories (Le Genest-Saint-Isle, France) at the age of 7 weeks. After a week of habituation, rats weighting an average body weight of 260 ± 20 g in males and 180 ± 10 g in females started the experimental protocol. Rats were housed in 365 mm × 265 mm × 230 mm plastic isolated ventilated cages (1 rat per cage) with Lab cob 12 bedding (Serlab, Montataire, France) in a temperature- (21°C ± 1°C) and humidity-controlled (30%–70%) environment with a 12-h light (7:00–19:00)/dark cycle, with free access to food diet n°3436 (Serlab, Montataire, France) and water. All experiments were performed between 2:00 p.m. and 5:00 p.m.

A first cohort of 19 rats (10 females and 9 males) was used for the dose responses experiments with the 3 forms of Baclofen. We chose a within-subject design as already published (González-Marín et al., 2018; Jeanblanc and Sauton, 2018). In this cohort, animals received the R(+)-Baclofen (3 doses in a random order, each dose was tested after at least a 2-day washout period). We previously showed that a total recovery of basal levels of alcohol self-administration is observed with Baclofen after a 2-day washout period (González-Marín et al., 2018; Jeanblanc and Sauton, 2018). One week after the last dose, they received S(−)-Baclofen (4 doses in a random order). Finally, 1 week after the last dose they received RS-Baclofen (5 doses in a random order).

A second cohort of 30 animals (15 females and 15 males) was used to test the individual variability of the dopamine efflux at the 1.5 mg/kg dose of the 3 forms of Baclofen. In this cohort, animals received all doses of the 3 forms of Baclofen in a random order. We also measured blood levels of Baclofen after injection of 1.5 mg/kg RS-Baclofen in all animals, in order to look for correlations between Baclofen effectiveness and its blood levels.

A third cohort of 20 animals (12 females and 8 males) was used, and not exposed to alcohol, for the measurements of Baclofen and its metabolites to investigate the sex effects after injection of the 3 different forms of Baclofen at the dose of 1.5 mg/kg.

2.3 Ethical statement

All of the experiments were submitted for prior approval to the local ethical committee (CREMEAP: Comité Régional d'Ethique en Matière d'Expérimentation Animale de Picardie) and validated by the French Ministry in charge of the Research under the number #2145-201510051547534v2. All experiments were performed in conformity with the European Community guiding principles for the care and use of animals (2010/63/UE, CE Off. J. 20 October 2010), the French decree n° 2013–118 (French Republic Off. J., 2013). All the procedures used were declared to and approved by the local animal welfare structure (Structure du Bien Etre Animal, SBEA).

2.4 Blood concentrations of Baclofen and metabolites

Blood collection was done on a separate day 30 and 90 min after the i.p. injection of the RS(±)-Baclofen 1.5 mg/kg). Rats were anesthetized under isoflurane (5% for 2 min) and blood was collected in heparinized tubes (±200 µl) from the sublingual vein. Samples were centrifuged and stored on ice. Blood levels of Baclofen (ng/mL) were determined by HPLC (High Performance Liquid Chromatography).

Baclofen and its deaminated metabolite [M1, 3-(4-chlorophenyl)-4-hydroxybutyric acid] were determined by liquid chromatography (Shimadzu, Marne-la-Vallée, France) coupled to a tandem mass spectrometer (3200Qtrap, Sciex, Les Ulis, France). Briefly, rats were i.p. injected with either one of the 3 forms of Baclofen at the dose of 1.5 mg/kg. Blood was collected 30 and 240 min after the injection using the same sublingual technique than described above. Then, Baclofen and its metabolite were extracted from 50 µL of plasma by adding 250 µL of an iced acetonitrile solution containing the internal standard (baclofen-d4) at 100 ng/mL. After centrifugation, 250 µL of the supernatant was evaporated to dryness and then taken up by 100 µL of a mixture acetonitrile/water (10/90, v/v) before transfer to a vial for injection into the chromatographic system. Chromatographic separation was performed at 40°C on an ultra PFP Propyl column (5 µm, 50 mm × 2.1 mm, Restek, Lisses, France). The column was eluted with a gradient of acetonitrile with 0.1% formic acid and ultra-pure water with 0.1% formic acid delivered at a flow rate of 0.5 mL/min. Data were acquired in multiple reaction monitoring mode after ionization in positive (for the Baclofen) or negative (for M1) electrospray ionization modes. We also measured Baclofen and its metabolites after an injection of 3 mg/kg RS-Baclofen in order

to get a result with a 1:1 ratio of both enantiomer (1.5 mg/kg of each enantiomer). We did not see any sex differences in this latter experiment (data not shown).

2.5 Self-administration of alcohol

Rats were trained to self-administer alcohol (0.1 mL of a 20% alcohol solution v/v per delivery) in a binge drinking pattern, as described previously (González-Marín et al., 2018; Jeanblanc and Sauton, 2018). Briefly, rats underwent a 2-bottle-choice 20% intermittent access paradigm for 4 weeks before the self-administration sessions. The schedule of self-administration sessions was: 2 overnight sessions under a fixed ratio 1 schedule (FR1), FR1—1 h for 5-7 sessions, FR3—1 h for 5-7 sessions, FR3—30 min for 5-7 sessions and finally FR3-15 min until stable baseline is reached. All sessions (except the overnight ones) were conducted between 2:00 p.m. and 5:00 p.m. This reduction in the duration of the sessions led to intoxicating levels of alcohol self-administration (Jeanblanc and Sauton, 2018). The number of active and inactive lever presses as well as the number of reinforcers obtained were recorded during each operant self-administration session. A within-subjects design was used in which each rat was its own control and thus received the different doses of the enantiomers in random order. Washout sessions were performed between each new session of drug test, as previously described (Echeverry-Alzate et al., 2020).

2.6 Mesolimbic phasic dopamine transmission: Fast-scan cyclic voltammetry (FSCV)

Rats were euthanized (deep anesthesia with Isoflurane 5% and decapitation) and coronal slices containing the NAcc were collected to measure electrically evoked dopamine transmission in the core of the NAcc (Figure 4 upper panels). Coronal slices corresponding to the Paxinos and Watson atlas (1998) slices from the +1.60 to +1.00 mm from Bregma were used for this study. Recording electrodes were implanted below the anterior commissure and the stimulating electrode 100 µm below the recording electrode. Rats were anesthetized with isoflurane (IsoVet, 5%) before being decapitated, and their brain were extracted and immersed in ice-cold artificial cerebrospinal fluid (aCSF) (NaCl 126 mM, KCl 2.5 mM, NaH_2PO_4 1.1 mM, $MgCl_2$ 1.4 mM, $CaCl_2$ 0.5 mM, $NaHCO_3$ 18 mM, Glucose 11 mM, ascorbic acid 0.4 mM, pH 7.2–7.4) and glued into a vibratome (Leica, VT 1200S). Coronal slices (250 µm thick) of the NAcc were selected and stored in a 31°C aCSF (NaCl 126 mM, KCl 2.5 mM, NaH_2PO_4 1.1 mM, $MgCl_2$ 1.4 mM, $CaCl_2$ 2.4 mM, $NaHCO_3$ 18 mM, Glucose 11 mM, pH 7.2–7.4) reservoir gassed with carbogen (95% O_2, 5% CO_2) for at least 1 h. After rest, the slices were transferred to a recording chamber and perfused with aCSF (3 ml/min, 31°C). Then, slices were placed in a recording chamber and were continuously superfused with an aCSF solution containing 2.4 mM $CaCl_2$ saturated with 95% O_2 and 5% CO_2. FSCV using carbon-fiber microelectrodes (7 µm diameter; 125 µm exposed surface; Goodfellow, Cambridge, United Kingdom) was used to detect extracellular DA concentration. The scan rate was 400 V/s with a sampling interval of 100 ms and the scan range was from −0.4 to +1.3 V (vs. Ag/AgCl). DA release was evoked by a single stimulation of 300 µA for 0.5 ms every 5min. The concentration of the extracellular DA was calculated based on a standard curve

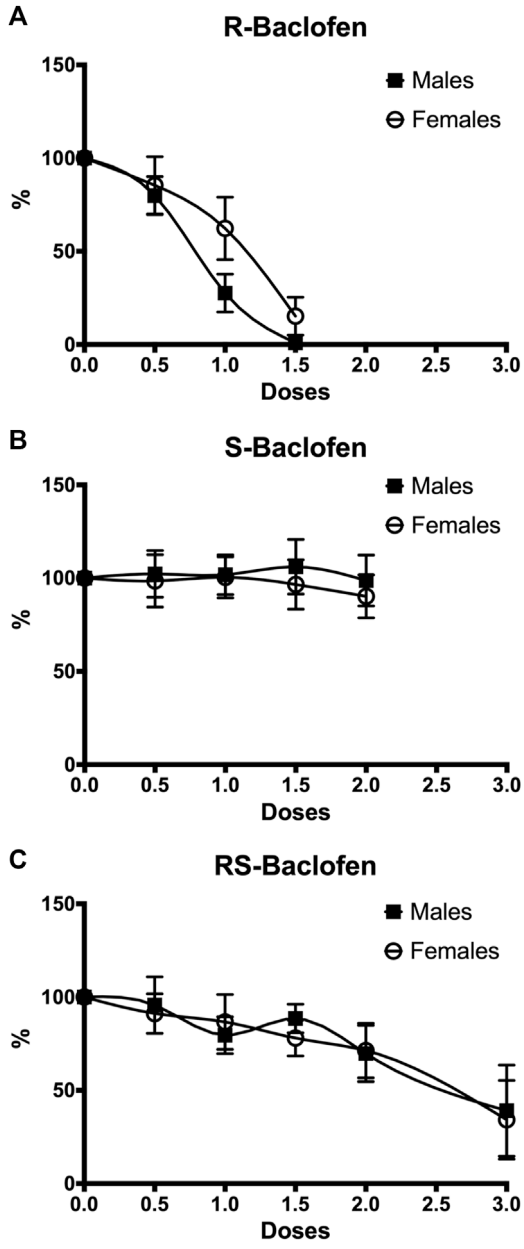

FIGURE 1
Dose-response effects on alcohol intake in both males (n = 9) and females (n = 10) for R(+)-Baclofen **(A)**, S(−)-Baclofen **(B)** and RS-Baclofen **(C)**. All doses of the different forms of Baclofen were administered in a random order. Rats received first the R(+)-Baclofen, then the S(−)-Baclofen and finally the RS-Baclofen. A significant dose and sex effect was found only for the R(+)-Baclofen. Data have been normalized so that the 100% represents the level of ethanol self-administration during the last session of the 5 consecutive sessions (days) of habituation (saline but no baclofen injection).

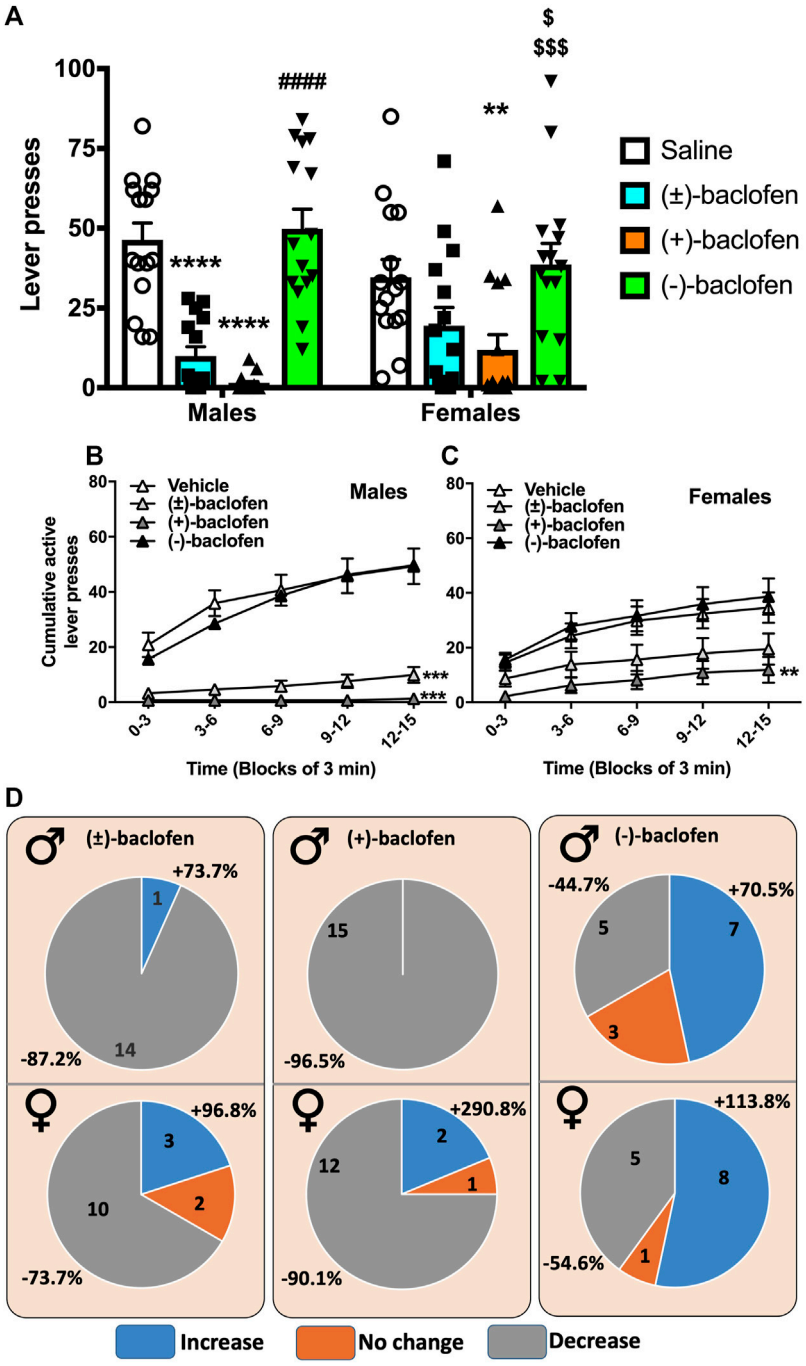

FIGURE 2
Effect of the different forms of Baclofen on alcohol operant self-administration in male and female rats. **(A)** The RS(±)-, the R(+)- and the S(−)-Baclofen were administered i.p. at the dose of 1.5 mg/kg 30 min prior to a 15-min session of alcohol self-administration. Each rat was its own control and received the 4 injections in random order. Results are expressed as Mean ± SEM of pure alcohol consumed in g/kg. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, **** $p < 0.0001$, #### $p < 0.0001$ vs. R (+) and RS (±)-Baclofen, and $$$$ $p < 0.0001$ vs. RS(±)-Baclofen. **(B)** Cumulative lever presses observed after the injection of the different forms of Baclofen in male rats. Results are expressed as Mean ± SEM of the cumulative presses in 3-min bins over the 15 min session. ***$p < 0.001$ vs. Vehicle. **(C)** Cumulative lever presses observed after the injection of the different forms of Baclofen in female rats. Results are expressed as Mean ± SEM of the cumulative presses in 3-min bins over the 15 min session. **$p < 0.01$ vs. Vehicle. **(D)** Distribution of animal responses regarding sex (M for males and F for females on the left corner) and the treatments. Numbers inside the circle indicate the number of animals over the total of 15 rats. Percentages outside the circle express the amplitude of the variation in alcohol self-administration as compared to the vehicle treatment. Light grey represents a decrease in alcohol self-administration. The mild grey represents no change (between (−10 and +10%) as compared to vehicle. The dark grey represents an increase in alcohol self-administration as compared to vehicle. The results depicted in each of these 4 panels were provided by the same cohort of rats, 15 males and 15 females.

(0.1, 1, and 10 μM DA) obtained for each microelectrode at the end of each recording session.

All analyses of release and uptake were conducted on the concentration-*vs.*-time traces. These traces were fit to a model describing dopamine signaling as a balance between release and uptake, using the Michaelis-Menten equation [see(Wu et al., 2001)], with the Lvit software (Scott Ng-Evans, Electronics and Materials Engineering Shop, Seattle, WA, United States). The equation was as follow:

$$d[\mathrm{DA}]/d\mathrm{t} = f[\mathrm{DA}]_p - V_{max}/((K_m/[\mathrm{DA}]) + 1)$$

Where [DA] is the instant extracellular concentration of DA released, f is the frequency of stimulation, $[DA]_p$ is dopamine concentration released per pulse, and V_{max} and K_m were respectively the velocity and affinity constants of the dopamine transporter (DAT). K_m was fixed at a constant value of 200 nM (Wu et al., 2001). $[DA]_p$ reflects presynaptic mechanisms regulating release as those of the auto-receptors (D2/D3 activity) (Kennedy et al., 1992). Peak dopamine concentration was extracted for each trace before fitting to the model in order to obtain a $[DA]_{max}$ value, reflecting maximum extracellular dopamine concentration, and was used as a parameter of dopamine release. $[DA]_p$ and V_{max} values were modulated until fitting the traces to the model, with a correlation coefficient of 0.8 or more with our experimental data, using the Lvit software.

2.7 Statistical analysis

Statistical analysis was done only on datasets of $n \geq 5$. Appropriate sample sizes using the expected variance and effect size were estimated from the previous experiments using similar methods (González-Marín et al., 2018; Jeanblanc and Sauton, 2018). Animals were randomly allocated to each experimental group. In general, the group sizes for each experiment are provided within the figure legends. All experiments were performed in a blinded manner in order to limit personal bias. The SigmaPlot 11.0 (Systat Software, Inc.) and Prism 8 (GraphPad) softwares were used for all statistical analyses. Data are expressed as Mean ± SEM and analyzed with an ANOVA (1- or 2-way) with repeated measures. Multiple comparisons were performed using the Tukey test. A Pearson test was used for the correlation studies. For non-parametric analysis (inactive lever presses) a Kruskal-Wallis test was used followed by a Dunn's Multiple Comparison Test. The significance of the analysis was set to 0.05. When not significant, probability of the test is summarized "ns".

3 Results

3.1 Effects of the different forms of Baclofen on alcohol self-administration

In a first cohort of 9 males and 10 females, dose-responses for the 2 enantiomers and the racemic form have been generated and results are presented in Figure 1. For the R(+)-Baclofen analysis, the 2-way RM ANOVA revealed a significant effect of the factor dose ($F_{(3,51)} = 6.61$, $p < 0.0001$) and of the factor sex ($F_{(1,17)} = 0.77$, $p = 0.046$) and showed no interaction between these factors ($F_{(3,51)} = 0.06$, $p = 0.83$). For the S(−)-Baclofen analysis, the 2-way RM ANOVA revealed no significant effect of the factor dose ($F_{(4,64)} = 0.19$, $p = 0.94$) and of the factor sex ($F_{(1,16)} = 0.16$, $p = 0.69$) and showed no interaction between these factors ($F_{(4,64)} = 0.10$, $p = 0.97$). For the RS(±)-Baclofen analysis, the 2-way RM ANOVA revealed a significant effect of the factor dose ($F_{(5,80)} = 7.01$, $p < 0.0001$) but not of the factor sex ($F_{(1,16)} = 0.02$, $p = 0.87$) and showed no interaction between these factors ($F_{(5,80)} = 0.12$, $p = 0.98$).

In a second cohort, the 3 forms of Baclofen were tested at the dose of 1.5 mg/kg vs. a saline injection and the results are depicted in Figure 2. We found that the S(−)-Baclofen had no effect on the average levels of alcohol consumed. The RS(±)-Baclofen at this dose and in this cohort was more efficacious in decreasing alcohol self-administration in males than in females. Regarding R(+)-Baclofen, it was more efficacious than the racemic form in both sexes.

The analysis of the self-administered ethanol expressed as the number of active lever presses (Figure 2A) with a 2-way RM ANOVA, revealed no effect of the factor sex ($F_{(1,28)} = 0.29$, $p = 0.86$), a significant effect of treatment ($F_{(3,84)} = 30.24$, $p < 0.0001$) and also a significant interaction between those factors ($F_{(3,84)} = 3.35$, $p = 0.022$). The *post hoc* analysis revealed significant differences between groups. Within the males, the Tukey test indicated a significant difference between the Saline group and both the RS(±)-Baclofen ($p < 0.0001$) and R(+)-Baclofen ($p < 0.0001$). The S(−)-Baclofen was significantly different from the R(+)- and the RS(±)-Baclofen ($p < 0.0001$) but not from the Saline group. Regarding the females, from the 3 forms of Baclofen, only the R(+) showed a significant difference from the Saline group ($p = 0.006$) and from the S(−)-Baclofen group ($p = 0.0009$). This S(−)-Baclofen group was also significantly different from the RS(±)-Baclofen group ($p = 0.029$). Between the sexes, the males displayed a significantly larger effect than the females with the RS(±)-Baclofen. Results were similar when analyzed by the self-administered ethanol expressed as g of pure ethanol per kg of body weight (Supplementary Figure 1A). Regarding inactive lever presses, only a moderate decrease in responding was observed after the R(+)-Baclofen injection in the males (Supplementary Figure 1B). But the response levels were already so low in average that this decrease was difficult to interpret. In the female group, no difference was observed for the numbers of inactive lever presses (Supplementary Figure 1C).

Patterns of self-administration in males and females are shown on Figures 2B, C and no statistical analysis is provided because of the nature (cumulative) of the data. In both sexes, the R(+)- and the RS(±)-Baclofen groups seemed different (lower cumulative responses) from both the Saline and the S(−)-Baclofen groups. Sex differences were observed by analyzing the inter-response intervals (IRI, Supplementary Figures 2A, B). In the Males group, we observed a decrease in the proportion of IRI within the (0, 1 s) interval for both the R(+) and the RS(±)-Baclofen ($p < 0.001$, Supplementary Figure 2A) and an increase of the proportion for the interval (1, 2 s) for the R(+)-Baclofen as compared to the Saline, the RS(±)- and the S(−)-Baclofen groups ($p < 0.001$). The longest IRI (20 s and more) were also increased in the males group after the administration of R(+) and RS(±)-Baclofen ($p < 0.001$). On the contrary, in the Females group (Supplementary Figure 2B), the

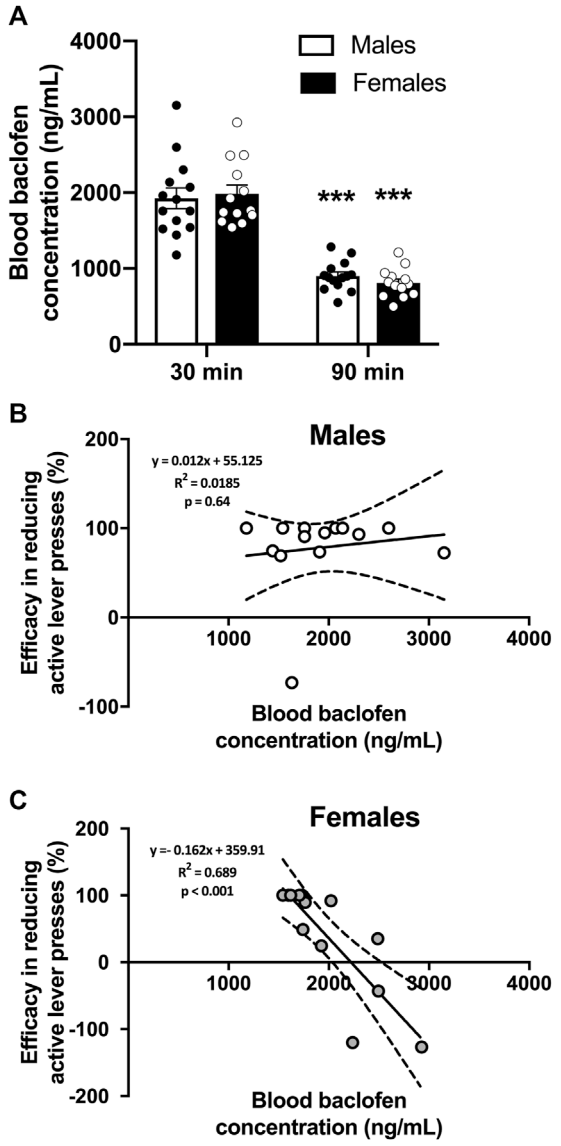

FIGURE 3
Blood RS(±)-Baclofen concentrations and correlation to its efficacy. **(A)** Blood samples were collected 30 and 90 min after the i.p. administration of a dose of 1.5 mg/kg of RS(±)-Baclofen. Results are expressed as Mean ± SEM blood Baclofen concentration in ng/mL. ***$p < 0.001$ vs. 30-min data within each sex. **(B,C)** Correlations between blood Baclofen concentration and efficacy in reducing alcohol operant self-administration in males **(B)** and females **(C)**. Blood Baclofen concentrations are expressed in ng/mL. Positive variations indicate an efficacy in reducing self-administration, negative numbers indicate opposite effect, meaning an increase in alcohol self-administration. For **(A–C)** males $n = 14$; females $n = 13$.

decrease in the short interval was only observed after the R(+)-Baclofen treatment ($p < 0.01$). No differences were observed for the last IRI (20, ∞) between the 4 treatment groups.

In a previous study (Echeverry-Alzate et al., 2020), we showed that, within a same group, behavioral responses can be very different from one individual to another. We thus analyzed the variation of alcohol consumed and categorized them into 3 groups: 1. no change meaning that the variation in alcohol self-administration was lower than 10% from the Saline; 2. decrease for the rats who showed a decrease of at least 10% from baseline; and finally, 3. increase, for the rats showing an increase of more than 10% of their baseline self-administration (Figure 2D). We found that for the RS(±)-Baclofen treatment, 14 of 15 male rats showed a decrease in alcohol self-administration with an amplitude of −87.2% while in the females rats only 10 showed a decrease for an average amplitude of −73.7%. In both groups we found few rats showing an increase (1 for the males: +73%; 3 for the females: +96.8%). The R(+)-Baclofen seemed more effective since the 15 males and 12 females showed a decrease (−96.5% and −90.1% respectively). Regarding S(−)-Baclofen, the results were close between the males and the females rats with 7 males and 8 females showing an increase in alcohol self-administration (+70.5 and +113.8% respectively), 5 males and 6 Females exhibiting a decrease (−44.7% and −54.6% respectively).

3.2 RS(±)-Baclofen's blood concentration and efficacy

Blood samples were collected 30 and 90 min after RS(±)-Baclofen (1.5 mg/kg) was i.p. injected in the same animals of the previous experiment. We found that RS(±)-Baclofen was similarly metabolized in males and females (Figure 3A). However, the efficacy of RS(±)-Baclofen was independent of its blood concentration in males while it was inversely correlated in females with an increase in alcohol self-administration at the highest RS(±)-Baclofen's blood concentrations. The concentration of Baclofen in the blood was measured by HPLC and the data analyzed using a 2-way RM ANOVA. Three samples were excluded because the detected levels were below the detection threshold. This analysis revealed an effect of the factor timepoint ($F_{(1,25)} = 290.75$, $p < 0.001$) but not of the factor sex ($F_{(1,25)} = 0.02$, ns) and no interaction between these factors ($F_{(1,25)} = 1.37$, ns). The Tukey test indicated a significant difference between the timepoints 30 and 90 min for both sexes ($p < 0.001$).

Then, we plotted the Baclofen concentration observed at the 30 min timepoint with the efficacy of the baclofen injection obtained from the previous experiment. The efficacy was calculated as the percentage of variation in the level of alcohol consumed between the RS(±)-Baclofen injection and the Saline injection. We found that there was no correlation (Pearson test, p = ns) between the blood Baclofen concentration in males (Figure 3B) whereas we observed a negative correlation (Pearson test, $p < 0.001$) in females (Figure 3C). In this latter group, we found that the highest Baclofen blood concentration resulted in an increase in alcohol self-administration while with lower baclofen concentrations the rats showed a decrease in alcohol self-administration.

3.3 Baclofen's enantiomers metabolism

Naïve rats received each of the different enantiomers (1.5 mg/kg i.p.) at least 5 days apart. Thirty and 240 min after each injection, blood was collected, centrifuged and plasma analyzed to measure the concentrations of Baclofen and its metabolites. For all the forms of Baclofen administered, the profile was quite different at the

TABLE 1 Statistical analysis of the blood concentration of the different baclofen enantiomers and their metabolites after an i.p. injection of a dose of 1.5 mg/kg at 30 and 240 min post-administration. Statistical analysis of the blood concentrations of the different forms of baclofen and their metabolites. The enantiomers and the racemic form were i.p. injected at a dose of 1.5 mg/kg in males and females, then blood was collected 30 and 240 min after the injection. Samples were analyzed by HPLC. Bold characters indicate a significant main effect and/or an interaction following a 2-way RM ANOVA.

Figure number	Factor name	F values	*p*-value
Figure 4A: Blood RS-Baclofen concentration in males and females	Sex	$F_{(1,13)} = 3.82$	$p = 0.073$
2-way RM ANOVA	**Timepoint**	$F_{(1,13)} = 105.89$	$\mathbf{p < 0.001}$
	Sex x Timepoint	$F_{(1,13)} = 4.23$	$p = 0.060$
Figure 4B: Blood Metabolite of RS-Baclofen concentration in males and females	Sex	$F_{(1,13)} = 1.70$	$p = 0.215$
2-way RM ANOVA	**Timepoint**	$F_{(1,13)} = 67.54$	$\mathbf{p < 0.001}$
	Sex x Timepoint	$F_{(1,13)} = 3.38$	$p = 0.086$
Figure 4C: Ratio Metabolites/RS-Baclofen blood concentration in males and females	Sex	$F_{(1,26)} = 2.161$	$p = 0.154$
2-way RM ANOVA	**Timepoint**	$F_{(1,26)} = 13.304$	$\mathbf{p < 0.001}$
	Sex x Timepoint	$F_{(1,26)} = 0.907$	$p = 0.35$
Figure 4D: Blood R-Baclofen concentration in males and females	**Sex**	$F_{(1,12)} = 6.37$	$\mathbf{p < 0.05}$
2-way RM ANOVA	**Timepoint**	$F_{(1,12)} = 208.35$	$\mathbf{p < 0.001}$
	Sex x Timepoint	$F_{(1,12)} = 6.62$	$\mathbf{p < 0.05}$
Figure 4E: Blood Metabolite of R-Baclofen concentration in males and females	Sex	$F_{(1,15)} = 1.26$	$p = 0.28$
2-way RM ANOVA	Timepoint	$F_{(1,15)} = 16.99$	$\mathbf{p < 0.001}$
	Sex x Timepoint	$F_{(1,15)} = 0.67$	$p = 0.427$
Figure 4F: Ratio Metabolites/R-Baclofen blood concentration in males and females	Sex	$F_{(1,30)} = 1.579$	$p = 0.219$
2-way RM ANOVA	**Timepoint**	$F_{(1,30)} = 4.834$	$\mathbf{p < 0.05}$
	Sex x Timepoint	$F_{(1,30)} = 0.076$	$p = 0.785$
Figure 4G: Blood S-Baclofen concentration in males and females	**Sex**	$F_{(1,13)} = 7.706$	$\mathbf{p < 0.05}$
2-way RM ANOVA	**Timepoint**	$F_{(1,13)} = 233.36$	$\mathbf{p < 0.001}$
	Sex x Timepoint	$F_{(1,13)} = 0.149$	$p = 0.706$
Figure 4H: Blood Metabolite of S-Baclofen concentration in males and females	**Sex**	$F_{(1,13)} = 6.37$	$\mathbf{p < 0.05}$
2-way RM ANOVA	**Timepoint**	$F_{(1,13)} = 59.47$	$\mathbf{p < 0.001}$
	Sex x Timepoint	$F_{(1,13)} = 0.213$	$p = 0.652$
Figure 4I: Ratio Metabolites/S-Baclofen blood concentration in males and females	**Sex**	$F_{(1,26)} = 10.104$	$\mathbf{p < 0.01}$
2-way RM ANOVA	**Timepoint**	$F_{(1,26)} = 128.23$	$\mathbf{p < 0.001}$
	Sex x Timepoint	$F_{(1,26)} = 12.784$	$\mathbf{p < 0.001}$
Blood concentrations of RS-Baclofen after a dose of 3 mg/kg in males and females	Sex	$F_{(1,12)} = 0.090$	$p = 0.77$
2-way RM ANOVA	**Timepoint**	$F_{(1,12)} = 1041.80$	$\mathbf{p < 0.001}$
	Sex x Timepoint	$F_{(1,12)} = 0.038$	$p = 0.849$

timepoint 30 min with sometimes a higher concentration in the female group [RS(±)-Baclofen] and for the others, the opposite. At the second timepoint, 240 min post-injection, no clear sex difference was observed between the enantiomers. The detailed ANOVAs are compiled in Table 1. The multiple comparisons performed using the Tukey test are described below. For all the forms studied [different enantiomers and their metabolite: 3-(4-Chlorophenyl)-4-hydroxybutyric acid] and for the ratios, the Tukey test revealed a significant difference between both timepoints within each sex group (all p's < 0.01). Some samples were excluded because the detected levels were below the detection threshold. In regards with sex groups analysis, the tests indicated a significant difference between males and females for the RS(±)-Baclofen (Figure 4A) and the R(+)-Baclofen (Figure 4B) for the timepoint 30 min ($p < 0.01$). Interestingly, for the RS(±)-Baclofen, the blood concentration was higher in the female group whereas for the R(+)-Baclofen it is the opposite. No differences were observed for the S(−)-Baclofen (Figure 4C). For all the 240 min timepoints, no differences were

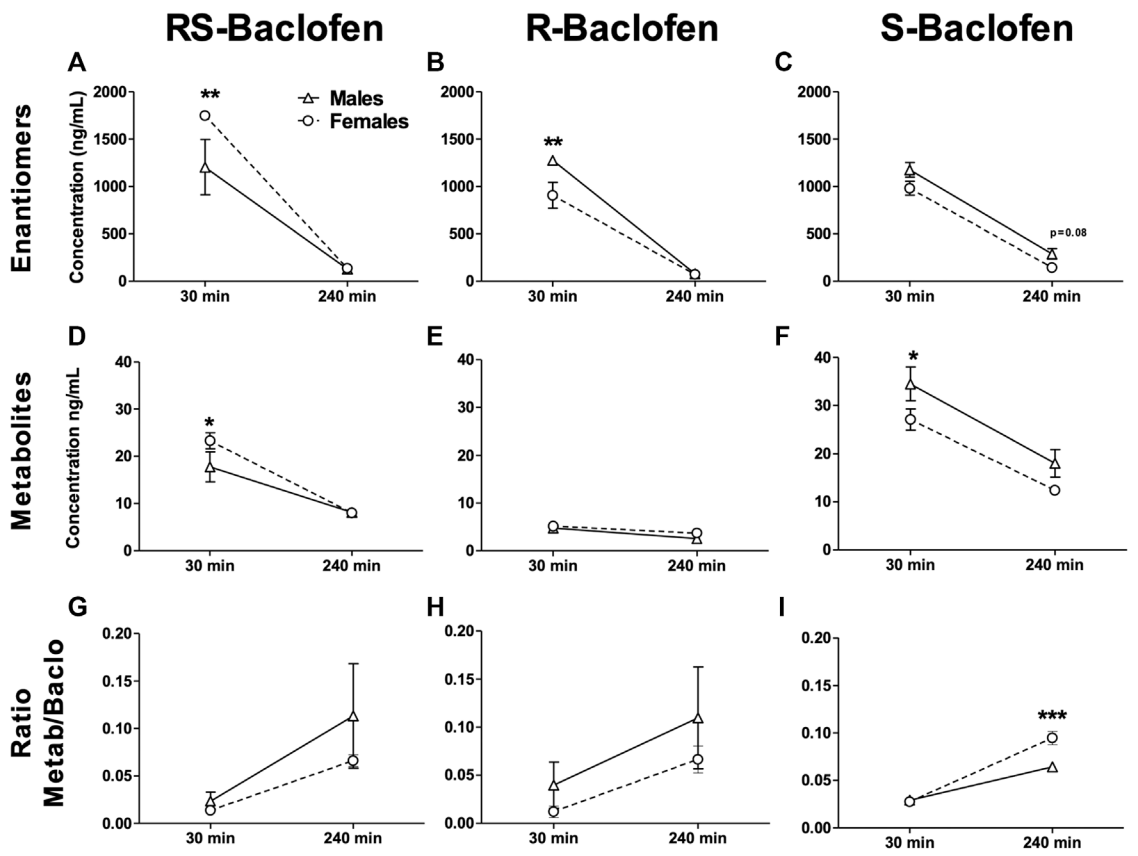

FIGURE 4
Metabolism of baclofen's enantiomers in naïve males and female rats. The 3 Baclofen forms were i.p. injected randomly at the dose of 1.5 mg/kg and blood was collected 30 and 240 min after the administration. HPLC analysis was used to analyze the concentration of the enantiomers **(A–C)**, and the metabolite 3-(4-Chlorophenyl)-4-hydroxybutyric acid **(D–F)**. The ratio metabolite over enantiomers concentrations was then calculated **(G–I)**. Results are expressed as Mean ± SEM of blood concentrations in ng/mL. For **(A,D,G)** males $n = 5$; females $n = 10$. For **(B,E,H)** males $n = 8$; females $n = 9$. For **(C,F,I)** males $n = 6$; females $n = 9$. For clarity purpose we did not depict the significant differences we found for all the comparisons between the 2 timepoints within each sex group. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$.

observed for any of the baclofen forms (Figures 4A–C). The level of the metabolites after the RS(±)-Baclofen injection was relatively low (Figure 4D) as compared to the Baclofen concentration suggesting a low level of metabolism and a high level of excretion. In regards with the R(+)-Baclofen, it is noteworthy that the levels of metabolites (Figure 4E) were, as expected (Sanchez-Ponce et al., 2012), even lower than previously observed with the racemic Baclofen (Figure 4D). At the 1st timepoint, sex differences were revealed by the *post hoc* for the racemic form of Baclofen (Figure 4D) and for the S(−)-Baclofen form (Figure 4F) with higher levels for the females groups with the racemic injection and the opposite with the S(−)-Baclofen (both p's < 0.05). For the 3 forms of baclofen the levels of metabolites (Figures 4D–F) were also systematically significantly lower at the timepoint 240 min compared to the timepoint 30 min (all p's < 0.01). Regarding the ratios (Figures 4G–I), no main effect was observed for the factor sex. An interaction between the factors sex and timepoint was revealed only for the S(−)-Baclofen (Table 1) with a significant difference between both sexes at the timepoint 240 min (Figure 4I) with the female group exhibiting a higher ratio metabolites/S(−)-Baclofen than the males.

The RS(±)-Baclofen was also injected at the dose of 3 mg/kg and we found about twice the concentration than for the 1.5 mg/kg dose (2,978.57 ± 138.61 and 2,967.14 ± 112.52 ng/mL at the 30 min timepoint, 235.14 ± 15.76 and 190.43 ± 7.48 ng/mL for the 240 timepoint for males and females respectively). No difference between sex groups were observed.

3.4 Baclofen's regulation of evoked dopamine release within the NAcc

Baseline levels of the 3 parameters were not changed by chronic alcohol self-administration except the [DA]p that was significantly decreased in females (Supplementary Figure S3). The 3 forms of Baclofen were tested vs. baseline at the dose of 100 µM in FSCV, and the results are depicted in Figure 5. Within the group of alcohol-naïve rats, we found a decrease of the DA concentrations induced by the RS(±)-, R(+)- and S(−)-Baclofen in both males and females. In alcohol-exposed group, we observed a small decrease (not significant) of the DA levels in males induced by the R(+)- and RS(±)-Baclofen whereas an increase in DA release was observed with

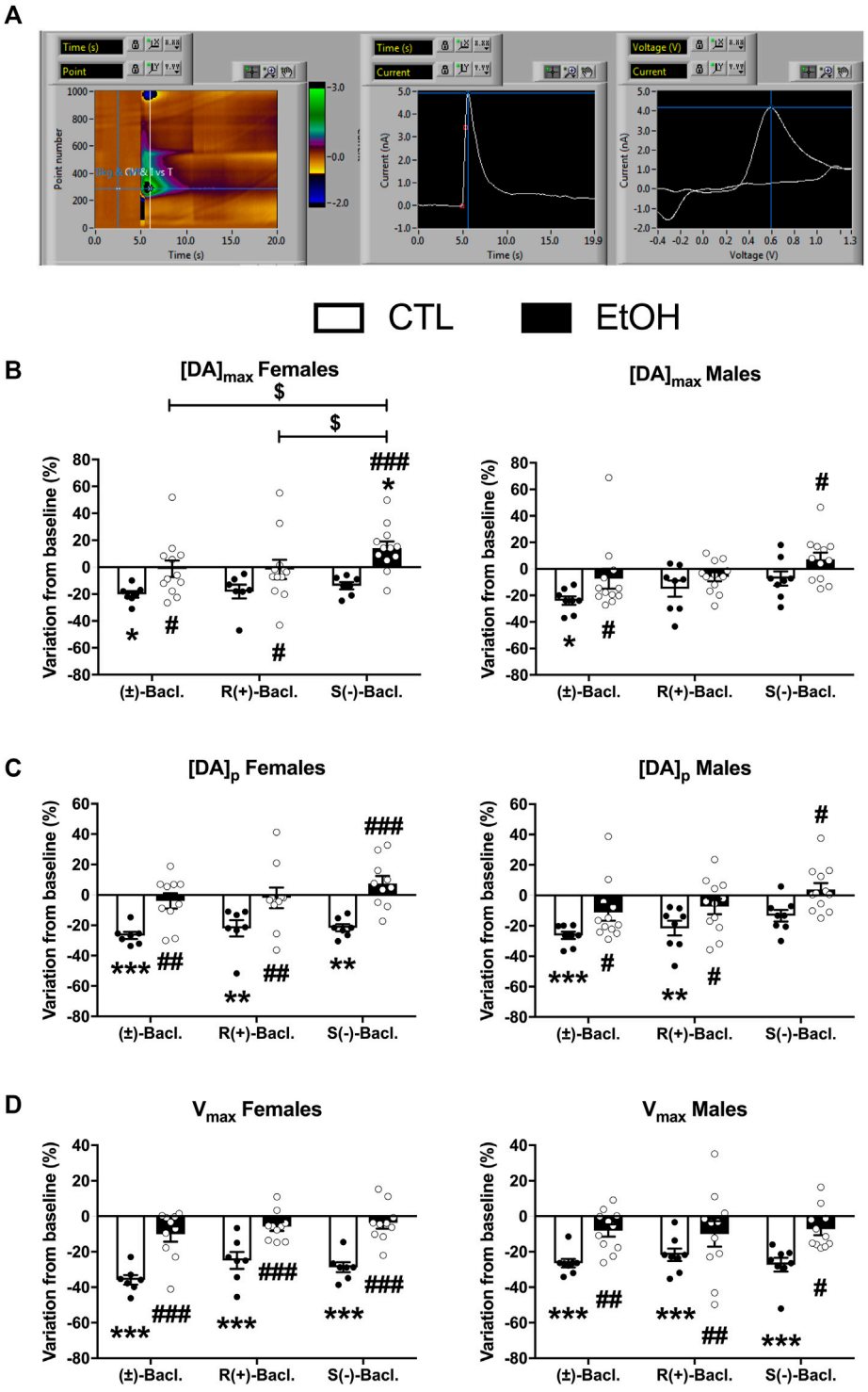

FIGURE 5
Effect of the different forms of Baclofen (100 μM) on phasic dopaminergic transmission in the nucleus accumbens core in male and female rats and in both control and alcohol groups. **(A)** Characteristic voltamogramm of dopamine, recorded currents. **(B–D)** Effect of different forms of Baclofen on $[DA]_{max}$, $[DA]_p$ and V_{max} in both male and female rats, respectively. Results are expressed as mean ± SEM of variation from baseline (%).

the S(−)-Baclofen. In females, the R(+) and the RS(±) forms had no effect on the evoked-DA levels but the S(−)-Baclofen also increased the DA release. See details of the statistical analysis for [DA]max, [DA]p and Vmax in Figure 3 and Table 2.

Because a correlation is expected between the peak of dopamine concentration and the V_{max} values, we checked the correlation at baseline and also after treatment with the different forms of Baclofen. We observed the expected correlations at baseline (data

TABLE 2 Statistical analysis of the Baclofen's regulation of evoked dopamine release within the NAcc, presented on Figure 4. Statistical analysis of the Baclofen's regulation of evoked dopamine release within the NAcc. Bold characters indicate a significant main effect and/or an interaction following a 2-way RM ANOVA.

Figure panel	Factor name	F values	*p*-value
$[DA]_{max}$: female rats (Figure 4B, left panel)	**Alcohol exposure slice treatment**	**F(1,51) = 9.42**	***p* < 0.01**
2-way RM ANOVA	**interaction**	**F(3,51) = 3.79**	***p* < 0.05**
		F(3,51) = 3.54	***p* < 0.05**
$[DA]_{max}$: male rats (Figure 4B, right panel)	**Alcohol exposure slice treatment**	**F(1,54) = 6.86**	***p* < 0.05**
2-way RM ANOVA	interaction	**F(3,54) = 5.5**	***p* < 0.01**
		F(3,54) = 1.24	ns
$[DA]_{p}$: female rats (Figure 4C, left panel)	**Alcohol exposure slice treatment**	**F(1,45) = 19.28**	***p* < 0.001**
2-way RM ANOVA	**interaction**	**F(3,45) = 5.24**	***p* < 0.01**
		F(3,45) = 4.67	***p* < 0.01**
$[DA]_{p}$: male rats (Figure 4C, right panel)	**Alcohol exposure slice treatment**	**F(1,51) = 9.81**	***p* < 0.01**
2-way RM ANOVA	interaction	**F(3,51) = 8.69**	***p* < 0.001**
		F(3,51) = 1.84	ns
V_{max}: female rats (Figure 4D, left panel)	**Alcohol exposure slice treatment**	**F(1,45) = 62.55**	***p* < 0.001**
2-way RM ANOVA	**interaction**	**F(3,45) = 19.02**	***p* < 0.001**
		F(3,45) = 7.33	***p* < 0.001**
V_{max}: male rats (Figure 4D, right panel)	**Alcohol exposure slice treatment**	**F(1,51) = 9.96**	***p* < 0.01**
2-way RM ANOVA	**interaction**	**F(3,51) = 13.25**	***p* < 0.001**
		F(3,51) = 3.27	***p* < 0.05**

not shown) and the different forms of Baclofen did not change the correlations (Supplementary Figure S4).

4 Discussion

4.1 Effects on alcohol self-administration

A first cohort of animals self-administering alcohol in a binge drinking pattern was tested with a full dose response analysis in which all rats received all doses of the different forms of Baclofen in a sequential order [R(+) > S(−) > RS(±)]. Our results showed dose-responses for RS(±)-Baclofen and R(+)-Baclofen and revealed that females seemed less sensitive than males for R(+)-Baclofen effects. Results on males and R(+)-Baclofen show that the dose-response was consistent with our previous study (González-Marín et al., 2018). We also previously showed that R(+)-Baclofen (both 1 and 2 mg/kg doses) was more effective than S(−)-Baclofen in alcohol dependent rats (Echeverry-Alzate et al., 2020). Since a within-subjects design has been used in the present study, a possible interactive effect between treatments cannot be ruled out and thus it may explain why the sensitivity to the RS(±)-Baclofen seemed reduced in the first cohort of animals compared with the sensitivity to single 1.5 mg/kg dose tested in the second cohort. It should be pointed out that between-subjects design is more conservative while within-subjects design has more power.

To deeply analyze individual responses, we tested the different Baclofen forms in another cohort of animals using the 1.5 mg/kg dose and we showed that both the racemic form and the R(+)-Baclofen were always more effective in males than in females. Moreover, we demonstrated here that the racemic form, at this dose, was not effective in reducing alcohol self-administration in female rats. Regarding S(−)-Baclofen, the average alcohol self-administration was not altered by its administration in either males or in females. Overall, regarding the number of rats and the amplitude of increase of alcohol self-administration, whatever the enantiomer, females displayed the highest amplitude of change. The bimodal effect of both RS(±)- or R(+)-Baclofen enantiomers in females, with many rats reducing their intake but also several ones remaining engaged in alcohol intake may reveal lower response to the effect of Baclofen to reduce alcohol intake. It is quite unlikely that this difference may be due to motor side effects because we previously showed a significant reduction in locomotion starting at 2 mg/kg R(+)-Baclofen in male rats and no locomotor effects have been reported in females up to the 3 m/kg dose of RS(±)-Baclofen (González-Marín et al., 2018; Haile et al., 2021). The effect of the S(−)-Baclofen was even more complicated to summarize since about half of the group, both in males and females, exhibited a decrease in alcohol self-administration and the other half showed no change or an increase in alcohol self-administration. A very recent study in Sprague-Dawley rats with 10% alcohol operant self-administration sessions for 60 min, suggested that Baclofen (0.3–3 mg/kg, i.p.) was more effective in female rats (females: 42% and 58% decrease, males:

0% and 54% decrease in the number of lever presses after 0.3 and 1 mg/kg Baclofen, respectively) (Haile et al., 2021). The latter study also indicated that the 3 mg/kg dose was sedative in males and that hyperlocomotion was observed in females at the 1 mg/kg dose after repeated treatment (4 consecutive days). It should be noted, however, that this study did not clearly indicate that it used RS(±)-Baclofen and did not directly compare males and females in its statistical analyses.

4.2 Cumulative responses and motivation

The analysis of the cumulative lever presses responding revealed more strikingly the differences between the male and the female groups. The pattern of self-administration was strongly altered in males with the RS(±)- and the R(+)-Baclofen while it was more moderately affected in female self-administration and keeping the same shape of the response curve with only a lower starting point. Moreover, our results showed that RS(±)- and R(+)-Baclofen reduced alcohol self-administration at the very beginning of the sessions and this may indicate a mechanism in which Baclofen was effective even before the beginning of the session, thus could affect the motivation to consume alcohol. In addition, as mentioned in previous study (Colombo and Gessa, 2018), evaluating the pattern of self-administration with the cumulative data also indicated a reduction in lever pressing at the beginning of the session after intra-VTA micro-infusion of Baclofen. In addition, we found that there was a rightward shift of the inter-response intervals curves for the RS(±) and the R(+) forms of Baclofen only in the males whereas this rightward shift was only observed with the R(+)-Baclofen in females. Thus, our data are in line with those of the few studies evaluating the effect of Baclofen on motivation using a previous study progressive ratio paradigm and that showed a reduction in breaking point (an index of motivation) induced by Baclofen (Walker and Koob, 2007; Maccioni et al., 2008; Maccioni et al., 2012) [for review see (Colombo and Gessa, 2018)]. In this regard, different mechanisms have been suggested to explain the potential effectiveness of Baclofen in AUD. Baclofen may block the alcohol priming effect, may act as a partial substitution therapy or may modulate the responses to an initial drink (Chick and Nutt, 2012; Hauser et al., 2016).

4.3 Comparison with results from human studies

In humans, Baclofen has been found to be more effective in patients that consumed a larger number of drinks at baseline (Pierce et al., 2018). We previously showed in the post-dependent state model of AUD that the blood Baclofen levels were correlated to the efficacy to decrease alcohol self-administration in male rats, at the two tested doses of RS(±)-Baclofen (1 or 2 mg/kg) (Echeverry-Alzate et al., 2020). Here we did not find this correlation in male rats and this lack of correlation is very likely due to the high efficacy in males and a very low level of variability in the response to 1.5 mg/kg RS(±)-Baclofen. In females, the response variability was greater and individuals displayed an increase in self-administration. Thus, it seems that in general, preclinical studies were in favor of the dose response effect of Baclofen on alcohol self-administration, which is contrary to what is observed in clinical studies (Agabio et al., 2018; Garbutt et al., 2021). Here we clearly demonstrated a dose-response with R(+)-Baclofen. It is possible that in our previous study with post-dependent state animals, specific neuroadaptations in response to the alcohol vapors exposure would render some of the individuals less responsive to the Baclofen's effect, thus, increasing the variability in response and the dose-response effect.

In contrast with the findings in males, we observed a negative correlation between the levels of blood RS(±)-Baclofen concentration and efficacy in reducing alcohol self-administration in the female group. Indeed, the higher the concentration was, the lesser efficacy was observed with a paradoxical increase of about 100% in the amount of alcohol consumed. To our knowledge, no previous preclinical data on the Baclofen's efficacy were obtained in females and our results would need confirmation in human studies. This point could be critical in the clinical practice since we found that the RS(±)-Baclofen was less effective in females and may worsen misuse of alcohol with elevated concentrations of circulating Baclofen. Our results seem to contradict those of a previous preliminary open-label study on a very limited sample size (9 men and 3 women) suggesting that women were among the best responders regarding number of drinks per drinking day, number of heavy drinking days, and number of abstinent days (Flannery et al., 2004). However, these latter results must be tempered due to the very low sample size and the fact that more women were using antidepressant medication, making it difficult to determine whether the Baclofen or the Baclofen in combination with the antidepressant medication was helpful in drinking reduction (Flannery et al., 2004). Results from a very recent clinical study also suggested better responding in women. The study showed that sex was a moderator of response, with men benefiting from 90 mg of baclofen/day but not from 30 mg/day, whereas women showed benefit from baclofen 30 mg/day, marginal benefit from 90 mg/day, and worsened tolerability at 90 mg/day (Garbutt et al., 2021). Thus, women may be more responsive to low doses of Baclofen but may also be more susceptible to adverse drug reactions. A recent study also suggested sex as a potential moderator for Baclofen response in AUD since Baclofen significantly delayed the time to lapse for women but not male participants (Morley et al., 2022).

4.4 Blood Baclofen and metabolites levels

No sex difference was observed in blood Baclofen levels at both 30 and 90 min after injection of RS(±)-Baclofen (1.5 mg/kg) in rats chronically self-administering alcohol. Interestingly, in a separate cohort of rats naive for alcohol, the blood Baclofen concentrations 30 min after an identical injection of 1.5 mg/kg of RS(±)-Baclofen were higher in female than in male rats suggesting a modification of the distribution/metabolism properties induced by prolonged alcohol self-administration. In contrast, the R(+)-Baclofen concentration was higher in males than in females at the 1st timepoint post-injection. Human studies have demonstrated a

higher sensitivity to side effects induced by RS(±)-Baclofen in women (Rigal et al., 2015). This suggest a differential mechanism of distribution of the different enantiomers and when both enantiomers are present together. This point emphasizes the importance of focusing the future research on the R(+)-Baclofen enantiomer and less on the racemic form. Concerning the Baclofen metabolites, our findings reveal that the blood levels of the S-Baclofen metabolites were 6 times higher than that of the R(+)-Baclofen after injection of each enantiomer separately and this result is in accordance with previous data in humans (Sanchez-Ponce et al., 2012). The level of the S(−)-Baclofen metabolite was even higher than the level of the RS(±)-Baclofen metabolite (at the same dose of 1.5 mg/kg), thus indicating a metabolic difference between enantiomers. Pharmacokinetic parameters of the R(+)- and S(−)-Baclofen enantiomers after a 20 mg oral dose of baclofen to normal human volunteers indicated similar plasma elimination half-lives (5.3 and 5.1 h respectively) but a slightly higher urinary excretion of R(+)-Baclofen relative to S(−)-Baclofen (Mutschler et al., 1990).

4.5 Mechanism of action of Baclofen of the different enantiomers

R(+)-Baclofen is more potent than S(−)-Baclofen (Witczuk et al., 1980; Falch et al., 2006). At the pharmacological level, R(+)-Baclofen and RS(±)-Baclofen may result in different behavioral outcomes because S(−)-Baclofen without being itself active, especially at a low dose, may increase or decrease the response to R(+)-Baclofen (Olpe et al., 1978; Fromm et al., 1990). A stereo-selective metabolic difference between R(+)- and S(−)-Baclofen, with no metabolites for observed after oral administration of the R(+)-enantiomer, whereas an oxidative deamination metabolite was observed after the administration of the R(+)- and S(−)-mixture, in humans (Sanchez-Ponce et al., 2012). Pharmacokinetic cannot explain the differences between enantiomers since the R(+)-Baclofen dose-dependently decreased ethanol self-administration, whereas a high S(−)-Baclofen dose increased ethanol self-administration when injected directly into the nucleus accumbens shell of C57Bl/6J mice (Kasten and Boehm, 2014). These latter results seem in line with our results since we also observed a decrease in alcohol self-administration after R(+)-enantiomer treatment and an increase in a significant proportion of animals after S(−)-Baclofen treatment, especially in females. A difference in the binding affinity of the two enantiomers and the existence of low- and high-affinity $GABA_B$ receptors with low-affinity sites more selective for S(−)-Baclofen may explain selective behavioural effects (Bowery et al., 1983; Kasten and Boehm, 2014). Different neurotransmitter targets could also be involved. R(+)-Baclofen may interact with non-gabaergic sites (Waddington and Cross, 1980), while S(−)-Baclofen may interact with norepinephrine as well (Karbon et al., 1984). Importantly, the different enantiomers may not reach or leave the central nervous system at the same rate/amount because of asymmetric transport rate by organic anion transporters at the blood brain barrier. In this regard, it is interesting to note that the transport of R(+)-Baclofen across the blood brain barrier has been shown to be 4 to 5 times higher than S(−)-Baclofen or the racemic form. Thus, difference in the stereoselective transport may be also of interest to explain the better efficacy of R(+)-Baclofen.

4.6 Dopamine release

Among the neurobiological mechanisms underlying the effect of Baclofen in AUD, inhibition of dopamine release within the mesolimbic reward pathway is thought to be crucial. A complete inhibition of DA neurons firing was reached at a concentration of 100 µM *in vitro*, the same dose that we used here in our FSCV study (Cruz et al., 2004). Preclinical drug studies have demonstrated that 100 µM R(+)-Baclofen induced a 25% inhibition of dopamine release in the core of the NAcc probably by inhibiting the release probability (Pitman et al., 2014). Here we showed that RS(±)-Baclofen decreased all parameters ($[DA]_{max}$, $[DA]_p$ and V_{max}) in control animals and that this effect was lost in the alcohol group, regardless of sex. R(+)-Baclofen also decreased $[DA]_p$ and V_{max} values in control animals but not in the alcohol group, regardless of sex. S(−)-Baclofen significantly decreased $[DA]_p$ in control groups but only in females, while V_{max} was decreased in both sexes. Strikingly, $[DA]_{max}$, was increased only in females of the alcohol group. The difference on $[DA]_{max}$ without altering in the V_{max} parameter suggest a change in DA release and not in DA transporter activity.

Even if we did not find any significant correlation between the effect of the different enantiomers on DA transmission and the effect on alcohol self-administration (data not shown), it seems that in general, the different forms of Baclofen were less effective to inhibit dopaminergic release in brain slices from animals that have chronically self-administered alcohol. The latter results seem to fit with our previous data showing that Baclofen was less effective in reducing alcohol self-administration of alcohol-dependent animals (Echeverry-Alzate et al., 2020). More interestingly, our results suggested that the increase in alcohol self-administration by S(−)-Baclofen, more frequent in females, may be associated with the increased dopamine release observed specifically in the alcohol group.

It is important to note that our experiment on DA release was designed to only explore the potential differential effects of the different forms of Baclofen in the same rats that consumed chronically alcohol and have also been treated with Baclofen *in vivo*. The use of the *ex vivo* FSCV technique is biased because we only measured the regulatory mechanisms involving the DA terminals and not the ones involving the somatic bodies located in the VTA and which are also the target of Baclofen (use of slices with disrupted neurocircuitries). The comprehensive explanation of the mechanism would require similar experiments but *in vivo*. To the best of our knowledge very few studies investigated the effect of Baclofen on DA release depending on the Baclofen enantiomer. In 1978, Waldmeier and Maitre, showed that the increasing effect of Baclofen (20 mg/kg) on striatal dopamine and metabolites (DOPAC and HVA) in rats was due to its S(−) but not R(+) enantiomer (Waldmeier and Maitre, 1978).

5 Conclusion

In the present study, we provided new and original data demonstrating that R(+)-Baclofen was the most powerful enantiomer in reducing the amount of alcohol consumed in a chronic self-administration model with a binge pattern of access. More importantly, more non-responders to RS(±)-Baclofen and to R(+)-Baclofen were present in females suggesting a sex difference in the efficacy that needs to be taken into account before administrating Baclofen. Moreover, more females than males displayed an increase in the total amount of alcohol consumed after the administration of the racemic form of Baclofen. We also demonstrated that the different enantiomers and the racemic Baclofen can act directly on the dopaminergic terminals within the NAcc and we observed a tendency for a bidirectional effect of Baclofen depending on the enantiomer especially in females. More generally, as in some pathologies the R(+) enantiomer is the one that should be preferred to others [S(−)-Baclofen and RS(±)-Baclofen] in the AUD therapy. For example, the R(+) enantiomer but not S(−)-Baclofen has been shown to reverse some deficits in animal models of autism (Silverman et al., 2015).

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was reviewed and approved by (CREMEAP: Comité Régional d'Ethique en Matière d'Expérimentation Animale de Picardie) and validated by the French Ministry in charge of the Research under the number #2145-201510051547534v2.

Author contributions

MN and JJ designed the experiments. SF, SS, PS, CH, and JJ contributed to the acquisition of animal and FSCV data. SB, LL, and MS conducted experiments to measure plasmatic levels of Baclofen. MN and JJ assisted with data analysis and interpretation of findings. MN, PS, CH, FV, and JJ wrote the paper. All authors critically reviewed content and approved final version for publication.

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Conflict of interest

FV has received academic grants (from the French Ministry of Health (PHRC-N-180777), the Investissements d'Avenir program managed by the ANR under reference ANR-11-IDEX-0004-02, 2016, the European Research Area Network (ERA net neuron 2017), and congress fees from Camurus AB (2018, 2019).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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A new statistical model for binge drinking pattern classification in college-student populations

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Background: Binge drinking (BD) among students is a frequent alcohol consumption pattern that produces adverse consequences. A widely discussed difficulty in the scientific community is defining and characterizing BD patterns. This study aimed to find homogenous drinking groups and then provide a new tool, based on a model that includes several key factors of BD, to assess the severity of BD regardless of the individual's gender.

Methods: Using the learning sample (N1=1,271), a *K*-means clustering algorithm and a partial proportional odds model (PPOM) were used to isolate drinking and behavioral key factors, create homogenous groups of drinkers, and estimate the probability of belonging to these groups. Robustness of our findings were evaluated with Two validations samples (N2=2,310, N3=120) of French university students (aged 18–25 years) were anonymously investigated via demographic and alcohol consumption questionnaires (AUDIT, AUQ, Alcohol Purchase Task for behavioral economic indices).

Results: The *K*-means revealed four homogeneous groups, based on drinking profiles: low-risk, hazardous, binge, and high-intensity BD. The PPOM generated the probability of each participant, self-identified as either male or female, to belong to one of these groups. Our results were confirmed in two validation samples, and we observed differences between the 4 drinking groups in terms of consumption consequences and behavioral economic demand indices.

Conclusion: Our model reveals a progressive severity in the drinking pattern and its consequences and may better characterize binge drinking among university student samples. This model provides a new tool for assessing the severity of binge drinking and illustrates that frequency of drinking behavior and particularly drunkenness are central features of a binge drinking model.

KEYWORDS

alcohol, binge drinking, high-intensity binge drinking, college students, drunkenness, classification tool, gender

1. Introduction

Binge drinking (BD) is a major public health problem that produces several harmful consequences (Rolland et al., 2017). As the most prevalent drinking habit among Western youth (Dormal et al., 2019; Maurage et al., 2020), binge drinking increases injuries and health risks, leading to brain and cognitive alterations (Squeglia et al., 2011, 2012; Petit et al., 2014). Beyond immediate health risks, BD produces long-lasting brain and psychological impacts, suggesting that this drinking pattern may be a first step toward drug disorders in the long term (Patrick et al., 2019; Tavolacci et al., 2019; Jaeger and Oshman, 2021). Despite this impact on public health, the research community is overwhelmed with a diversity of definitions and denominations of BD (Rolland et al., 2017). Irrespective of cultural influences on the patterns of consumption, such diversity in the definition of BD leads to high variability among the markers of prevalence (Varela-Mato et al., 2012; Mahmood et al., 2016). Differences in such definitions affect categorizations of BD both within and across studies, and these differences could have a profound impact on both the results and implications of the studies.

Globally, two main definitional streams have emerged among the proposed criteria for BD. The first concerns *quantity or quantity-frequency* based definitions (Wechsler and Nelson, 2001; Rolland et al., 2017). These definitions define BD with respect to quantity of alcohol consumed, blood alcohol concentration (BAC), and/or standard alcohol dose measures (Maurage et al., 2020) (i.e., the WHO definition of ≥60 g of ethanol per occasion and the NIAAA definition of ≥56 g for women and ≥70 g drinks for men in a 2-h interval and blood alcohol concentration ≥0.8 g/L). The strictly *quantity-based definitions* have two main drawbacks, despite their ease of use and prevalence in epidemiological studies. First, accurate estimates of alcohol consumption are difficult to achieve for several reasons: (i) the amount of alcohol in a "standard drink" varies between countries (e.g., 10 g in France, 20 g in Austria, 14 g in US, and 8 g in UK); (ii) young adults frequently consume non-standardized drinks (plastic cups, etc.) (Morrell et al., 2021) in private dwellings (e.g., at home) or in a public place (e.g., public park) (Labhart et al., 2013) and (iii) the number of standard doses consumed does not take into account the consumer's physical characteristics (tolerance, sex and body mass index) that affect BAC. Second, the use of "cut-offs," or delineating participant groups according to the number of drinks consumed (e.g., fewer than 5/4 drinks for men/women as "non-binge" drinking), generates erroneous dichotomization and inaccurate labeling (i.e., broad categorization into a group) (DeCoster et al., 2009; Pearson et al., 2016). The use of cut-offs underestimates real consumption and mitigates actual consequences. As a dichotomous variable, BD has little predictive value for public health impact whereas a clear dose effect links BD frequency, intensity, and many negative health consequences, including mortality (Donat et al., 2021). The addition of a frequency dimension to quantity (i.e., *quantity-frequency*) improves the drinking assessment, as frequency is highly related to severity of drinking consequences (Williams et al., 1994; Greenfield, 2000). For example, the Timeline Follow Back (TLFB) (Collins et al., 2008) has been used to track BD episodes during a period of 7 days to 12 months. The degree to which a given quantity of consumption occurs within that time period provides an important temporal dimension (Williams et al., 1994; Greenfield, 2000).

The second stream of BD definitions concerns *behavioral patterns* (Townshend and Duka, 2002), or more subjective behavioral drinking "phenotypes," such as frequency of drunkenness and hangovers. Such definitions include the adaptations of known questionnaires to rank consumption (Tuunanen et al., 2007; Olthuis et al., 2011; Cortés-Tomás et al., 2016). For example, the AUDIT questionnaire is sometimes used to assess the severity of BD (Motos-Sellés et al., 2020), although it remains incomplete for several reasons (Shakeshaft et al., 1998; Tuunanen et al., 2007; Mota et al., 2010; Olthuis et al., 2011; Cortés-Tomás et al., 2016; Motos-Sellés et al., 2020). In particular, the AUDIT questionnaire does not assess the number of drunkenness episodes or the speed of drinking, which are essential characteristics of BD behavior (Maurage et al., 2020). In addition, cut-offs for AUDIT total scores require careful adjustment to remain valid in college populations (Olthuis et al., 2011). To deal with these limitations, other behavior-based models of BD have been developed to include physiological and subjective intoxication criteria such as *drunkenness* and *frequency of drunkenness*. For example, the BD score proposed by Townshend and Duka (2002) includes a sum of *consumption speed*, *number of drunkenness episodes,* and *percentage of drunkenness episodes out of 10 drinking occasions*. Because of their subjectivity, drunkenness and frequency of drunkenness are recognized as both highly predictive of social consequences and symptoms of alcohol dependence and alcohol-related harm, and therefore, may be more valid than the amount of alcohol by subject experience, biological factors and demographic criteria (Midanik, 1999; Paljärvi et al., 2012; Sznitman et al., 2017). Speed of drinking, also included in the "BD score," is another index of severity (López-Caneda et al., 2013; Poulton et al., 2016), increasing more rapidly in high-risk drinking (Groefsema and Kuntsche, 2019). Despite these advantages of the BD score, its utility is hampered by the percentile method used to categorize groups of participants: The lowest third is said to constitute "social drinkers" and the upper third is considered "binge drinkers," but the intermediate percentile remains unclear and designated "intermediate." Thus, these cutoffs will necessarily vary depending on the distribution of consumption in a given sample (Townshend and Duka, 2002).

In addition to wide variability among BD definitions, there is also variability in the inclusion of gender in these definitions. Indeed, some studies use gender-specific measures (e.g., 5+ and 4+ US standard drinks, or 70 g+/56 g+, respectively for men and women) (Wechsler and Nelson, 2001), whereas others do not (e.g., the AUDIT uses 60 g of ethanol) (Saunders et al., 1993; Babor et al., 1994; Graham et al., 1998; Wilsnack et al., 2018). Thus, lowering a threshold to define BD among women may increase the prevalence of this behavior among women (Chavez et al., 2012). Even though physiological factors, such as drunkenness, depend on the metabolism of alcohol in accordance to sex, no study to date has been able to quantify binge drinking in a manner that is valid regardless of gender.

This lack of standardization and consensus in BD definitions illustrates the variability that makes it difficult to compare findings across studies (Cortés-Tomás et al., 2016). This methodological difficulty has become a barrier to advancing public health, given the pervasiveness of BD in the population and its spectrum of consequences (Rolland et al., 2017; Maurage et al., 2020). Taken together, the adverse consequences of BD, the lack of clarity regarding BD as a mode of consumption and resulting obfuscation of research

findings justify the need for a novel instrument to define and detect BD (Cortés-Tomás et al., 2016).

Therefore, the current study had three research aims: (1) starting with recognized BD criteria, develop a better tool for characterizing BD behavior that takes into account behavioral, quantitative and physiological consumption features and that defines homogeneous groups keeping all individuals from the whole population (2) with this tool, provide a stable, specific, and reproducible way to investigate other BD-related questions, especially those regarding severity and gender variability; and (3) further characterize BD groups using alcohol-related consequences and behavioral economic indices (e.g., demand intensity and breakpoint).

2. Methods

2.1. Design

2.1.1. Participants

The learning sample and validation samples were recruited from three French universities (Rennes, Amiens and Reims) with different methods of recruitment.

2.1.1.1. Learning sample

An online anonymous survey was distributed to all students from the University of Rennes. In total, 29,000 students were invited to complete the questionnaire via their personal university email address. A total of 1,870 students which consisted primarily of Caucasian responded to the questionnaire. Criteria of inclusion were age between 18 and 25 and drinking 5 or more drinks (50 g) per week. This population was already described in a previous study (Rolland et al., 2017). For the current study, we excluded participants with missing data, leading to a final sample of 1,277 participants (77.3% female). 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). With respect to the students' academic programs, 39% reported law, economy, management, or human sciences; 28% were pursuing health studies; and 33% were in the field of sciences, engineering and technologies.

2.1.1.2. Validation samples

2.1.1.2.1. Validation sample 1

The validation sample 1 included 2,310 participants from two French universities (University of Reims Champagne-Ardenne and University of Picardy Jules Verne), primarily of Caucasian, who responded to the questionnaire. Recruitment of university students was performed via an e-mail advertisement. All participants freely gave their formal, informed consent at the beginning of the study by using the consent button after reading the consent form. Criteria of inclusion were age between 18 and 25 and drinking 5 or more drinks (50 g) per week. No compensation was given.

2.1.1.2.2. Validation sample 2

The validation sample 2 was selected based on BD indices for a brain imaging study with a total of 120 students (60 males and 60 females). All participants freely signed the inform consent form at the beginning of the study. This sample of 120 came from a broader sample of 391 participants (age, 18 to 24 years; 215 females and 176 males, all Caucasian regarding the genetic part of the study) among students at two French universities (Amiens and Reims). Inclusion and exclusion criteria fulfilled the requirements of the behavioral, brain imaging and genetic parts of the study.

2.2. Procedures and measurements

The online survey used for all three samples assessed demographic characteristics (age, gender, academic level and discipline, and living situation), drug use (alcohol, cigarettes, and cannabis), AUDIT score (Gache et al., 2005) and Binge drinking score (Mehrabian and Russell, 1978) (Tables 1, 2).

2.3. Alcohol-related measures

2.3.1. Alcohol use disorders identification test

The AUDIT is a 10-item screening tool developed by the WHO to assess hazardous alcohol consumption, drinking behaviors, and alcohol-related problems (Saunders et al., 1993; Gache et al., 2005). AUDIT is a self-assessment questionnaire that measures frequency and quantity of alcohol consumed (such as the frequency of consuming 6+ drinks), behaviors associated with alcohol use, and negative outcomes related to alcohol consumption. *When you drink, how fast do you drink*? Total AUDIT scores were calculated by adding the scores for all 10

TABLE 1 Demographic data and drug consumption for the learning sample.

		N	%
Gender	M	290	22.7
	F	987	77.3
	Total	1,277	
	Mean ± sem		
Age	21.13 ± 0.05		
<21		530	41.5
21–23		571	44.7
≥24		176	13.8
Academic year			
First-year		277	21.7
Second-year		290	22.7
Third-year		268	21.0
Fourth-year		248	19.4
Fifth-year		194	15.2
Age at first alcohol consumption	15.05 ± 0.05		
Cigarette			
Smokers		331	25.9
Non-smokers		946	74.1

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TABLE 2 Comparison of the learning sample with the validation sample 1 and the validation sample 2.

		Learning sample		Validation sample 1		Learning sample vs. Validation sample 1	Validation sample 2		Learning sample vs. Validation sample 2
		N	%	*N*	%	*p*	*N*	%	*p*
Gender	Distribution					<0.0001***			<0.0001***
	M	290	22.7	952	41.2		60	41.2	
	F	987	77.3	1,358	58.8		60	58.8	
Age	Mean ± sem Min-Max	21.13 ± 0.05 18–26		20.29 ± 0.05 17–30		<0.0001***	21.28 ± 0.16 18–25		<0.05*
	Distribution					<0.0001***			<0.05*
	< 21	530	41.47	1,444	62.5		44	36.7	
	21–23	571	44.70	663	28.7		59	49.2	
	≥ 24	176	13.8	203	8.8		17	14.1	
AUDIT	Mean ± sem Min-Max	7.12 ± 0.14 1–29		7.06 ± 0.113 0–33		= 0.174	9.19 ± 0.58 0–30		<0.0001***
	Distribution of the different levels					<0.0001***			<0.0001***
	Low risk	570	44.6	1,370	59.9		56	46.7	
	Hazardous	541	42.4	622	26.9		33	27.5	
	High risk	166	13.1	318	13.8		30	25	
BD score	Mean ± sem Min-Max	13.58 ± 0.34 1.32–106		20.07 ± 0.40 1.33–172		<0.0001***	28.26 ± 2.35 0–132		<0.0001***
	Distribution of the different groups of drinking					<0.0001***			<0.0001***
	Social	913	71.5	1,293	56		63	52.5	
	Intermediate	252	19.7	413	17.9		3	2.5	
	Binge	112	8.8	604	26.1		54	45.0	

*$p < 0.05$; ***$p < 0.0001$. AUDIT, Alcohol Use Disorder Identification Test. BD Score, Binge drinking score. Comparison between means were performed using the Student t test. Comparison between distribution were conducted using the Chi square. AUDIT groups were typically defined as follows: low risk level of dependance score < 7 for men and < 6 for women, hazardous level of dependance score ≥ 7 and for men and ≥ 6 for women and < 13, high risk level of dependance score ≥ 13. Binge drinking score is defined as < 15 for social drinking group, ≥17 and < 23 for intermediate drinking group and ≥ 24 for binge drinking group with Binge score = (4 × AUQ 10) + AUQ 11 + (0.2 × AUQ 12) with AUQ 10: When you drink, how fast do you drink?; AUQ 11: How many times have you been drunk in the last 6 months? and AUQ 12: What percentage of the times that you drink do you get drunk? (Townshend and Duka, 2005).

items (Saunders et al., 1993). The Cronbach's alpha for the full sample on this scale was 0.792.

2.3.2. The alcohol use questionnaire-revised (AUQ-R)

We used a French version of the revised version of the Alcohol Use Questionnaire (Townshend and Duka, 2002) initially developed by Mehrabian and Russell (1978). This version allows for the calculation of weekly level of alcohol use (units of alcohol by week, considering that in France 1 unit of alcohol is defined as 10 g of ethanol) and a binge score. This score was calculated for all participants on the basis of the information provided regarding: speed of drinking (average drinks per hour), number of times being drunk in the previous 6 month, and percentage of times getting drunk when drinking (for more details, see Townshend and Duka, 2002; Gierski et al., 2015).

2.3.3. Alcohol purchase task (for behavioral economic indices)

The Alcohol purchase task (APT) (Murphy and MacKillop, 2006) is a self-report measure that assesses behavioral economic demand for alcohol, or consumption as a function of price. Demand indices on the APT are strongly correlated with clinical alcohol use (Zvorsky et al., 2019; Martínez-Loredo et al., 2021). The APT asks participants to read a vignette describing a typical alcohol-drinking context and report how many standard drinks they would consume at a variety of prices. In the current study, the vignette specified a 5-h drinking occasion and the prices ranged from 0 to 20 euros. The consumption data were screened for violations of trend, bounce, and reversals from zero using the criteria of Stein et al. (2015). Among the 1,261 participants who had APT data, 82 were excluded for one or more violation, leaving a final sample of 1,179. Behavioral economic parameters included the observed indices of intensity (reported consumption at zero price), Omax (maximum product of price × consumption) Pmax (price at Omax), and breakpoint-1 (BP1) (the highest price with non-zero consumption). These parameters were calculated for each participant using the Foster and Reed Excel tool (Foster et al., 2020). Finally, participant-level derived behavioral economic parameters of Q0 (derived intensity) and alpha (rate of change in elasticity) were produced using the exponentiated demand function of Koffarnus et al. (2015) (6), Q = Q0 * 10^(k(ê(−alpha * Q0 * C) − 1)), with the zero euro price replaced with 0.01, and the span parameter (k) set to

3.20, which represented the highest range of participant-level consumption in log units plus 0.50. For each participant, these alpha and k values were used to produce Essential Value (EV), a standardized measure of reinforcing value, with EV = 1/(100 * alpha * k1.5) (Hursh and Roma, 2013).

2.4. Selection of items for clustering

Cluster items were selected from the AUDIT and AUQ-R to capture a variety of BD-associated characteristics (1) consumption frequency (*How often do you have a drink containing alcohol*?), (2) drinks per typical day (*How many drinks containing alcohol do you have on a typical day when you are drinking*?), (3) frequency of consuming 6+ drinks (*How often do you have six or more drinks on one occasion*?), (4) consumption speed (*When you drink, how fast do you drink*?), (5) drunkenness frequency (*How many times have you been drunk in the last 6 months?*), (6) proportion of drunkenness episodes out of 10 drinking occasions (*What percentage of the times that you drink do you get drunk*? reported on a scale of 10 occasions), (7) proportion of hangover episodes out of 10 drinking occasions (*What percentage of the times you drink have you had a hangover*? reported on a scale of 10 occasions).

2.5. Statistical analyses

For descriptive statistics, quantitative variables were expressed as mean ± standard error of the mean (SEM) and qualitative variables were presented as percentages. Comparisons between samples were performed using χ^2 tests for qualitative variables and ANOVA or Student's test for quantitative variables. Comparison and analyze were conducted with Student *t*-test, ANOVA and chi-square performed with SPSS, version 23.

The particularity of our analysis is that the dependent variable (Binge group) is not yet available at the beginning of the analyses. Therefore, we first used Kmeans to classify patients and then used the partial proportional odds to internally reproduce the Kmeans results before testing the generalizability of our results in independent samples without re-running the Kmeans algorithm. The external validation step's aim was to evaluate the robustness and consistency of our results found in the learning sample. The increasing mean values of the useful variables (variables included in the Kmeans) were compared between the four groups.

2.5.1. *K*-means clustering method

For exploratory determination of alcohol consumption patterns, the unsupervised *K*-means clustering method in the learning sample aimed to determine clusters of individuals who are as similar as possible (in contrast to individuals from different clusters, who should be as different as possible). Briefly, the *K*-means algorithm is an iterative algorithm that partitions the dataset into *K* pre-defined, distinct, and non-overlapping clusters whereby each individual belongs to only one cluster. The algorithm assigns data points to a cluster such that the sum of the squared distance between the individuals and the cluster's centroid (i.e., the arithmetic means of all the individuals that belong to that cluster) is at its minimum. The less variation within clusters, the more homogeneous the individuals are within the same cluster. The optimal number of clusters was evaluated using the Elbow method (Figure 1). Afterward each participant had been classified in his/her corresponding cluster, we calculated cluster means for each of the variables used in the *K*-means method. Then, we ranked the clusters according to the progression of variables (Table 3).

2.5.2. Partial proportional odds model

We first modeled the probability of group membership using a PPOM allowing for unequal regression coefficients with the *K*-means clusters variable as the dependent variables. PPOM is a regression modeling technique aiming to assess the association between independent predictors and an ordinal outcome variable. After model building, the predictors' regression coefficients could be used to predict the outcome. Instead, proportional odds model (POM), PPOM assumes that the effect some independent variable may not be uniform for all levels of the dependent variable (group variable). After determining the regression equations using variables significant at the 0.05 level of alpha on the PPOM, we estimated the probability $P_i\ (Group \geq j)$ for individual *i* to belong to at least group *j*. Thus for the probability of individual *i* to belong to group $j = 2, \ldots, K\text{-}1$ was estimated by $P_i\ (Group \geq j) - P_i\ (Group \geq j + 1)$, except for the first and last groups (Group 1 and Group 4) for which the probability of membership was estimated as 1 – Pi (Group ≥2) and Pi (Group ≥4) respectively. Then, two phases of validation were followed (Moons et al., 2012a,b). For internal validation in this sample, each individual was assigned to the group for which his/her probability of membership was the highest. Next, we compared the group membership from the clustering method and the group membership estimated from the PPOM model with a calculation of misclassification error from the PPOM model using the groups derived from clustering as the gold standard. For external validation, individuals in the two validation samples were assigned to the group for which their probability of belonging estimated from the PPOM model was the highest. Next, for the validation database we estimated the means for each of the PPOM independent variables across the groups.

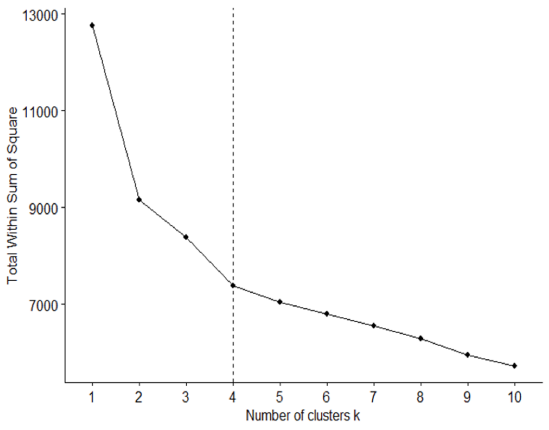

FIGURE 1
Optimal number of clusters. The Elbow method determined that four is the optimal number of clusters.

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TABLE 3 Cluster means for each of the variables used in the *K*-means method for the four groups in the learning sample.

	Consumption frequency	Number of drinks per typical day	6-drink frequency	Consumption speed	Drunkenness frequency	Number of drunkenness episodes/10 drinking occasions	Number of hangovers/10 drinking occasions
1 ($n=721$)	1.79	0.70	0.90	1.47	0.93	1.24	1.23
2 ($n=404$)	2.19	1.54	1.89	2.32	5.82	4.95	4.15
3 ($n=106$)	2.60	2.04	2.66	2.85	19.28	6.10	4.65
4 ($n=46$)	3.02	2.76	2.65	3.17	39.26	6.52	3.94

Cluster variables were selected from the AUDIT and AUQ-R questionnaires: (1) Consumption frequency or AUDIT 1 "How often do you have a drink containning alcohol?", (2) Drinks per typical day or AUDIT 2 "How manny drinks containing alcohol do you have on a typical day when you are drinking?", (3) 6 drinks frequency or AUDIT 3 "How often do you have six or more drinks on one occasion?", (4) Consumption speed or AUQ 10 "When you drink, how fast do you drink?", (5) Drunkenness frequency or AUQ 11 "How many times have you been drunk inn the last 6 months?", (6) Number of drunkenness episodes/10 drinnkinng occasions or AUQ 12 "What percentage of the times that you drink do you get drunk?" reported on a scale of 10 occasions, (7) Number of hangovers/10 drinking occasions or "What percentage of the times you drink have you had a hangover?" reported on a scale of 10 occasions.

PPOM and model validation were performed with R software, version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) through the RStudio interface, version 1.0.143. The *K*-means and function were used in the learning database and the VGAM library for PPOM modeling.

2.6. Ethical approval

The personal identity of the participants completing the anonymous questionnaire was unknown to the researcher. Each participant provided electronic informed consent after reading the consent form, which described the purpose of research, participation, procedure, confidentiality, and researcher's contact information. Raw data were stored on a computer not connected to an internet network. We removed the access link to the data collected online at the end of the study. Learning sample was part of a study approved by the regional ethics committee (Comité de Protection des Personnes Nord-Ouest II). Validation samples were part of a bigger study approved by the regional ethics committee (Comité de Protection des Personnes Est I).

3. Results

3.1. Demographic data and description of drugs consumptions for the learning sample

We calculated the mean and SEM of each continuous variable (e.g., age, age at first alcohol use) and the percentages on each demographic item – age, gender, age of first consumption, year in school (Table 1).

3.2. Comparison of the learning population with the two validation samples

The 2 validation samples differ significantly from the learning sample with respect to parameters such as the gender ratio and consumption parameters (AUDIT and BD group distribution) (Table 2). These significant differences between the 3 samples reinforce the validity of our model.

3.3. Cluster analyses

Using the Elbow method, we determined four clusters, designated groups 1, 2, 3, and 4 (Figure 1). This number of groups resulted from maximizing the number of individuals in each group.

3.4. Partial proportional odds model

3.4.1. Major factors in the classification

On the 7 items initially selected (see section 2.4, Selection of items for clustering), we found that 5 of them (1) 6 drinks frequency or AUDIT 3 "How often do you have six or more drinks on one occasion?", (2) Consumption speed or AUQ 10 "*When you drink, how fast do you drink?*", (3) Drunkenness frequency or AUQ 11 "*How many times have you been drunk inn the last 6 months?*", (4) Number of drunkenness episodes/10 drinking occasions or AUQ 12 "*What percentage of the times that you drink do you get drunk?*" reported on a scale of 10 occasions, (5) Number of hangovers/10 drinking occasions or "*What percentage of the times you drink have you had a hangover?*" reported on a scale of 10 occasions, were significant at the 0.05 level on the PPOM analyses (Table 4). For the final selection of items, we considered multicollinearity, that is, strongly correlated dependent variables. In particular, of the first 3 AUDIT items, we selected item 3 (6-drink frequency), which had the most impact on our model (Table 4). Mean scores on each of the five significant items (Table 3) were calculated for each group. The results show that the mean scores increased gradually from group 1 to group 4 (Table 3), with minor exceptions from group 3 to 4.

3.4.2. Cumulative probability equations

The partial proportional model generated the four equations below. These equations permit calculation of the probability of belonging to each group for each individual.

TABLE 4 Results of the partial proportional odds model (PPOM) for the variable of group membership (the four groups derived from the *K*-means model) as the dependent variable.

PPOM: significant items					
	Group	Regression coefficients	Std. Error	*Z* value	*p* value
AUDIT 1 - Consumption frequency	≥2, ≥ 3, = 4	0.18809	0.15811	1.190	0.23418
AUDIT 2 - Drinks per typical day	≥2, ≥ 3, = 4	−0.01347	0.09327	−0.144	0.88520
AUDIT 3–6 drinks frequency	≥2, ≥ 3, = 4	0.42646	0.14719	2.897	<0.01**
AUQ 10 - Consumption speed	≥2	0.20057	0.10606	1.891	0.05859
	≥ 3	0.07370	0.12862	0.573	0.56665
	= 4	−0.12883	0.20744	−0.621	0.53455
AUQ 11 - Drunkenness frequency	≥2, ≥ 3, = 4	0.33708	0.02394	14.083	<0.001***
AUQ 12 – Number of drunkenness episodes (out of 10 drinking occasions)	≥2	0.68408	0.06473	10.568	<0.001***
	≥ 3	0.11046	0.08512	1.298	0.19439
	= 4	0.02215	0.13689	0.162	0.87146
Number of hangovers (out of 10 drinking occasions)	≥2	0.36077	0.05103	7.070	<0.001***
	≥ 3	0.05129	0.06900	0.743	0.45725
	≥ 4	−0.34092	0.12573	−2.712	<0.01**

**$p < 0.01$; ***$p < 0.001$. The items "6 drinks frequency," "Drunkenness frequency," "Number of drunkenness episodes (out of 10 drinking occasions)" and "Number of hangovers (out of 10 drinking occasions)" were significant at a 5% level of significance, and the item "Consumption speed" tended to a 5% level of significance. This result indicated that they were the most important deterministic factors in the classification. The three independent variables "Consumption speed," "Number of drunkenness (out of 10)" and "Number of hangover (out of 10)" did not meet the proportional odds assumption and had different coefficients for each of three modeled probabilities, P (Group ≥ 2), P (Group ≥ 3) and P (Group = 4).

$$P(Group \geq 2) = \frac{e^{-5.87+0.43*Freq_{six-drinks}+0.20*speed+0.34*Freq_{drunkeness}+0.68*Number_{Drunkeness\,on\,10}+0.36*Number_{Hangover\,on\,10}}}{\left(1+e^{-5.87+0.43*Freq_{six-drinks}+0.20*speed+0.34*Freq_{drunkeness}+0.68*Number_{Drunkeness\,on\,10}+0.36*Number_{Hangover\,on\,10}}\right)}$$

$$P(Group \geq 3) = \frac{e^{-7.37+0.43*Freq_{six-drinks}+0.07*speed+0.34*Freq_{drunkeness}+0.11*Number_{Drunkeness\,on\,10}+0.05*Number_{Hangover\,on\,10}}}{\left(1+e^{-7.37+0.43*Freq_{six-drinks}+0.07*speed+0.34*Freq_{drunkeness}+0.11*Number_{Drunkeness\,on\,10}+0.05*Number_{Hangover\,on\,10}}\right)}$$

$$P(Group = 4) = \frac{e^{-8.46+0.43*Freq_{six-drinks}-0.13*speed+0.34*Freq_{drunkeness}+0.02*Number_{Drunkeness\,on\,10}-0.34*Number_{Hangover\,on\,10}}}{\left(1+e^{-8,46+0.43*Freq_{six-drinks}-0.13*speed+0.34*Freq_{drunkeness}+0.02*Number_{Drunkeness\,on\,10}-0.34*Percent_{Hangover\,on\,10}}\right)}$$

$$P(Group = j) = P(Group \geq j) - P(Group \geq j+1) \text{ for } j = 2 \text{ or } 3,$$
$$P(Group = 1) = 1 - P(Group \geq 2) \text{ and } P(Group = 4) = P(Group \geq 4)$$

3.4.3. Internal validation

The risk of misclassification of one individual in each group was obtained by cross-referencing the result from the *K*-means method with the resultant prediction of the equations above reapplied to the learning sample. This level of risk of misclassification indicates a good internal validation of our model. The internal validation with low risk of misclassification of the PPOM confirms the reliability of the distribution (Table 5).

3.5. External validation

We tested the reproducibility of our classification method by comparing the mean values of the 5 identified items in the learning sample with their mean values on these items obtained in each group for the validation samples (i.e., samples 2 and 3 in the present study).

The probability of belonging to each group was calculated for each individual in the validation samples. The means for each item were calculated for the two validation samples tested. Despite the marked disparities between the 3 samples we tested, the means obtained for each item in each group were very similar between the 3 samples, indicating the strong validity of our model (compare Table 6 with Table 3).

3.6. The influence of gender

We next checked whether gender affected the specificity of the group classification in the learning sample (see Figure 2 for gender

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TABLE 5 Concordance between the results from the *K*-means and the PPOM model for the learning sample.

	PPOM grouping				
	N	Group 1	Group 2	Group 3	Group 4
K-means grouping	Group 1	705	16	0	0
	Group 2	33	370	1	0
	Group 3	0	11	90	5
	Group 4	0	0	0	46

N, number of participants. Misclassification risks were: 16/721 = 2.2% in group 1; 34/404 = 8.4% in group 2; 16/106 = 15.1% in group 3; 0 in group 4.

TABLE 6 Cluster means on each of the variables for validation samples 1 and 2.

Groups	6 drinks frequency	Consumption speed	Drunkenness frequency	Number of drunkenness (out of 10)	Number of hangovers (out of 10)
Validation sample 1					
1 (n = 1,496)	0.86	1.72	1.05	1.36	1.50
2 (n = 559)	1.94	2.94	6.27	5.09	4.28
3 (n = 125)	2.70	3.60	19.18	6.48	4.97
4 (n = 121)	2.94	4.00	43.08	6.88	4.45
Validation sample 2					
1 (n = 53)	1.13	1.51	1.66	1.11	1.37
2 (n = 25)	2.00	2.96	8.60	4.84	3.86
3 (n = 10)	2.40	3.10	19.20	5.70	4.70
4 (n = 23)	3.02	3.48	43.17	6.87	4.44

By applying the equations in our 2 validation samples, mean results were identical to those of the learning sample (Table 3). Significant items means gradually increased from group 1 to group 4 (except for the number of hangovers). This result illustrates the reproducibility of the equations.

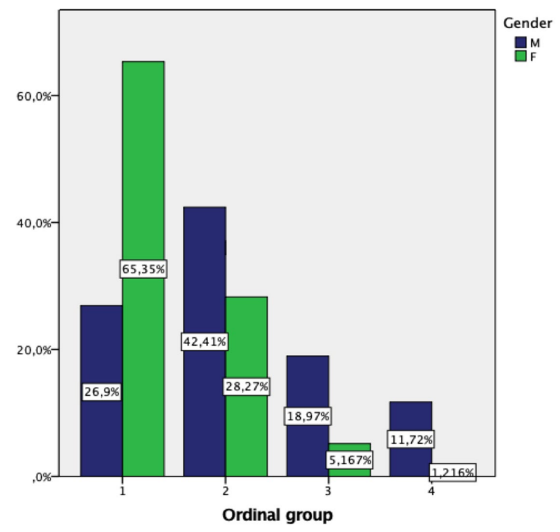

FIGURE 2
The percentage of women was highest in group 1 (65.35%) and decreased sharply in groups 2 (28.27%), 3 (5.17%) and 4 (1.22%). The percentage of men was highest in group 2 (42.41%) and comparatively higher than the percentage of women in groups 3 (18.97%) and 4 (1.22%).

distribution) by calculating the risk of misclassification with or without the inclusion of gender in the PPOM model (Tables 7A,B). Overall, we found that the integration of the gender parameter in the PPOM did not improve the specificity of the classification. More precisely, the inclusion of the gender parameter into the equation had no effect on the classification in group 1 (2.1% versus 2.2%) and group 4 (0 versus 0). However, our analysis revealed a slight difference for groups 2 (8.4% versus 9.2%) and group 3 (15.1% versus 16%) (Tables 7A,B). Therefore, our model of classification is valid regardless of gender.

3.7. Group characterization

3.7.1. Comparison between the 4 groups

We next analyzed the 4 groups with known items from the AUDIT questionnaire (Table 8) and behavioral economic indices from the APT (Table 9) in order to evaluate the concordance of our groups with other indices of alcohol use, severity, and demand. In general, the severity of the alcohol consumption or its consequences increases from group 1 to 4. Moreover, there was no significant difference by gender, particularly for groups 3 and 4.

With respect to the alcohol demand indices, we observed a significant omnibus effect of group on breakpoint-1, observed intensity, observed O_{max}, and Q_0 (derived intensity), with increases in each of these demand indices across groups 1 to 4, except for breakpoint-1 (Table 9).

3.7.2. Comparison of groups 3 and 4

All of the alcohol consumption criteria were significantly different between drinking groups 3 and 4 (Table 8). As shown in Table 8, comparing the incidence risk ratios (IRRs) for groups 3 and 4 reveals

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TABLE 7 A and B: Influence of the gender parameter.

(A) Risk of misclassification without the gender parameter						
	Derivation					
	N	Group 1	Group 2	Group 3	Group 4	Error
K-means	Group 1	705	16	0	0	2.2%
	Group 2	33	370	1	0	8.4%
	Group 3	0	11	90	5	15.1%
	Group 4	0	0	0	46	0

(B) Risk of misclassification with the gender parameter						
	Derivation					
	N[a]	Group 1	Group 2	Group 3	Group 4	Error
K-means	Group 1	706	15	0	0	2.1%
	Group 2	34	370	0	0	9.2%
	Group 3	0	10	89	7	16%
	Group 4	0	0	0	46	0

N, number of participants. Error risk did not differ significantly with the inclusion of gender.

two different drinking profiles, which also are reflected in the behavioral economic data (Tables 9, 10). Specifically, the comparison of alcohol demand indices between groups 3 and 4 revealed significant differences in both intensity measures (observed and derived Q_0), with significantly higher demand intensity for group 4.

3.7.3. Comparison between genders in the four groups

Means of consumptions items (AUDIT Score, Binge drinking Score) and behavioral related to consumption items (Age of start of consumption, AUDIT 2, 4, 5, 6, 8, 9, 10 listed in Table 11) differ between men and women in groups 1 and 2. No significant differences were found in the same criteria between women and men in groups 3 and 4.

4. Discussion

The goal of the current study was to develop an objective and simple tool for identification and characterization of BD for both genders based on a progressive severity. To our knowledge, this is the first study to propose an integrative model of BD that captures comprehensive features of BD and has led to a global definition combining 5-item (Appendix, online access to two tools: a population sample classification tool,[1] and an individual characterisation tool[2]).

The analyses we performed on our student learning sample revealed 4 homogeneous groups, defined by 5 salient items that together, capture a set of key BD factors (Maurage et al., 2020) including quantitative aspects of consumption (quantity-frequency with "6-drink frequency"), behavior (speed of consumption), and physiology (frequency of drunkenness, frequency of hangover). As such, ours is the only existing model that combines all of these key factors in a single and consistent measure. Moreover, our use of the statistical PPOM validation has 2 key advantages: (i) it ensures an objective, reliable and reproducible model, and (ii) it avoids the duplication of highly correlated items and selects only salient and statistically significant factors (i.e., 6-drink frequency and not consumption frequency nor drinks per typical day). The internal validation and low classification error of the PPOM that we found confirm construct validity of the 4 groups (McAloney et al., 2013).

The magnitude of all 5 final items progressively increased from group 1 to group 4 (Table 3), with only minor exceptions between the two most severe groups (3 and 4). In addition, the regression equations effectively predicted a participant's probability of belonging to each group. In contrast to the methods using cut-off delimitations in the identification of the population groups, the present approach does not constrain analysis of BD into a dichotomous variable (McAloney et al., 2013). Rather, our model describes a progressive severity to categorize the binge-drinking level of a given participant and accurately map the drinking pattern.

Following the PPOM validation, the external validation confirmed the reproducibility of our method and generalization to two additional samples (Debray et al., 2015; Ramspek et al., 2021). The external validation samples differed from the learning population in many ways, such as sample size, gender ratio, and alcohol consumption metrics (Table 2). Despite these differences, our findings reveal a strong reproducibility of our validation items and confirm that the model variables are robust and that the groups are consistent. Thus, unlike prior studies (Townshend and Duka, 2005), the current model provides a valid characterization of BD independent of the characteristics of the sample.

To further confirm the validity of the 4 groups, they were reassessed using known criteria related to alcohol use and consequences. Specifically, we found that percentage of participants in high consumption scores sub-groups (high BD and AUDIT

1 https://extra.u-picardie.fr/bdct/macro/

2 https://extra.u-picardie.fr/bdct/

TABLE 8 Alcohol consumption and alcohol-related behaviors data by AUDIT items distributed among the four groups.

Group		1	2	3	4	*p*	I.R.R. 4 vs. 3
		%	%	%	%		
Gender						<0.0001***	
	M	10.8	30.6	51.9	73.9		1.4
	F	89.2	69.4	48.1	26.1		0.5
First drink before 12 years old		5.1	6.2	8.5	17.4	<0.0001***	
Binge Group according to Binge Score							
	Mean ± sem	7.07 ± 4.02	16.14 ± 5.65	31.90 ± 6.85	53.26 ± 15.19	<0.0001***	
						<0.0001***	
	Social drinkers	96.4	53.7	0	0		0
	Intermediate drinkers	3.6	43.5	48.1	0		0
	Binge drinkers	0	2.7	51.9	100		1.9
Audit Group							
	Mean ± sem	4.53 ± 0.41	9.03 ± 3.80	13.47 ± 4.8	16.57 ± 5.4	<0.0001***	
						<0.0001***	
	Low risk level	69.7	15.4	1.9	2.2		1.1
	Hazardous level	29.5	65.7	50	23.9		0.5
	High risk level	0.8	18.9	48.1	73.9		1.5
AUDIT 2 *Number of drinks containing alcohol on a typical day*						<0.0001***	
	1 or 2	48.5	17.7	12.3	10.9		0.9
	3 or 4	35.4	28.4	17	10.9		0.6
	5 or 6	14.8	45.3	48.1	23.9		0.5
	7. 8. or 9	0	0	0	0		0
	10 or more	1.2	8.7	22.6	54.3		2.4
AUDIT 4 *Not able to stop drinking once you had started*						<0.0001***	
	Never	87.3	60.7	41.5	41.3		1.0
	Less than monthly	11.8	26.4	24.5	17.4		0.7
	Monthly	0.6	11.4	17	26.1		1.5
	Weekly	0.1	1.5	16	15.2		1.0
	Daily or almost daily	0.3	0	0.9	0		0
AUDIT 5 *Failed to do what is normally expected*						<0.0001***	

(Continued)

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TABLE 8 (Continued)

Group		1	2	3	4	*p*	I.R.R. 4 vs. 3
		%	%	%	%		
	Never	80.6	51.5	26.4	21.7		0.8
	Less than monthly	18.9	39.3	44.3	39.1		0.9
	Monthly	0.4	8	20.8	23.9		1.1
	Weekly	0	1.2	8.5	15.2		1.8
AUDIT 6 *Needed a first drink in the morning*						<0.0001***	
	Never	97.1	85.1	66	47.8		0.7
	Less than monthly	2.4	10.4	17.9	26.1		1.5
	Monthly	0.4	4.5	13.2	15.2		1.1
	Weekly	0.1	0	1.9	10.9		5.7
	Daily or almost daily	0	0	0.9	0		0
AUDIT 7 *Feeling of guilt or remorse after drinking*						<0.0001***	
	Never	72.3	42.8	34.9	43.5		1.2
	Less than monthly	26.3	46.3	48.1	37		0.8
	Monthly	1	9.7	14.2	17.4		1.2
	Weekly	0.4	1	1.9	0		0
	Daily or almost daily	0	0.2	0.9	2.2		2.4
AUDIT 8 *Unable to remember what happened the night before*						<0.0001***	
	Never	82.6	51	25.5	13		0.5
	Less than monthly	16.6	40.5	42.5	45.7		1.1
	Monthly	0.3	7.5	27.4	34.8		1.3
	Weekly	0	0.2	3.8	6.5		1.7
	Daily or almost daily	0.6	0.7	0.9	0		0
AUDIT 9 *Someone else been injured*						<0.0001***	
	No	92.4	82.8	71.7	63		0.9
	Yes but not in the last year	5.5	9	17.9	10.9		0.6
	Yes during the last year	2.1	8.2	10.4	26.1		2.5
AUDIT 10 *Relative/friend/ doctor concerned about your drinking*						<0.0001***	

(Continued)

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TABLE 8 (Continued)

Group		1	2	3	4	*p*	I.R.R. 4 vs. 3
		%	%	%	%		
	No	97.1	89.8	80.2	60.9		0.8
	Yes, but not in the last year	1.7	5.2	6.6	10.9		1.7
	Yes, during the last year	1.2	5	13.2	28.3		2.2
AUQ 11 *Number of times being drunk in the last 6 months?*						<0.0001***	
	1 or less	47.4	0.7	0	0		
	1 to 5	52.6	49.5	0	0		
	6 to 25	0	49.8	100	0		
	30 to 50	0	0	0	100		
Consumption of 4 or more drinks per hour		2.7	12	19.8	32.8		1.7

***$p < 0.0001$. IRR, incidence rate ratio. Comparison between means were performed using ANOVA. Comparison between distribution were conducted using the Chi square. The 4 groups are depicted by the increasing severity of the alcohol-related consumption and consequences items. IRR illustrates differences between group 3 and group 4.

scores) and high adverse consequences sub-groups (AUDIT 2, 4–10, 14; first drink before 12 years old; consumption of 4 or more drinks in one occasion) as well as means of consumption scores (Table 8), and behavioral economic indices (Table 9) gradually increased across groups. Our behavioral economic results confirm consumption criteria. Previous studies reported correlations between behavioral economic indices and risky drinking. APT indices are correlated with measure of alcohol use, alcohol-related consequences, and alcohol use disorder criteria (Gaume et al., 2022). In particular, the demand metrics of "intensity" (i.e., amount of alcohol consumed at zero or very low price, or "How much alcohol would you consume if alcohol were free?") and Omax (i.e., maximum expenditure on alcohol in one occasion) predict clinical alcohol problems, beyond alcohol consumption alone (MacKillop and Murphy, 2007) and 6-month binge drinking and alcohol problems (Dennhardt et al., 2015). Furthermore, since we did not observe a difference in elasticity (alpha) between the groups, our results do not support addictive behavior in the binge drinking group.

These results highlight both the homogeneity within each group and the severity scale across groups. Therefore, we propose the following category labels based on the characteristics of each group: low-risk drinking (group 1), hazardous drinking (group 2), BD (group 3) and high-intensity BD (group 4). By differentiating binge drinking and high-intensity BD as we do for groups 3 and 4, respectively, our approach offers new opportunities to better identify and describe individuals with these drinking profiles (Gmel et al., 2007; Read et al., 2008; Patrick and Azar, 2018; Fairlie et al., 2019). Indeed, the present results reveal some distinctions. For example, compared to group 3, group 4 users are more likely to start drinking before the age of 12, consume more than 10 drinks (100 g) per occasion, fail to do what is expected, need a first drink in the morning, experience weekly black-outs, and drink 4 (40 g) or more drinks per hour. In addition, only group 4 users reported being drunk more than 30 times in the last 6 months meaning at least one episode of drunkenness per week (Table 8). Participants in group 4 also display greater behavioral economic demand, specifically with significantly higher demand intensity, consistently associated with clinical severity of alcohol use.

Results of consumptions items and behavioral economics items confirm the severity of the consumption-related consequences in the high-intensity BD. High-intensity BD is linked to alcohol-related injuries, alcohol poisoning, risky sexual behavior, vomiting, fainting, long-term damage (Patrick and Azar, 2018). The link between high-intensity BD and addictive behaviors will be further investigated. Because high-intensity BD is identified as a strong prospective marker of risk for AUD symptoms in adults (Patrick et al., 2021), our tool could be decisive in identifying this drinking profile early and thereby improving prevention (Enoch et al., 2006; Maurage et al., 2020). Considering the widespread use of BD in adolescents and young adults, the accurate identification of High-intensity BD is highly relevant for providing personalized feedback and awareness-raising to these populations.

Another strength of our model is its applicability across genders (Table 6). In fact, adding the gender factor to the regression equations had no effect on misclassification error, indicating stability of a participant's classification in one of the 4 groups, regardless of gender. In our

TABLE 9 Comparison of the behavioral economic indices among the 4 groups.

Group	1	2	3	4	*p*
Breakpoint-0	11.31 ± 0.18	11.77 ± 0.25	12.40 ± 0.45	10.89 ± 0.68	0.089
Breakpoint-1	11.15 ± 0.18	12.07 ± 0.25	12.92 ± 0.4	11.84 ± 0.79	<0.001**
Observed intensity	6.13 ± 0.17	10.22 ± 0.37	12.31 ± 0.62	16.13 ± 1.42	<0.0001***
Observed Omax	15.97 ± 0.38	20.92 ± 0.75	25.86 ± 2.01	27.00 ± 2.28	<0.0001***
Observed Pmax	6.61 ± 0.16	6.07 ± 0.20	6.48 ± 0.47	6.02 ± 0.63	0.212
Q_0	6.36 ± 0.16	10.45 ± 0.36	12.37 ± 0.58	16.66 ± 1.40	<0.0001***
Alpha	0.014 ± 0.007	0.005 ± 0.0001	0.004 ± 0.0003	0.005 ± 0.0013	0.693

**$p < 0.001$; ***$p < 0.0001$. Values are presented as Mean ± SEM. Comparison between means were performed using ANOVA. Q_0 and alpha represent the derived indices of demand intensity and rate of change in elasticity, respectively, produced from fits of the Koffarnus et al. (2015) exponentiated demand equation to the participant-level demand data Observed intensity represents reported consumption at zero price; breakpoint-0 is the first price at which consumption is suppressed; breakpoint-1 is the last price of non-zero consumption; observed Omax is the maximum product of price × consumption; and observed Pmax is the price at which observed Omax occurs. Group 4 displayed significantly higher demand intensity (both observed and derived) compared with group 3 suggesting a more problematic use of alcohol in group 4, as seen in other population with AUD. Since we did not observe difference in elasticity (alpha) between groups, our results do not support an addictive behavior in the binge drinking group.

TABLE 10 Comparison of consumption parameters and demand indices between Groups 3 and 4.

Group	3	4	*p*
	Mean±sem	Mean±sem	
Consumption criteria			
Units per week	9.68 ± 0.73	14.26 ± 1.30	<0.0001****
Pints of beer per week	5.62 ± 0.507	9.65 ± 1.043	<0.0001****
Spirits per week	4.09 ± 0.388	6.11 ± 0.865	<0.05*
AUDIT Score	13.47 ± 0.461	16.57 ± 0.800	<0.0001****
AUDIT 6 - first drink in the morning	0.54 ± 0.084	0.89 ± 0.153	<0.05*
Binge score	32 ± 0.67	53 ± 2.24	<0.0001****
Demand parameters			
Breakpoint 0	12.40 ± 0.45	10.89 ± 0.68	0.063
Breakpoint 1	12.92 ± 0.4	11.84 ± 0.79	0.234
Observed intensity	12.31 ± 0.62	16.13 ± 1.42	<0.005**
Observed Omax	25.86 ± 2.01	27.00 ± 2.28	0.735
Observed Pmax	6.48 ± 0.47	6.02 ± 0.63	0.574
Q0	12.37 ± 0.58	16.66 ± 1.40	<0.001***
Alpha	0.004 ± 0.0003	0.005 ± 0.0013	0.398

*$p < 0.05$; **$p < 0.005$; ***$p < 0.001$; ****$p < 0.0001$. Values are presented as Mean ± SEM. Comparison between means were performed using Student *t*-test.

exploratory analyses of gender differences, we found differences in drinking behavior within groups 1 and 2, but not in the more severe groups (Table 11). Given that social factors impact drinking habits differently between genders (Graham et al., 1998; Wilsnack et al., 2018), these results may indicate that the impact of such factors is stronger in the less severe groups compared with the more severe ones. The reliability of our model for each gender opens up the ability to study gender-specific differences in consumption behavior with a high degree of confidence.

Our results reveal three additional aspects of interest. First, the frequency of hangovers differentiates low risk drinking from other profiles. Specifically, we found that groups 2, 3, and 4 reported significantly more frequent hangovers compared with group 1, suggesting that hangover is specific to risky drinking patterns; however, we also found that the frequency of hangover was significantly *lower* in group 4 compared with group 3. This finding indicates that hangover does not linearly increase with severity of consumption (Swift and Davidson, 1998) and that high-intensity BD group may not be motivated by experiencing hangover. Second, the frequency of drunkenness is weighted heavily and effectively differentiates hazardous drinking from BD and, even more powerfully, BD from high-intensity BD (Tables 3, 6). These findings confirm that drunkenness is a strong marker of BD severity and should be taken into account in such definitions, as noted by others (Lannoy et al., 2021). Third, and perhaps most importantly, our model confirms that BD should be considered over time and not as a single instance of behavior (i.e., not simply a single instance of 4+/5+ drinks). As noted by Gmel et al. (2011), the frequency of "risky single-occasion drinking" (RSOD) may differ widely between groups, with moderate drinkers displaying RSOD rarely (Gmel et al., 2011). A model that considers the chronicity of BD episodes is necessary to discriminate consequences of occasional BD from chronic BD, in terms of (a) severity of harm and tolerance and (b) experience in managing these effects at equivalent levels of blood alcohol concentrations (Gmel et al., 2011). Our

TABLE 11 Consumptions and behavioral measures related to consumption per group per sex.

	Group 1*N*=723 (56.62%)			Group 2*N*=402 (31.48%)			Group 3*N*=106 (8.30%)			Group 4*N*=46 (3.60%)		
Gender	M	F		M	F		M	F		M	F	
	N=78 (26.90%)	*N*=645 (65.34%)		*N*=123 (42.41%)	*N*=279 (28.27%)		*N*=55 (18.96%)	*N*=51 (5.16%)		*N*=34 (11.7%)	*N*=12 (1.22%)	
	Mean±sem		*p*	Mean±sem		*p*	Mean±sem		*p*	Mean±sem		*p*
Age of start of consumption	14.97 ± 0.252	15.45 ± 0.074	<0.05*	14.61 ± 0.168	14.90 ± 0.082	0.142	14.20 ± 0.179	14.12 ± 0.176	0.790	13.65 ± 0.286	14.58 ± 0.358	0.084
AUDIT	7.03 ± 0.385	4.23 ± 0.096	<0.0001****	11.17 ± 0.385	8.09 ± 0.189	<0.0001****	13.93 ± 0.66	12.98 ± 0.65	0.303	16.50 ± 0.926	16.75 ± 1.657	0.939
Binge Drinking Score	10.26 ± 0.487	6.68 ± 0.150	<0.0001****	17.83 ± 0.50	15.39 ± 0.33	<0.0001****	32.78 ± 0.91	30.95 ± 0.96	0.194	51.60 ± 2.06	57.98 ± 6.31	0.228
AUDIT 4 *Not able to stop drinking once you had started*	0.38 ± 0.084	0.11 ± 0.014	<0.0001****	1.10 ± 1.14	1.15 ± 1.13	<0.01**	1.22 ± 0.168	0.98 ± 0.144	0358	1.09 ± 0.186	1.33 ± 0.3767	0.585
AUDIT 5 *Failed to do what is normally expected*	0.27 ± 0.054	0.19 ± 0.016	0.095	0.73 ± 0.072	0.53 ± 0.038	<0.01**	1.05 ± 0.123	1.18 ± 0.124	0.469	1.29 ± 0.172	1.42 ± 0.288	0.740
AUDIT 6 *Needed a first drink in the morning*	0.13 ± 0.053	0.02 ± 0.007	<0.0001****	0.33 ± 0.057	0.13 ± 0.024	<0.0001****	0.45 ± 0.096	0.63 ± 0.140	0.230	0.91 ± 0.191	0.83 ± 0.241	0.766
AUDIT 8 *Unable to remember what happened the night before*	0.23 ± 0.048	0.19 ± 0.019	0.506	0.78 ± 0.068	0.51 ± 0.040	<0.001***	1.15 ± 0.123	1.10 ± 0.116	0.687	1.32 ± 0.138	1.42 ± 0.229	0.762
AUDIT 9 *Someone else been injured*	0.41 ± 0.117	0.17 ± 0.026	<0.01**	0.83 ± 0.128	0.37 ± 0.062	<0.0001****	0.87 ± 0.193	0.67 ± 0.174	0.400	1.29 ± 0.303	1.17 ± 0.520	0.862
AUDIT 10 *Relative or friend concerned about your drinking*	0.38 ± 0.127	0.05 ± 0.014	<0.0001****	0.62 ± 0.120	0.16 ± 0.041	<0.0001****	0.80 ± 0.198	0.51 ± 0.184	0.268	1.24 ± 0.293	1.67 ± 0.595	0.522
Mediane												
AUDIT 2 *How many drinks in a typical day*	1[£]	0[£]		2[£]	2[£]		3[£]	3[£]		3[£]	3[£]	

*$p < 0.05$; **$p < 0.005$; ***$p < 0.001$; ****$p < 0.0001$. [£]0 = 1 or 2 drinks/typical day 3 = 7, 8 or 9 drinks/typical day. 1 = 3 or 4 drinks/typical day 4 = 10 or more drinks/typical day. 2 = 5 or 6 drinks/typical day. Means comparison were performed with ANOVA.

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model addresses both of these needs and fills an important gap noted by several others.

Despite its strengths, our model has some limitations. For example, the learning sample and both validation samples originated from only one country. Although the three samples differed in many ways (such as average level of consumption and gender distribution), replication is warranted in future studies, with external geographical validation, to confirm that the model remains valid despite cultural differences. Moreover, a larger sample would allow the recruitment of more participants displaying high-intensity BD to better characterize this type of drinking. Reliance on self-report is also a limitation (Creswell et al., 2020) since young adults may minimize or exaggerate their drinking levels. Another limitation of this study is that it is conducted in a student population. Future studies may look at other populations in terms of age and geographical region. Our model could indeed address the growing need to study BD in middle-aged adults, particularly among women (age 30–44), for whom the incidence of BD has nearly doubled in the past decade (Han et al., 2019; Patrick et al., 2019). Finally, the reference period for the AUDIT is 1 year, and thus the recall for past drinking experiences may have been less reliable on these items.

In conclusion, the current model provides a novel approach to characterizing BD based on a strong statistical model. This model combines salient items with strong clinical validity to offer an objective pattern of BD consumption, independent of consumption cut-offs and population type, that is applicable regardless of gender. We now have a useful instrument to assess each participant's BD severity [Appendix and online access (see footnote 1)] or to identify 4 homogeneous groups of alcohol drinking in a whole sample and differentiate types of drinking, including BD and high-intensity BD with a gradual severity [Appendix and online access (see footnote 2)]. With a simple to use model, the BD severity of each subject, male or female, can be determined according to a global definition that includes consumption, behavioral, and physiological criteria.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Comité de Protection des Personnes Nord-Ouest II and Comité de Protection des Personnes Est I. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JA and MN developed the study. JA, MN, MM, and MD contributed to the study design. JA and FG conducted the data collection and data analyses were performed in collaboration with JA, MN, MM, MD, and OO. JA drafted the manuscript in collaboration with MN, MM, and MD. OP provided critical revisions. FF provided the website. All authors approved the final versions of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Appendix

(A) To characterize consumption for a whole population.

A,1: Excel file online access: https://extra.u-picardie.fr/bdct/macro/

A,2: R-code

```
##six_drink_frq=0 (never); six_drink_frq=1 (<once/month);six_drink_frq=2 (once/month);six_drink_frq=3 (once/week);six_drink_frq=3 (almost every day)
###cons_speed in number of drinks per week
##drunkness_freq (number of times drunk in the last 6 months)
##drunkness_perc (de 0 ‡ 10)
##hang_perc (de 0 ‡ 10)
Bing_category=function(six_drink_freq,cons_speed,drunkness_freq,drunkness_perc,hang_perc)
{
P_sup2=exp(-5.87+0.43*six_drink_freq+0.20*cons_speed+0.34*drunkness_freq+0.68*drunkness_perc+0.36*hang_perc)/(1+exp(-5.87+0.43*six_drink_freq+0.20*cons_speed+0.34*drunkness_freq+0.68*drunkness_perc+0.36*hang_perc))
P_sup3=exp(-7.37+0.43*six_drink_freq+0.07*cons_speed+0.34*drunkness_freq+0.11*drunkness_perc+0.05*hang_perc)/(1+exp(-7.37+0.43*six_drink_freq+0.07*cons_speed+0.34*drunkness_freq+0.11*drunkness_perc+0.05*hang_perc))
P4=exp(-8.46+0.43*six_drink_freq-0.12*cons_speed+0.34*drunkness_freq+0.02*drunkness_perc-0.34*hang_perc)/(1+exp(-8.46+0.43*six_drink_freq-0.12*cons_speed+0.34*drunkness_freq+0.02*drunkness_perc-0.34*hang_perc))
return(c(1-P_sup2,P_sup2-P_sup3,P_sup3-P4,P4))
}
### if six_drink_frq=0; cons_speed=2; drunkness_freq=1; drunkness_perc=2 (20%) and hang_perc=3 (30%)
Bing_category(0,2,1,2,3)
```

Note: The PPOM algorithm R-code categorizes the consumption of the whole population by providing the probability of belonging to one of the four group for each subject.

(B) The 5 items tool to characterize the consumption of one participant.

Online access: https://home.mis.u-picardie.fr/~furst/bdbq.html

This questionnaire evaluates your **Binge Drinking** habits. Binge Drinking is a massive, occasional and repeated alcohol consumption to get drunk.

Please select the answer that fits you best for each of these 5 questions

1- How often do you have six or more drinks on one occasion?

Never	*0*
Less than once in a month	*1*
Once in a month	*2*
Once in a week	*3*
Almost every day	*4*

2- When you drink, how fast do you drink?

1 drink in 3 hours	*1/3*
1 drink in 2 hours	*1/2*
1 drink in 1 hour	*1*
2 drinks per hour	*2*
…	…
+ 20 drinks per hour.	*20*

3- How many times have you been drunk in the past 6 months?

Being drunk involves loss of coordination, nausea and/or inability to speak clearly.

Never	*0*
…	…
50 times	*50*

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4- In 10 drinking occasions, how many times have you been drunk after drinking?

Never	*0*
1 time out of 10	*0,1*
….	…
10 times out of 10	*10*

5- In 10 drinking occasions, how many times have you had a «hangover» after drinking?

Never	*0*
1 time out of 10	*0,1*
….	…
10 times out of 10	*10*

The BDQ score is calculated with the PPOM algorithm.

Note: The probability of belonging to one of the four groups for each participant is calculated with the PPOM algorithm.

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A subchronic history of binge-drinking elicits mild, age- and sex-selective, affective, and cognitive anomalies in C57BL/6J mice

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Introduction: Alcohol abuse is a risk factor for affective and cognitive disorders, with evidence indicating that adolescent-onset excessive drinking can result in long-term deficiencies in emotional regulation and cognition, with females more susceptible to the negative emotional and cognitive consequences of excessive alcohol consumption. However, our prior examination of the interactions between sex and the age of drinking-onset indicated minimal signs of anxiety-like behavior during alcohol withdrawal, which may have related to the concurrent anxiety testing of male and female subjects.

Methods: The present study addressed this potential confound by assaying for alcohol withdrawal-induced negative affect separately in males and females and expanded our investigation to include measures of spatial and working memory.

Results: Following 14 days of drinking under modified Drinking-in-the-Dark procedures (10, 20, and 40% alcohol v/v; 2 h/day), adolescent and adult binge-drinking mice of both sexes exhibited, respectively, fewer and more signs of negative affect in the light-dark shuttle-box and forced swim tests than their water-drinking counterparts. Adolescent-onset binge-drinking mice also exhibited signs of impaired working memory early during radial arm maze training during early alcohol withdrawal. When tested in late (30 days) withdrawal, only adult female binge-drinking mice buried more marbles than their water-drinking counterparts. However, adolescent-onset binge-drinking mice exhibited poorer spatial memory recall in a Morris water maze.

Discussion: These findings indicate that a subchronic (14-day) binge-drinking history induces mild, age- and sex-selective, changes in negative affect and cognition of potential relevance to understanding individual variability in the etiology and treatment of alcohol abuse and alcohol use disorder.

KEYWORDS

adolescence, Morris water maze, radial arm maze, negative affect, sex differences

Introduction

One of the most common risk factors for the development of dementia and cognitive decline is a history of alcohol abuse (Schwarzinger et al., 2018; Nunes et al., 2019; Wiegmann et al., 2020). Numerous studies have identified that both alcohol use disorder (AUD) and dementia, particularly Alzheimer's Disease (AD), have a high incidence of cooccurrence (Hersi et al., 2017; Hoffman et al., 2019). Recent evidence suggests that excessive drinking may play a significant role in the development of early-onset dementia and related disorders (Piazza-Gardner et al., 2013; Heymann et al., 2016; Huang et al., 2018; Ledesma et al., 2021). According to evidence from both rodent and human studies, repetitive binge-drinking episodes throughout adolescence are sufficient to generate disruptions within the mesocorticolimbic system that may cause long-term deficiencies in emotional regulation and poor cognitive abilities that become apparent later in adulthood (Novier et al., 2015; Cservenka and Brumback, 2017).

Characterized as stage of rapid neurodevelopment, adolescence normally takes place between 12 and 17 years of age in humans and 28–50 postnatal days (PND) in laboratory mice. Adolescence is commonly recognized as a transitional period marked by the onset of puberty and accompanied by rapid neurobiological, social, and cognitive development (Spear, 2000a,b). As a result of these changes, heightened risk-taking is a hallmark characteristic of adolescence that contributes to the incidence and prevalence of substance use disorders, including AUD (Steinberg, 2007; MacPherson et al., 2010). In contrast to adults, adolescents also exhibit milder affective disturbances and are less vulnerable to the sedative and cognitive deficits that often occur during alcohol withdrawal (Varlinskaya and Spear, 2004; Lee et al., 2016). Thus, research suggests that the perceived advantages of binge-drinking are often more pronounced during this age and such an age-specific attenuation in sensitivity to alcohol's aversive properties may serve as a permissive factor that contributes to the maintenance of binge drinking patterns among adolescents (Varlinskaya and Spear, 2004; Spear and Varlinskaya, 2005).

The motivational factors that drive drinking to intoxication differ between biological sexes in both humans and laboratory rodents. Evidence suggests that human females are more likely to engage in alcohol binge-drinking to alleviate physical and psychological distress, compared to males (Rodriguez et al., 2020). Although both sexes report a high rate of comorbid mood disorders with AUD, females demonstrate a heighted susceptibility to both the psychological and physiological consequences of excessive drinking (Pollard et al., 2020; Rodriguez et al., 2020). Further, a few findings allude to the notion that females with a history of alcohol abuse experience earlier and greater cognitive-behavioral impairments than their male counterparts (Hebert et al., 2013; Agabio et al., 2017; Ferretti et al., 2018). While several hypotheses attempt to explain why females experience more severe biopsychological effects than males because of alcohol, there is relatively little research that directly examines for sex differences in the effects of excessive drinking on affect or cognitive function, let alone how the age of drinking-onset might interact with biological sex to impact the severity of affective and/or cognitive disturbances during alcohol withdrawal.

Toward this end, we published a study in 2020 designed to examine for sex by age interactions in the expression of negative affect during early (1 day) versus protracted (70 days) alcohol withdrawal in C57BL/6J (B6) mice (Jimenez Chavez et al., 2020). In contrast to other published findings from our laboratory that studied a single sex (e.g., males: Lee et al., 2015, 2016, 2017b, 2018a,b; females: Szumlinski et al., 2019), we detected relatively few behavioral signs of alcohol withdrawal-induced anxiety-like behavior, irrespective of the age of binge-drinking onset. However, when effects of alcohol withdrawal were detected, the magnitude of the effect was comparable between male and female subjects. Two procedural differences might account for the discrepancies in findings between our study of sex differences (Jimenez Chavez et al., 2020) and those employing a single sex (Lee et al., 2016, 2017a,b, 2018a,b; Szumlinski et al., 2019). The first relates to the duration of the alcohol withdrawal period as earlier work compared anxiety-like behavior between 1- and 30-days withdrawal and showed that (at least in adult male B6 mice with a 2-week history of binge-drinking) signs of negative affect dissipate by the 30-day withdrawal time-point (Lee et al., 2017b, 2018a). In contrast, some signs of alcohol-induced negative affect persist for at least 30 days in adult female B6 mice (Szumlinski et al., 2019), but may dissipate at some time between 30 and 70 days withdrawal (Jimenez Chavez et al., 2020). The second procedural difference relates to the concurrent testing of males and females and the potential for sex-related pheromones to influence the affective responses of mice of the opposite sex. Indeed, chemosensory social stimuli, such as those in vaginal secretions, are reported to alter neuronal activity within the mesocorticolimbic system differentially in adolescent versus adult males to affect motivated behavior (Romeo et al., 1998; Bell et al., 2013a,b). Further, exposure to adult female urinary pheromones during testing for anxiety-like behavior produces a testosterone-driven anxiolytic effect in male rats and mice (Aikey et al., 2002; Fernández-Guasti and Martínez-Mota, 2005; Frye et al., 2008). While it is known that affective behavior varies with the estrous cycle in adult female rodents (Fernandez-Guasti and Picazo, 1992), to the best of our knowledge, there is no published report examining how exposure to adult male pheromones might alter anxiety-like behavior in female rodents.

The present study attempted to address both procedural issues by staggering binge-drinking procedures so that anxiety-like behavior was assayed separately in male and female mice on withdrawal days 1 and 30 (respectively, WD1 and WD30). As recent work indicated that mature adult females are more sensitive than their male counterparts to alcohol-induced cognitive impairment (Jimenez Chavez et al., 2022), mice in this study then underwent training under Morris water maze and radial arm water maze procedures to examine for sex by age interactions in alcohol-induced deficits in spatial and working memory in younger adult mice (see **Figure 1**). Based on the current literature (Szumlinski et al., 2019; Ledesma et al., 2021; Jimenez Chavez et al., 2022), it was hypothesized that alcohol-induced changes in affective and cognitive behavior would be more pronounced in females than males and that a history of binge-drinking during adolescence would induce more robust and/or enduring changes in behavior than that produced by a history of binge-drinking during adulthood.

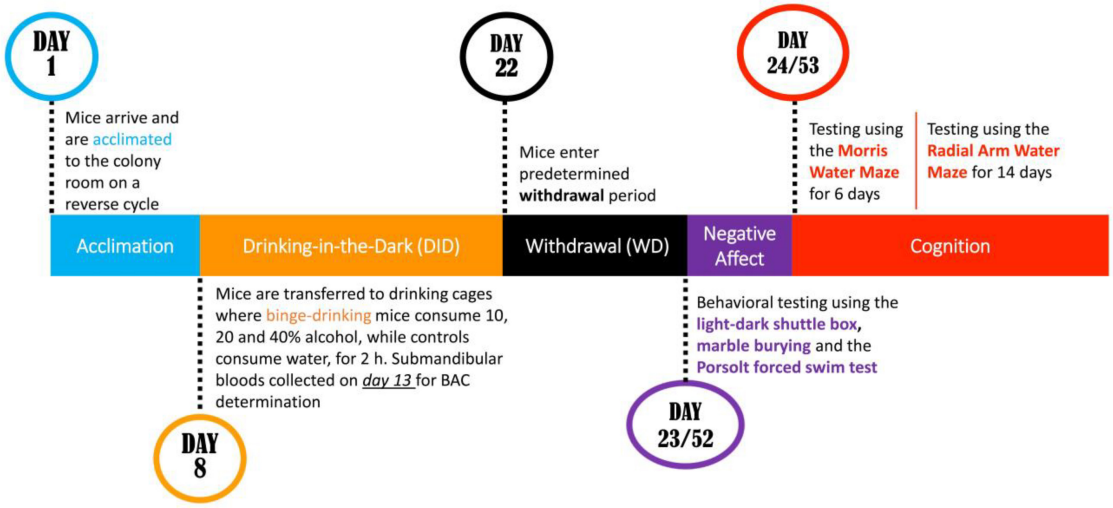

FIGURE 1
Cartoon of the procedural time-line of the experiments conducted in the present study.

Materials and methods

Subjects

This experiment employed adolescent (postnatal day; PND 21) and adult (PND 49), male and female B6 mice sourced from The Jackson Laboratory (Sacramento, CA, United States). Upon arrival to the vivarium, the mice were immediately housed in groups of four with others of the same age and sex. Mice were allowed 7 days to acclimate to a colony room in a temperature-controlled vivarium under a 12-h reverse light/dark cycle (lights off at 10:00 h). To accommodate space constraints in our vivarium and testing facility, the mice in both withdrawal groups were subdivided into two cohorts, each cohort with a relatively equal number of animals in each group, matched for age, sex and drinking history. In the first cohorts, male mice began drinking a day before the female mice, to ensure that males and females were tested for anxiety-like behavior on different days, thereby minimizing the influence of chemosensory stimuli from the opposite sex; the inverse was done on the subsequent cohorts (Jimenez Chavez et al., 2020, 2022). All animals were identified via tail markings, with access to food and water *ad libitum*, except during the 2-h alcohol-drinking session. In accordance with standard vivarium protocols, drinking cages were lined with sawdust bedding. To minimize any external stressors from unfamiliar handling and changes in the environment, routine cage cleaning activities were halted 5 days before behavioral testing. All experimental methods remained complaint with The Guide for the Care and Use of Laboratory Animals (2014) and all protocols were approved by the Institutional Animal Care and Use Committee of the University of California, Santa Barbara.

Drinking-in-the-Dark (DID)

A total of 92 mice were subjected to 14-days of binge drinking using a multi-bottle DID procedure that involved concurrent access to unsweetened 10, 20, and 40% (v/v) ethanol. At 13:00 h, all alcohol-drinking mice were relocated from their home cages to individual drinking cages, fitted with a wire lid, located on a free-standing rack in the same colony room within the vivarium. All animals were given 1 h to habituate to their drinking cages prior to alcohol presentation. At 14:00 h, the binge-drinking mice were provided with three alcohol-containing sipper tubes atop the wire cage lid for 2 h (14:00 h–16:00 h), with the position of the sipper tubes randomized each day. As a result of limited space on the freestanding rack, the water-drinking control mice were group housed in drinking cages with their cage mates and received one sipper tube containing water as conducted in comparable studies (e.g., Lee et al., 2018b; Szumlinski et al., 2019; Jimenez Chavez et al., 2020, 2022). Following the 2-h drinking session, all sipper tubes were removed, and the mice were transferred back into their respective home cages. The alcohol-containing sipper tubes were weighed to determine individual consumption. Throughout the drinking period, mice were weighed every 4 days and their weights were utilized to calculate their overall alcohol intake.

Blood alcohol concentrations

On the 13th day of drinking, submandibular blood samples were collected from the alcohol-drinking mice immediately following their 2-h drinking session. Analytical methods for determining blood alcohol concentrations (BAC) are similar to those employed in our previous studies (Fultz and Szumlinski, 2018; Jimenez Chavez et al., 2020, 2022). Blood samples were stored at −20°C until processing and BACs were determined using headspace gas chromatography. The analysis was performed using a Shimadzu GC-2014 gas chromatography system (Shimadzu, Columbia, MD, USA), and the data was obtained using the GC Solutions 2.10.00 software. To determine the alcohol concentration in each sample, the samples were diluted with non-bacteriostatic saline at a ratio of 1:9, with 50 μl of the sample, and toluene

was used as the pre-solvent. The analysis was conducted within 7–10 days of sample collection.

Behavioral test battery for negative affect

Evidence from our prior work indicated that adolescent male B6 mice with a 2-week history of binge-drinking do not display any noticeable signs of negative affect when tested at 1 day withdrawal (e.g., Lee et al., 2016, 2017b, 2018a,b; Szumlinski et al., 2019; Jimenez Chavez et al., 2020, 2022), we conducted a comprehensive 1-day behavioral test battery including the light-dark shuttle box test, the marble burying test and the Porsolt forced swim test to measure withdrawal-induced changes in negative affect, as detailed below. The order of testing in the various procedures was pseudo-randomized, except for the forced swim test, which occurred last in the test battery in accordance with our animal use protocol. To mitigate any potential impact of chemosensory stimuli from the opposite sex on behavior, we tested males and females on separate days.

Light–dark shuttle box test

The light-dark shuttle box test is a behavioral paradigm employed in preclinical research to evaluate anxiety-like behaviors in rodents (Crawley, 1985; Bourin and Hascoët, 2003). In this test, mice are placed in the dark side of a polycarbonate box (46 cm × 22 cm × 24 cm) comprised of two distinct (light vs. dark) environments of equal areas. The light side of the box was white with no lid, while the dark side was black with a black lid. A central divider with an opening allowed the mice to access both sides throughout the 5-min test. The behavioral indices of anxiety-like behaviors, including latency to enter the light side, total time spent in the light side, and the total number entries to the light side, were measured using AnyMaze tracking software (Stoelting Co., Wood Dale, IL, USA). After each testing session, the apparatus was disinfected with Rescue Disinfectant Veterinary Wipes (Virox Animal Health, Oakville, ON, Canada) and the mice were returned to their home cages.

Marble burying test

The marble burying test is an established rodent behavioral paradigm that is sensitive to alcohol withdrawal-induced changes in negative affect (Lee et al., 2016, 2017a,b; Szumlinski et al., 2019; Jimenez Chavez et al., 2020, 2022). Mice were placed in a polycarbonate box (12 cm × 8 cm × 6 cm) filled with sterilized sawdust bedding 5 cm deep and 20 round glass black marbles arranged equidistantly in a 4 × 5 square pattern. Animals were allowed to explore the environment and bury marbles for 20 min, where more burying behaviors indicated increased negative affect. After each session, the total number of marbles buried was tallied by the experimenter, the sawdust bedding was replaced with clean bedding, and the mice were returned to their home cages.

Porsolt forced swim test

The Porsolt forced swim test is a behavioral paradigm often used to evaluate the reversal of passive coping behavior by antidepressant therapies (Porsolt et al., 2001). The increased swimming behavior observed in this assay can be reversed by pretreatment with anxiolytic agents (Lee et al., 2017a) and therefore, we incorporated it as an additional measure of negative affect. In this assay, mice were placed into a cylindrical glass container (11 cm in diameter) filled with room temperature water for 6 min. Using the AnyMaze tracking software, we measured the latency to the first immobile episode, the total time the animal was immobile, and the number of immobile episodes. Following completion of the test, the mice were returned to their home cages and were monitored until they were dry before returning to the colony room.

Morris water maze

Following the 1-day test battery for negative affect, conducted on either withdrawal day 1 (WD1) or 30 (WD30), all mice underwent a Morris water maze procedure to assay spatial learning and memory (see **Figure 1**). The Morris water maze procedures were like those employed previously by our group, using digital video-tracking and AnyMaze software (Lominac et al., 2005; Datko et al., 2017; Jimenez Chavez et al., 2022). The maze is a stainless-steel circular tank (200 cm x 60 cm) containing black intra-maze cues (sun, checkerboard, stripes, moon) one at each four compass coordinate points (N,S,W,E). The tank was filled with room temperature water such that the water level was just above the top of the clear, glass, escape platform. On the first day, a "flag test" was conducted that assayed for visually cued spatial navigation and examined for group differences in swimming speed. For this, a red flag, extending 6 inches above the water, was attached to the escape platform so that the platform location was visible to the mice and the platform was positioned in the NW quadrant. The mice were allowed 2 min to locate the platform and were returned to their home cage upon platform location. If a mouse failed to locate the platform, additional 2-min sessions were conducted until the mouse located the flagged platform. The subsequent 4 days consisted of maze acquisition training, during which the flag was removed and the hidden platform remained situated in the NE quadrant. During acquisition, mice were released from one of the four compass points and allowed 2 min to locate the hidden platform. Once found, mice remained on the platform for 15 s, prior to being returned to the home cage. Once all of the mice completed the first compass point, they were released from the other three compass points so that each mouse underwent four 2-min trials per day. If a mouse failed to locate the hidden platform at any point during maze acquisition, it was guided gently to the platform using long forceps and remained on the platform for 15 sec prior to being returned to the home cage. Twenty-four hours following the fourth acquisition training day, a "probe test" was conducted in which the hidden platform was removed from the tank, and mice swam freely for 2 min and the time spent swimming in the NE quadrant that formerly contained the platform was recorded to index spatial recall. The day following the probe test, a reversal test was conducted in which the hidden platform was positioned in the SW quadrant (i.e., the quadrant opposite to that employed during maze acquisition), and mice underwent four 2-min trials (one for each compass point) in which they were to find the new platform location.

Water version of the radial arm maze

Following a 1–2 day break, mice were then trained to locate 4 hidden platforms in a water version of the radial arm maze to evaluate working and reference memory. Akin to prior studies (Lominac et al., 2005; Szumlinski et al., 2005; Jimenez Chavez et al., 2022), the maze featured eight arms, four of which had underwater platforms, with the platform locations remaining constant throughout the 14-day training period, but varied for each mouse. Each mouse underwent four, 3-min, trials per day and the trials were conducted in series until the mouse located all four hidden platforms. Upon location of a hidden platform, the mouse remained on the platform for 15 s, at which time it was transferred to a heated holding cage for a 30-s period and the platform was removed from the maze. This was repeated until all four platforms were located. Trained researchers observed the mice throughout each 3-min trial and documented their arm entries in order to calculate the number of reference errors (first entry into an arm that never contained a platform; total of 4 possible), the number of working memory correct errors (entries into an arm that previously contained a platform), the number of working memory incorrect errors (repeated entries into an arm that never contained a platform), chaining behavior (consecutive entries into adjacent arms, irrespective of platform location; a non-spatial navigation strategy) and the time required to locate the platform. The first day of testing was considered a training day and thus was excluded from statistical analysis. The number of each type of error, the number of chains and the time taken during each trial were each summed across the four trials to provide a total for each variable for each training day.

Replicate study of withdrawal-induced negative affect

The results of the large-scale study described above yielded relatively few signs of alcohol withdrawal-induced negative affect. As assays were conducted concurrently with other testing, we attempted to reduce the influence of any concurrent testing and related personnel traffic in a replicate study more in line with prior studies by our group (e.g., Lee et al., 2016, 2018a,b; Szumlinski et al., 2019). We also single-housed the water-drinking controls during drinking procedures to equate the daily 3-h periods of social isolation across the drinking groups. Otherwise, the drinking and behavioral testing procedures for this replicate study were identical to those employed in the larger scale study described above. Again, males and females were tested for anxiety-like behavior on different days to avoid chemosensory cues from the opposite sex. As the withdrawal-induced negative affect exhibited by adult mice in early withdrawal is robust according to our earlier studies (Lee et al., 2016, 2017a,b, 2018a,b; Szumlinski et al., 2019), we opted to examine behavior at this time-point only in this replicate study with two expectations: (1) adolescent water controls would exhibit more anxiety-like behavior than adults and (2) adult, but not adolescent, alcohol-drinking mice would exhibit signs of anxiety-like behavior. Based on recent work (Jimenez Chavez et al., 2020, 2022), coupled with the majority of results from the present large-scale study (see "Results"), we did not predict any sex difference in the manifestation of withdrawal-induced negative affect. Thus, we employed a sample size of $n = 6$/sex/age/drinking history.

Statistical analysis

To ensure comparable alcohol intake and BECs between the groups of mice slated to be tested on withdrawal day 1 versus withdrawal day 30 (respectively, WD1 versus WD3), these variables were analyzed using a Sex × Age × Withdrawal ANOVA. The data for alcohol intake in the replicate study was analyzed using a Sex × Age ANOVA. Previous findings from our laboratory suggest that the magnitude of alcohol withdrawal-induced negative affect is influenced by the length of withdrawal (Lee et al., 2016, 2017b, 2018a; Szumlinski et al., 2019; Jimenez Chavez et al., 2020). Therefore, to reduce the complexity of the statistical analyses and increase interpretability of the results from the large-scale study, the data for our measures of negative affect and cognitive function were analyzed separately for early (starting on WD1) and late (starting on WD30) withdrawal using a Sex × Age × Drinking History ANOVA. Alpha was set at 0.1 for all analyses as we had *a priori* predictions that: (1) adolescent water-drinking mice would exhibit higher baseline emotionality than their adult counterparts (Lee et al., 2016, 2017a,b); (2) adult binge-drinking mice would exhibit robust signs of negative affect, particularly on WD1 (Lee et al., 2015, 2016, 2017b, 2018a,b; Szumlinski et al., 2019; Jimenez Chavez et al., 2022); and (3) signs of alcohol withdrawal-induced negative affect expressed by adolescent-onset binge-drinkers would be more robust on WD30 compare to WD1 (Lee et al., 2016, 2017b, 2018a,b). For the cognitive data, we conducted Sex x Age x Drinking ANOVAs, with the repeated measures variables of Day/Trial, when appropriate. To increase the statistical power to identify lower-level age and sex differences in our cognitive measures, alpha was set at 0.05 for all analyses and *post hoc* LSD comparisons were performed. For all analyses where sphericity was violated, a Greenhouse–Geisser correction was used. Outliers were identified and excluded from the analyses using the $\pm$ 1.5 × IQR rule, however, in instances were too many outliers were identified, we adopted the $\pm$ 3 × IQR rule to ensure that only the most extreme outliers were removed. IBM SPSS Statistics software (version 27.0 for Macintosh) was used for all statistical tests, and GraphPad Prism software (version 9.3.1 for Macintosh) was used to create all graphs.

In addition to our primary analyses employing a general linear model, we sought to enhance the comprehensiveness of the data analysis for the large-scale study by employing generalized linear models (GLMs) for our between-subjects analyses. Within this framework, we selected specific GLM types provided by SPSS that were suitable for the nature of our response variables. GLMs are particularly used when assumptions underlying traditional general linear models are violated, allowing for a more flexible modeling approach that adapts to various data distributions and response types (Neal and Simons, 2007; Ng and Cribbie, 2017). For continuous (scale) responses, we implemented two GLM variations: (1) a linear GLM with a normal distribution assumption and the identity link function, and (2) a gamma GLM with a gamma distribution assumption and the logarithmic link function. For count-based response variables, we employed (1) a Poisson loglinear GLM assuming a Poisson distribution and the logarithmic

link function, and (2) a negative binomial GLM assuming a negative binomial distribution and the logarithmic link function. Finally, for the dependent variable measuring the number of marbles buried, we utilized a binary logistic GLM with a binomial distribution assumption and the logit link function, as well as a Poisson loglinear GLM. The binary logistic GLM was chosen due to the variable's bounded maximum value of 20 marbles. Overall, these additional analyses remained consistent with the results from the general linear model (3-way ANOVA; see **Tables 1–3**).

To address concerns pertaining to sphericity and homogeneity of variance, we re-analyzed our mixed-model ANOVA results using multilevel models. In contrast with traditional mixed-model ANOVAs, multilevel models do not make assumptions of sphericity or homogeneity of variance (Quené and Van den Bergh, 2004). Moreover, multilevel models are more robust than traditional ANOVAs to violations of distributional assumptions (Schielzeth et al., 2020). These analyses employed a random intercept model, with observations nested within subjects. For ease of interpretation, the Day/Trial variable was treated as a continuous parameter. Overall, the pattern of results resembled those found using traditional mixed model ANOVAs, with only minor exceptions (see **Table 4**). These statistical analyses were performed in R, utilizing the lmerTest and lme4 packages. As the results of the multilevel model approach failed to yield results that were much different from the mixed-model ANOVA, the data for the replicate study were analyzed using a mixed-model ANOVA, adjusting for violations of sphericity and homogeneity of variance.

Results

Alcohol intake and BECs

A univariate Sex × Age × Withdrawal ANOVA was conducted to determine group differences in the amount of alcohol consumed during the 14 days of drinking and to confirm equivalent intakes between mice slated to be tested for behavior on WD1 and WD30. While a statistically significant main effect of Withdrawal was observed [$F(1,84) = 3.99$, $p = 0.049$, $\eta^2p = 0.045$], its practical significance may be limited due to the relatively weak effect size and the unequal sample sizes in our study. As such, the data are presented as collapsed across the two withdrawal time-points in **Figure 2**. Adolescent mice exhibited higher alcohol intake than adult mice [**Figure 2A**; Age effect $F(1,84) = 45.491$, $p < 0.001$, $\eta^2p = 0.351$], as well as higher alcohol intake by female mice than males [**Figure 2A**; Sex effect $F(1,84) = 40.326$, $p < 0.001$, $\eta^2p = 0.324$]. No significant 3-way interaction was observed for the average alcohol intake ($p = 0.754$, $\eta^2p = 0.001$) and no other significant interactions were observed (all p's > 0.066).

The average BEC attained on Day 13 of drinking (**Figure 2B**) exhibited a pattern of group differences that was comparable to that of the average alcohol intake of the mice [Age effect: $F(1,62) = 15.05$, $p < 0.001$, $\eta^2p = 0.195$; Sex effect: $F(1,62) = 10.06$, $p = 0.002$, $\eta^2p = 0.140$] and consistent with this, a Pearson's correlation showed a positive relationship between BEC levels and alcohol intake ($r = 0.59$, $p < 0.001$, **Figure 2C**).

Light dark box shuttle test

Latency to first enter light side

A Sex × Age × Drinking History ANOVA failed to detect any significant differences for the latency to first enter the light-side of the light-dark shuttle-box on either WD1 (**Figure 3A**) (3-way ANOVA: $p = 0.883$, $\eta^2p = 0.000$; all other p's > 0.160) or WD30 (**Figure 3B**; 3-way ANOVA: $p = 0.330$, $\eta^2p = 0.011$, all other p's > 0.228).

Time in the light side

On WD1, an Age × Drinking History interaction [$F(1,85) = 6.65$, $p = 0.012$, $\eta^2p = 0.073$] and a Sex × Age interaction [$F(1,85) = 4.35$, $p = 0.040$, $\eta^2p = 0.049$] were found for the time spent in the light side (**Figure 3C**). As illustrated in **Figure 3D**, the Age × Drinking History interaction reflected less time spent in the light-side by adult binge-drinking mice versus both adult water controls ($p = 0.069$, $d = 0.554$) and adolescent binge-drinking mice ($p = 0.004$, $d = 0.935$). Adolescent water control mice also spent less time in the light side when compared to their binge-drinking counterparts ($p = 0.075$, $d = 0.532$). The Sex × Age interaction (**Figure 3E**) reflected more time spent in the light-side by adult female versus adult male mice ($p = 0.001$, $d = 1.001$), with no sex difference apparent in adolescent animals ($p = 0.680$, $d = 0.122$). Additionally, adolescent males spent more time in the light-side compared to the adult males ($p = 0.006$, $d = 0.832$). On WD30, no significant effects or interactions were detected (**Figure 3F**; 3-way ANOVA: $p = 0.396$, $\eta^2p = 0.009$; all other p's > 0.140).

Light side entries

On WD1, a Sex × Age × Drinking History ANOVA detected a significant Sex × Drinking History [$F(1,85) = 3.59$, $p = 0.062$, $\eta^2p = 0.041$] and an Age × Drinking History interaction [$F(1,85) = 4.75$, $p = 0.032$, $\eta^2p = 0.053$] for the number of entries into the light-side (**Figure 3G**). As illustrated in **Figure 3H**, the Sex × Drinking History interaction reflected a higher number of light side entries in male binge-drinking mice versus the female binge-drinking mice ($p = 0.072$, $d = 0.563$). Although inspection of **Figure 3I** suggested that adolescent binge-drinking mice made more light side entries than their water controls, while the opposite was true for adult binge-drinking mice, deconstruction of the Age × Drinking History interaction indicated no significant Water-EtOH difference in the adolescent or adult mice (Adolescents: $p = 0.119$, $d = 0.459$; Adults: $p = 0.135$, $d = 0.456$). On WD30, a main Sex effect was observed for the number of light-side entries [$F(1,88) = 9.48$, $p = 0.003$, $\eta^2p = 0.097$; all other p's > 0.203], with females entering the light-side more, overall, than males (**Figure 3J**).

Marble burying test

The data for the number of marbles buried on WD1 by all of the groups are presented in **Figure 4A**. An analysis of these data indicated more marbles buried by adult versus adolescent mice (**Figure 4B**) [Age effect: $F(1,88) = 4.01$, $p = 0.048$, $\eta^2p = 0.044$], but no other effects or interactions were found at this withdrawal time-point (Sex × Age × Drinking History ANOVA: $p = 0.511$, $\eta^2p = 0.005$; all other p's > 0.496). The data for the number of

TABLE 1 Comparative analysis of significant statistical results on continuous data for the measures of negative affect and cognition using a general linear model, gamma generalized linear model with log link function (Gamma), and linear generalized linear model (Linear).

Withdrawal day 1						
Dependent variable	General linear model		Generalized linear model (Gamma)		Generalized linear model (Linear)	
	Interaction	*P*-value	Interaction	*P*-value	Interaction	*P*-value
Latency to enter the light side	None	all *p*'s > 0.160	None	all *p*'s > 0.169	None	all *p*'s > 0.139
Time spent in the light side	Age × DID Sex × Age Age Effect Sex Effect	0.012 0.040 0.066 0.009	Age × DID Sex × Age Age Effect Sex Effect	0.011 0.022 0.049 0.008	Age × DID Sex × Age Age Effect Sex Effect	0.007 0.029 0.052 0.005
Latency to immobility	DID effect	0.040	DID effect	0.025	DID effect	0.029
Time spent immobile	3-way Inx. Age Effect	0.047 0.019	3-way Inx. Age Effect	0.063 0.027	3-way Inx. Age Effect Sex Effect	0.034 0.012 0.095
Flag test time	None	all *p*'s > 0.500	None	all *p*'s > 0.553	None	all *p*'s > 0.479
Latency to enter platform area	Age × DID	0.021	Age × DID Sex × Age	0.007 0.056	Age × DID	0.014
Time in the probe test	None	all *p*'s > 0.221	None	all *p*'s > 0.215	None	all *p*'s > 0.198
Withdrawal day 30						
Latency to enter the light side	None	all *p*'s > 0.228	None	all *p*'s > 0.247	None	all *p*'s > 0.204
Time spent in the light side	None	all *p*'s > 0.140	None	all *p*'s > 0.162	None	all *p*'s > 0.119
Latency to immobility	Sex Effect	0.006	Sex Effect	0.004	Sex × DID Sex Effect	0.084 0.003
Time spent immobile	Sex × DID Age Effect Sex Effect	0.072 0.032 0.003	Sex × DID Age Effect Sex Effect	0.059 0.033 0.003	Sex × DID Age Effect Sex Effect	0.057 0.022 0.002
Flag test time	None	all *p*'s > 0.222	None	all *p*'s > 0.222	None	all *p*'s > 0.199
Latency to enter platform area	None	all *p*'s > 0.461	None	all *p*'s > 0.441	None	all *p*'s > 0.281

TABLE 2 Comparative analysis of significant statistical results on count data for the measures of negative affect and cognition using a general linear model, poisson generalized linear model with log as the link function (Poission loglinear), and negative binomial generalized linear model with log as the link function (Negative binomial).

Withdrawal day 1						
Dependent variable	General linear model		Generalized linear model (Poisson loglinear)		Generalized Linear model (Negative binomial)	
	Interaction	*P*-value	Interaction	*P*-value	Interaction	*P*-value
Entries to the light side	Age × DID Sex × DID	0.032 0.062	Age × DID Sex × DID	0.033 0.065	None	all *p*'s > 0.621
Immobile episodes	3-way Inx. Age Effect	0.005 0.034	3-way Inx. Age Effect Sex Effect	<0.001 <0.001 0.036	None	all *p*'s > 0.256
Entries to platform area	None	all *p*'s > 0.386	None	all *p*'s > 0.286	None	all *p*'s > 0.710
Withdrawal day 30						
Entries to the light side	Sex Effect	0.003	3-way Inx. Age x DID Sex Effect	0.086 0.098 <0.001	None	all *p*'s > 0.352
Immobile episodes	Age × DID Sex × DID Sex Effect	0.094 0.052 0.007	Age × DID Sex × DID DID Effect Sex Effect	0.044 0.011 0.076 <0.001	None	all *p*'s > 0.402
Entries to platform area	Age × DID	0.012	Age × DID	0.001	None	all *p*'s > 0.280

TABLE 3 Comparative analysis of significant statistical results on count data for the number of marbles buried in the marble burying test using a general linear model, binary logistic generalized linear model with logit as the link function (Binary logistic), and poisson generalized linear model with log as the link function (Poisson loglinear).

Withdrawal day 1						
Dependent variable	General Linear model		Generalized Linear model (Binary logistic)		Generalized Linear model (Poisson loglinear)	
	Interaction	*P*-value	Interaction	*P*-value	Interaction	*P*-value
Number of marbles buried	Age Effect	0.048	Age Effect Sex Effect	<0.001 0.045	Age Effect	0.003
Withdrawal day 30						
Number of marbles buried	Age Effect Sex Effect	0.055 0.002	3-way Inx. Sex × DID DID Effect Age Effect Sex Effect	0.002 0.025 0.041 <0.001 <0.001	3-way Inx. Sex × DID DID Effect Age Effect Sex Effect	0.013 0.068 0.072 0.006 < 0.001

TABLE 4 Comparative analysis of significant statistical results on continuous cognitive data using a general linear mixed model (Mixed model) versus a multilevel model nested within subjects.

Withdrawal day 1				
Dependent variable	General linear model (Mixed model)		Multilevel model (Nested within subjects)	
	Interaction	*P*-value	Interaction	*P*-value
Acquisition time in the Morris water maze	Day Effect	<0.001	Day Effect	<0.001
Time in the reversal test	Day Effect	<0.001	Day Effect	0.005
Number of reference memory errors	Day × Age Day Effect	0.020 0.004	None	0.124
Number of working memory correct errors (WMC)	4-way Inx. Day Effect	0.041 <0.001	4-way Inx. Day × Sex × DID	0.012 0.029
Number of Working Memory Incorrect Errors (WMI)	Day × Age × DID Day × DID Day Effect	0.025 0.037 <0.001	Day × Age × DID Day Effect	0.012 0.004
Number of chaining episodes	Day × Sex × DID Day × Sex Day Effect	0.016 0.005 <0.001	None	0.102
Time in the Radial Arm Maze	Day Effect	<0.001	4-way Inx. Day × Age × DID Day Effect	0.029 0.045 0.011
Withdrawal day 30				
Acquisition time in the Morris water maze	Day × Age Day Effect	0.009 <0.001	Day × Age Age Effect Day Effect	0.006 <0.001 0.046
Time in the reversal test	Day × Age Day Effect	0.005 <0.001	Day × Age Age Effect	0.002 0.003
Number of reference memory errors	Day × Age Day Effect	0.020 0.004	None	0.124
Number of working memory correct errors (WMC)	Day × DID Day Effect	<0.001 <0.001	4-way Inx. Day × Sex × DID	0.017 0.021
Number of working memory incorrect errors (WMI)	Day × Age × DID Day × DID Day Effect	0.025 0.037 <0.001	Day × Age × DID Day Effect	0.012 0.004
Number of chaining episodes	Day × Sex Day Effect	0.036 <0.001	None	0.129
Time in the radial arm maze	Day × DID Day Effect	0.001 <0.001	4-way	0.046

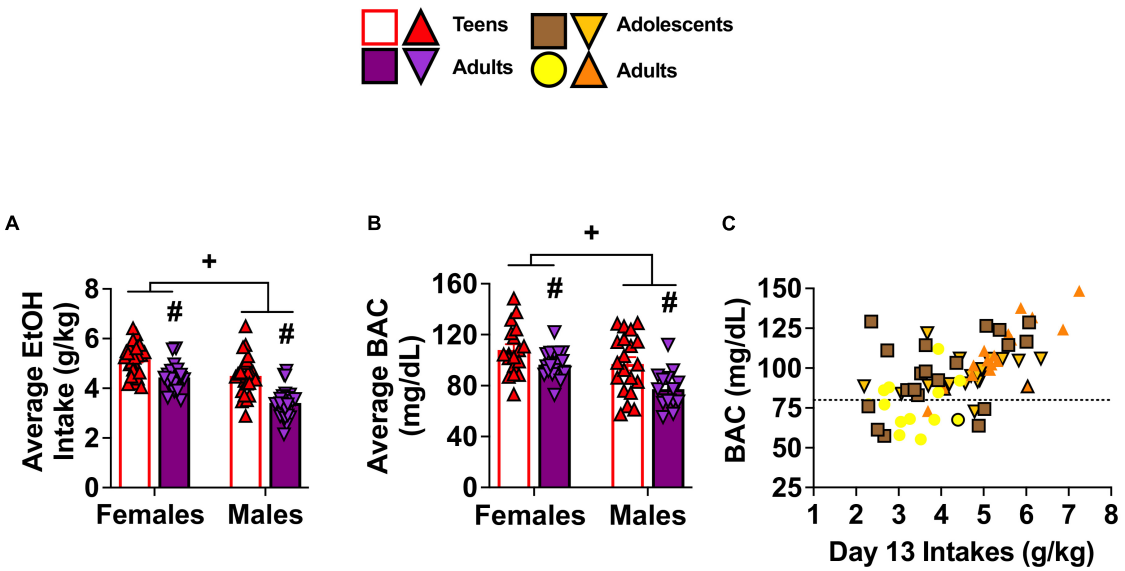

FIGURE 2
Depiction of age and sex differences in alcohol intake and corresponding BACs. As there were no Withdrawal effects or interactions, the data for alcohol intake and BACs are collapsed across mice slated to be tested on WD1 and WD30. **(A)** On average, adolescent (Adol.) mice consumed more alcohol than adult mice and females consumed more than males [females: adolescents (n = 24), adults (n = 20); males: adolescents (n = 24), adults (n = 24)]. **(B)** The average BAC levels obtained on Day 13 of drinking paralleled group differences in alcohol intake [females: adolescents (n = 18), adults (n = 18); males: adolescents (n = 20), adults (n = 14)] and **(C)** a positive correlation was observed between BACs and alcohol consumption on Day 13 of drinking [sample sizes same as panel **(B)**]. The data in panels **(A,B)** are presented as the means ± SEMs for the respective number of mice indicated above. $^{+}p < 0.05$, Female vs. Male (main Sex effect); $^{\#}p < 0.05$, adolescents vs. adults (main Age effect).

marbles buried on WD30 by all of the groups are presented in Figure 4C. For these mice, no significant interactions were found [3-way ANOVA, p = 0.104, η^2p = 0.030; all other interactions p's > 0.255]. However, significant main effects of Sex (Figure 4C) and Age (Figure 4D) were detected [Sex effect: $F(1,88)$ = 10.16, p = 0.002, η^2p = 0.104]; Age effect: $F(1,88)$ = 3.77, p = 0.055, η^2p = 0.41], indicating that females buried more marbles versus the male mice, and adult mice buried more marbles compared to their adolescent counterparts.

Porsolt forced swim test

Latency to first immobile episode

The data for the latency to first float in the forced swim test on WD1 are presented in Figure 5A. A Sex × Age × Drinking History ANOVA detected no interactions with respect to the latency to first float in the forced swim test on WD 1 [Sex × Age Drinking History ANOVA: p = 0.161, η^2p = 0.024, all other interactions p's > 0.525]. However, a significant main effect of Drinking History was detected (Figure 5B) [$F(1,80)$ = 4.34, p = 0.040, η^2p = 0.051] that reflected a longer latency to immobility in binge-drinking mice, relative to their water-drinking counterparts. For the mice tested on WD30, a significant main effect of Sex [$F(1,84)$ = 8.07, p = 0.006, η^2p = 0.088] reflected a shorter immobile latency for females versus males, irrespective of their binge-drinking history or age of binge-drinking onset (Figure 5C; all other p's > 0.102).

Time spent immobile

The data for the time spent immobile during the forced swim test on WD1 are presented in Figure 5D. On WD1, a significant Sex x Age x Drinking History interaction was observed for the total time spent immobile during the forced swim test [$F(1,84)$ = 4.08, p = 0.047, η^2p = 0.046]. To investigate potential age differences, this interaction was split along the Sex factor and revealed a significant Age x Drinking History interaction for the male mice (Figure 5D, right) [$F(1,43)$ = 4.41, p = 0.042, η^2p = 0.093], but no significant main effect or interactions for the females (Figure 5D, left) [ANOVA: p = 0.378, η^2p = 0.019]. As illustrated in Figure 5E, adolescent male binge-drinking mice spent more time immobile than their water-drinking counterparts (p = 0.031, d = 0.032) and the adult male binge-drinking mice (p = 0.004, d = 1.260). To analyze for sex-related differences in the time spent immobile, the 3-way interaction was also deconstructed along the Age variable. This deconstruction found a Sex × Drinking History interaction for the adolescent mice, but not for the adult mice [Adolescent: $F(1,42)$ = 4.08, p = 0.050, η^2p = 0.089; Adult ANOVA: p = 0.419, η^2p = 0.016]. As illustrated in Figure 5F (left vs. right), adolescent female water-drinking mice spent more time immobile than their male counterparts (p = 0.050, d = 0.844). Additionally, the adolescent male binge-drinking mice also spent more time immobile than the water-drinking control mice (Figure 5F, right; p = 0.055, d = 0.823).

The data for the time spent immobile on WD30 is presented in Figure 5G. On WD30, a Sex × Drinking History interaction was found for the total time spent immobile [$F(1,87)$ = 3.33, p = 0.072, η^2p = 0.037]. This interaction reflected a longer time spent immobile by female binge-drinking mice compared to the male binge-drinking mice (Figure 5H; p = 0.001, d = 0.991). No other significant interactions were observed for this variable

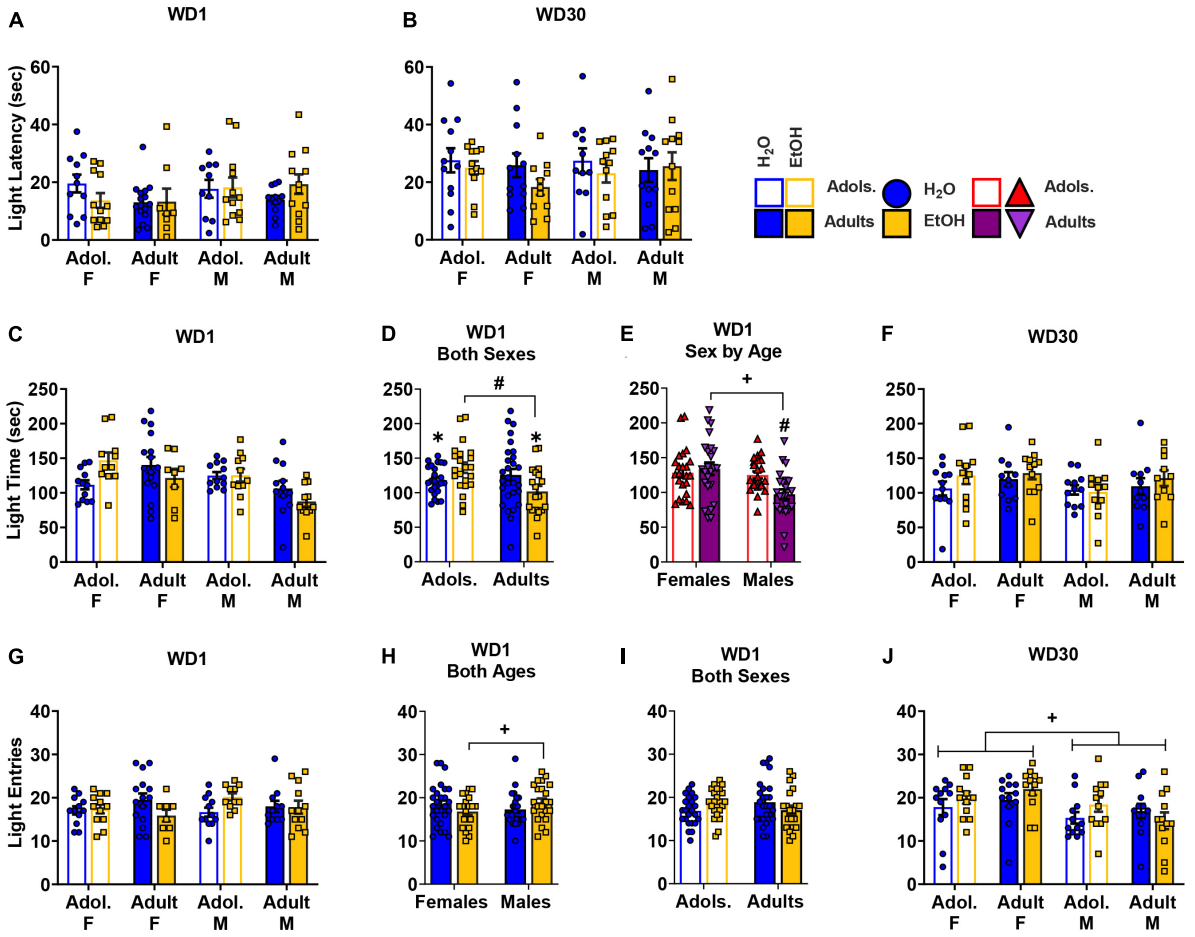

FIGURE 3
Depiction of the results of the Sex × Age × Drinking History ANOVAs conducted for behavior in the light dark box shuttle test. No group differences were observed for the latency to enter the light side of the shuttle box on either WD1 **(A)** [females: adolescents/Adol. H2O (n = 11), EtOH (n = 12); adults H2O (n = 16), EtOH (n = 8); males: adolescent H2O (n = 10), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12)] or WD30 **(B)** [females: adolescents H2O (n = 12), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 11); males: adolescent H2O (n = 11), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12)]. **(C)** Summary of the results for the time spent in the light side for all groups tested on WD1 [females: adolescents H2O (n = 12), EtOH (n = 11); adults H2O (n = 16), EtOH (n = 8); males: adolescent H2O (n = 12), EtOH (n = 11); adults H2O (n = 12), EtOH (n = 11)]. **(D)** On WD1, an Age by Drinking History interaction was observed for the time spent in the light side that reflected less time spent by adult binge-drinking (EtOH) mice versus both adult water (H2O) and adolescent (Adol.) EtOH mice. Additionally, adolescent H2O mice spent less time in the light side than their age-matched EtOH counterparts [adolescents: H2O (n = 24), EtOH (n = 22); adults: H2O (n = 28), EtOH (n = 19)]. **(E)** Also on WD1, we detected a Sex by Age interaction that reflected more time spent on the light side by adult females (F) versus adult males (M), while no sex difference was apparent in adolescent mice. Adolescent males, however, spent more time in the light side compared to the adult males [females: adolescents (n = 23), adults (n = 24); males: adolescents (n = 23), adults (n = 23)]. **(F)** On WD30, no group differences were detected for the total time spent in the light side of the shuttle box [females: adolescents H2O (n = 12), EtOH (n = 12); adults H2O (n = 11), EtOH (n = 12); males: adolescent H2O (n = 12), EtOH (n = 12); adults H2O (n = 11), EtOH (n = 10). **(G)** Results for the total number of entries into the light side of the shuttle box test indicated significant interactions on WD1 between Sex by Drinking History and Age by Drinking History [females: adolescents H2O (n = 12), EtOH (n = 12); adults H2O (n = 15), EtOH (n = 8); males: adolescent H2O (n = 12), EtOH (n = 11); adults H2O (n = 11), EtOH (n = 12)]. **(H)** Follow-up analysis of the Sex by Drinking History interaction revealed that male EtOH mice exhibited more entries into the light side compared to female EtOH mice [females: H2O (n = 27), EtOH (n = 20); males: H2O (n = 23), EtOH (n = 23)]. **(I)** The Age by Drinking History interaction on WD1 did not reflect any significant effect of EtOH in either age group [adolescents: H2O (n = 24), EtOH (n = 23); adults: H2O (n = 26), EtOH (n = 20)]. **(J)** On WD30, female mice exhibited a greater number of entries into the light side compared to male mice, irrespective of age or drinking condition [females: adolescents H2O (n = 1)2, EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12); males: adolescent H2O (n = 12), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12). The data represent the means ± SEMs for the number of mice indicated above. $^{+}p < 0.10$, Female vs. Male; $^{\#}p < 0.10$, adolescents vs. adults.

on WD30 [3-way ANOVA: p = 0.641, η^2p = 0.003; all other p's > 0.132).

Immobile episodes

The data for the number of immobile episodes on WD1 are presented in Figure 5I. A 3-way Sex × Age × Drinking History interaction was revealed for this variable [$F(1,88)$ = 8.29, p = 0.005, η^2p = 0.086]. To examine for age differences, the interaction was first deconstructed along the Sex factor, which resulted in significant Age × Drinking History interactions for both male [$F(1,44)$ = 5.05, p = 0.030, η^2p = 0.103] and female subjects [$F(1,44)$ = 3.39, p = 0.072, η^2p = 0.072]. As illustrated for males in Figure 5I (right), the 2-way interaction reflected a higher number of immobile episodes for the adolescent binge-drinking mice versus their water-drinking counterparts (p = 0.082, d = 0.727). Additionally, adolescent male binge-drinking mice had

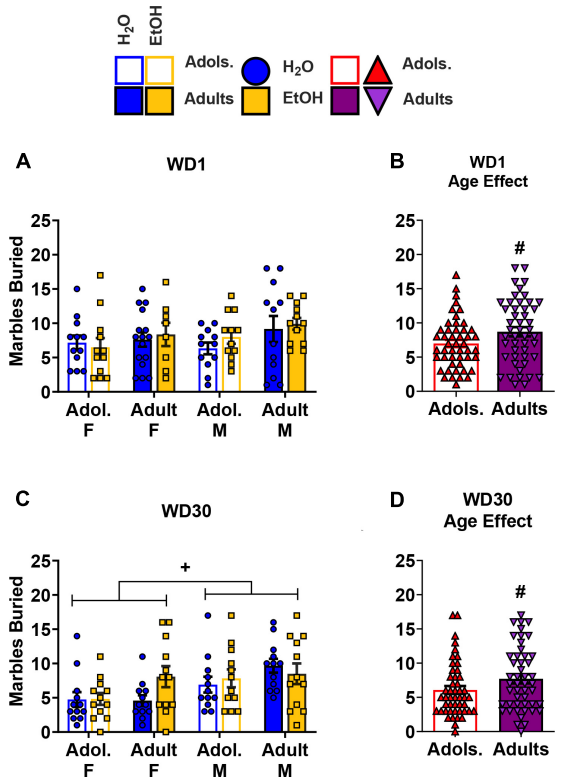

FIGURE 4
Depiction of the results of the Sex × Age × Drinking History ANOVAs conducted for behavior in the marble burying test. **(A)** On WD1, no significant interactions were observed for the number of marbles buried [females: adolescents/Adol. H2O (n = 12), EtOH (n = 12); adults H2O (n = 16), EtOH (n = 8); males: adolescent H2O (n = 12), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12)]. However, **(B)** adult mice buried more marbles than the adolescent mice [adolescents (n = 48), adults (n = 48)]. **(C)** On WD30, females buried a greater number of marbles compared to the male mice [females: adolescents H2O (n = 12), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12); males: adolescent H2O (n = 12), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12)]. **(D)** Similar to the mice in WD1, adult mice buried more marbles than their adolescent counterparts [adolescents (n = 48), adults (n = 48)]. The data represent the means ± SEMs for the number of mice indicated above. $^{+}p < 0.10$, Female vs. Male; $^{\#}p < 0.10$, adolescents vs. adults.

a higher number of immobile episodes versus adult binge-drinking males (p = 0.006, d = 1.81). In contrast, as illustrated in Figure 5I (left), the 2-way interaction detected in females reflected water-alcohol differences for adult mice only (p = 0.056, d = 0.849). We also observed a higher number of immobile episodes for adolescent water-drinking females versus their adult counterparts (p = 0.021, d = 0.911). To examine for sex-related differences in basal and withdrawal-induced behavior, the 3-way interaction was analyzed also along the Age factor. This deconstruction revealed a significant Sex × Drinking History interaction for both adult [$F(1,44) = 5.603$, p = 0.022, η^2p = 0.113] and adolescent mice [$F(1,44) = 2.841$, p = 0.099, η^2p = 0.061]. Thus, the data in Figure 5I was re-arranged to better illustrate the age-dependency of these sex differences (Figure 5J). As illustrated in Figure 5J (right), the Sex × Drinking History interaction in adult mice reflected a sex difference in binge-drinkers, but not water controls, where adult female binge-drinkers had more immobile episodes versus the adult male binge-drinking mice (p = 0.028, d = 1.035). For the adolescent mice (Figure 5J, left), no significant water-alcohol differences were observed in female mice, however, adolescent male binge-drinking mice had more immobile episodes than their water-drinking counterparts (p = 0.086, d = 0.717).

The data for the number of immobile episodes on WD30 are presented in Figure 5K. On WD30, significant Sex × Drinking History [$F(1,87) = 3.88$, p = 0.052, η^2p = 0.043] and Age x Drinking History [$F(1,87) = 2.87$, p = 0.094, η^2p = 0.032] interactions were detected. As illustrated in Figure 5L, male binge-drinking mice exhibited fewer immobile episodes than their water controls (p = 0.022, d = 0.674), while female binge-drinking mice exhibited more immobile episodes than their male binge-drinking counterparts (p = 0.001, d = 0.973). As illustrated in Figure 5M, the Age x Drinking History interaction revealed fewer immobile episodes by the adolescent binge-drinking mice versus their water controls (p = 0.037, d = 0.618) and the adolescent water control mice also exhibited more immobile episodes than their adult counterparts (p = 0.051, d = 0.572). No other significant interactions were observed (3-way ANOVA: p = 0.773, η^2p = 0.001).

Morris water maze

Flag test

Sex × Age × Drinking History ANOVAs failed to detect any significant interactions or main effects for the time taken to locate the flagged platform during either early [all p's > 0.582] or later withdrawal [all p's > 0.343]. The data are presented in Table 5 and indicate comparable visual and swimming ability across our different experimental groups prior to maze training. These findings also indicate that group differences in the Porsolt swim test, conducted 1–2 days prior (Figure 5), did not carry over to the Morris water maze.

Morris maze acquisition

No significant Day × Sex × Age × Drinking History interaction was noted for the time taken to locate the hidden platform across the 4 days of the Morris maze acquisition for the mice tested in early withdrawal (4-way ANOVA: p = 0.865, ηp^2 = 0.001). As depicted in Figures 6A–D, all mice successfully acquired the maze as indicated by a main Day effect [$F(1.49, 123.79) = 65.95$, $p < 0.001$, η^2p = 0.443; all other p's > 0.118]. We also detected no significant Day × Sex × Age × Drinking History interaction for the time taken to complete the Morris maze by mice tested in later withdrawal [Figures 6E–H; 4-way ANOVA: p = 0.464, η^2p = 0.008]. However, a significant Day × Age interaction was detected in later withdrawal [$F(1.41, 116.64) = 5.83$, p = 0.009, η^2p = 0.066]. As illustrated in Figure 6I, this interaction reflected more time taken by adolescent-onset versus adult-onset mice to locate the hidden platform on the first day of training, irrespective of their sex or alcohol-drinking history (p = 0.004).

Probe test

The data for the latency to enter the platform's former location on WD1 are presented in Figure 6J. Analyses of a Sex × Age × Drinking History ANOVA for the mice tested in early withdrawal failed to detect a significant 3-way interaction for

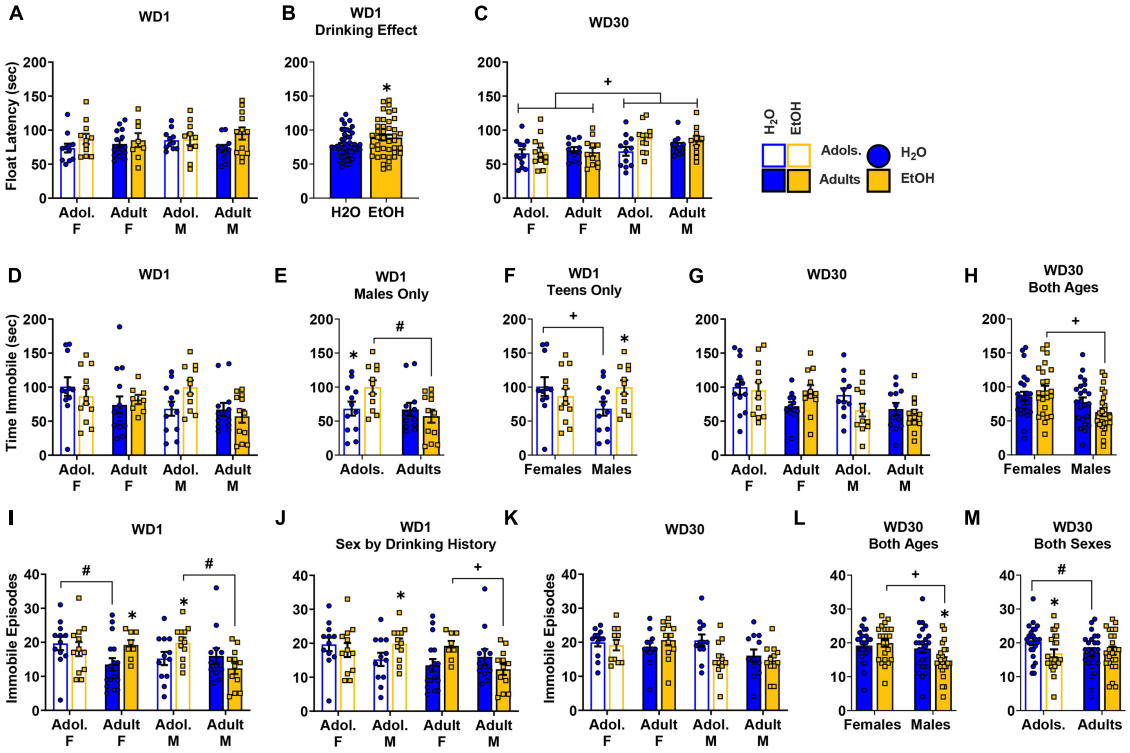

FIGURE 5
Depiction of the results of the Sex × Age × Drinking History ANOVAs conducted for behavior in the Porsolt forced swim test. **(A)** On WD1, we detected no significant 3-way interaction for the latency to immobility [females: adolescents/Adol. H2O (n = 11), EtOH (n = 11); adults H2O (n = 14), EtOH (n = 8); males: adolescent H2O (n = 11), EtOH (n = 10); adults H2O (n = 11), EtOH (n = 12)]. **(B)** However, binge-drinking (EtOH) mice had a longer latency to immobility, overall, than water (H2O) mice, on WD1 [sample size. **(C)** Overall, males (M) exhibited a longer latency to immobility on WD30 than females (F) [females: adolescents H2O (n = 12), EtOH (n = 12); adults H2O (n = 11), EtOH (n = 11); males: adolescent H2O (n = 12), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 10)]. **(D)** On WD1, a significant 3-way interaction was detected for the time spent immobile, that reflected a longer time spent immobile by adolescent (Adol.) EtOH males versus both adolescent H2O and adult EtOH males **(E)** [females: adolescents H2O (n = 11), EtOH (n = 12); adults H2O (n = 14), EtOH (n = 8); males: adolescent H2O (n = 12), EtOH (n = 11); adults H2O (n = 12), EtOH (n = 12)]. **(F)** When deconstructed along the Age factor, adolescent male EtOH mice spent more time immobile than their H2O counterparts [females: H2O (n = 11), EtOH (n = 12); males: H2O (n = 12), EtOH (n = 11). **(G)** For WD30, no significant 3-way interaction was detected for the time spent immobile [females: adolescents H2O (n = 12), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12); males: adolescent H2O (n = 11), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12)]. **(H)** However, a Sex by Drinking History interaction found that female EtOH mice spent more time immobile than male EtOH mice [females: H2O (n = 24), EtOH (n = 24); males: H2O (n = 23), EtOH (n = 24)]. **(I)** A significant Sex by Age by Drinking History interaction was observed for the number of immobile episodes on WD1, and results deconstructed along the Sex factor revealed that adolescent male EtOH mice had more immobile episodes than their H2O counterparts and adult EtOH males, while adult female EtOH mice also had more episodes than their H2O counterparts [females: adolescents H2O (n = 12), EtOH (n = 12); adults H2O (n = 16), EtOH (n = 8); males: adolescent H2O (n = 12), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12)]. **(J)** Analysis along the Age factor identified sex-related differences where adult female EtOH had more immobile episodes than adult male EtOH, and adolescent male EtOH had more immobile episodes than their H2O counterparts [sample sizes same as panel **(J)**]. **(K)** For WD30, a significant Sex by Drinking History and Age by Drinking History interaction were detected [females: adolescents H2O (n = 12), EtOH (n = 11); adults H2O (n = 12), EtOH (n = 12); males: adolescent H2O (n = 12), EtOH (n = 12); adults H2O (n = 12), EtOH (n = 12)]. **(L)** Follow-up analyses revealed that male H2O mice had more immobile episodes than their EtOH counterparts and that females EtOH mice had more immobile episodes than their EtOH male counterparts [females: H2O (n = 24), EtOH (n = 23); males: H2O (n = 24), EtOH (n = 24)]. **(M)** An Age by Drinking History interaction indicated that adolescent H2O mice had more immobile episodes than their EtOH counterparts and the adult H2O mice [adolescents: H2O (n = 24), EtOH (n = 23); adults: H2O (n = 24), EtOH (n = 24)]. The data represent the means ± SEMs for the number of mice indicated above. $^{*}p < 0.10$, EtOH vs. H2O; $^{+}p < 0.10$, Female vs. Male; $^{\#}p < 0.10$, adolescents vs. adults.

the latency to first enter the platform's former location (p = 0.333, η^2p = 0.011); however, a Age x Drinking History interaction was detected for this variable [$F(1,85) = 5.50$, p = 0.021, η^2p = 0.061]. This interaction reflected a shorter latency to first enter the platform location by adolescent-onset mice relative to their age-matched water-drinking counterparts (p = 0.047, d = 0.589), and to the adult binge-drinking mice (Figure 6K; p = 0.036, d = 0.651). For the mice tested in later withdrawal, no significant main effects or interactions were found with respect to this variable [Figure 6L; Sex × Age × Drinking History ANOVA: p = 0.703, η^2p = 0.002, all other p's > 0.306].

As alternate indices of spatial recall, we also examined the number of entries into the platform's former location. No significant main effects or interactions were observed for the number of entries into the platform's former location for mice tested in early withdrawal [Figure 6M; 3-way ANOVA: p = 0.444, η^2p = 0.007; all other p's > 0.386]. However, a significant Age x Drinking History interaction was observed for the number of former platform entries for the mice tested in later withdrawal [Figure 6N; $F(1,87) = 6.63$, p = 0.012, η^2p = 0.071]. This interaction reflected a trend for more entries by adolescent-onset water controls versus their binge-drinking counterparts, with a medium

TABLE 5 Summary of the negative results for the time taken (in sec) to locate the flagged platform in the Morris water maze.

	Early withdrawal		Late withdrawal	
	Females	Males	Females	Males
Adolescent-H2O	70.39 ± 13.60 *n* = 12	70.32 ± 12.16 *n* = 12	53.35 ± 13.20 *n* = 12	46. 62 ± 11.39 *n* = 12
Adolescent-EtOH	67.89 ± 13.18 *n* = 12	57.23 ± 12.35 *n* = 12	54.31 ± 13.32 *n* = 12	59.58 ± 13.12 *n* = 12
Adult-H2O	74.84 ± 10.89 *n* = 16	63. 76 ± 12.52 *n* = 12	53.37 ± 13.48 *n* = 12	69.49 ± 14.17 *n* = 12
Adult-EtOH	68.45 ± 12.41 *n* = 8	65.75 ± 13.17 *n* = 12	38.28 ± 9.50 *n* = 12	54.65 ± 11.98 *n* = 12

The data represent the means ± SEMs for the number of mice indicated.

effect size (Figures 6O, F, left; $p = 0.087$, $d = 0.500$), with a similarly sized, but opposite, group difference was noted for the adult-onset mice (Figure 6O, right; $p = 0.060$, $d = 0.557$). Lastly, adolescent-onset water-drinking controls made more entries, overall, than their adult-onset counterparts (Figure 6O; $p = 0.036$, $d = 0.614$).

Reversal test

For the mice tested in early withdrawal (Figures 6P–S), a Trial × Sex × Age × Drinking History ANOVA revealed no significant group differences for the time taken to locate the repositioned platform during the reversal test [all ANOVAs p's > 0.158]. In contrast, a significant Trial x Age interaction was detected for the mice tested in later withdrawal (Figures 6T–W) [$F(1.88, 152.49) = 5.66$, $p = 0.001$, $\eta^2p = 0.065$] that reflected a longer time taken to find the repositioned platform by adult-onset versus adolescent-onset mice on the initial reversal trial (Figure 6X; Trial 1: $p = 0.034$). No other significant interactions were observed between the binge-drinking and water-drinking groups, however, a main effect of Trial illustrated a progressive reduction in the time required to locate the platform [Trial Effect: $F(1.88,152.49) = 46.07$, $p < 0.001$, $\eta^2p = 0.363$].

Radial arm water maze

Number of reference memory errors

For the mice tested in early withdrawal, a significant Day × Sex × Age × Drinking History interaction was detected for the number of reference memory errors during the first week of radial arm maze training (Figures 7A–D) [$F(4.32, 380.37) = 3.27$, $p = 0.010$, $\eta^2p = 0.036$]. This 4-way interaction was first analyzed along the Sex factor and indicated a significant Day × Age × Drinking History interaction for the female mice [$F(4.20, 184.67) = 4.00$, $p = 0.003$, $\eta^2p = 0.083$]. The Day x Age x Drinking History interaction observed in female mice was further deconstructed along the Age factor and indicated a significant Day × Drinking History interaction for the adolescent-onset females [$F(3.93, 86.46) = 3.03$, $p = 0.022$, $\eta^2p = 0.121$]. However, while it appeared that adolescent-onset binge-drinking females committed more reference memory errors than their water-drinking counterparts on several days during this initial training (Figure 7A), *post-hoc* tests did not indicate any statistically significant water-alcohol differences (all p's > 0.072). The comparable follow-up analysis of the significant Day × Age × Drinking History interaction for adult-onset females indicated only a significant main effect of Day (Figure 7C) [$F(3.69,127.17) = 3.76$, $p = 0.009$, $\eta^2p = 0.146$]. Thus, a prior history of binge-drinking during adulthood did not influence reference memory in adult females tested during early alcohol withdrawal. For the males tested in early withdrawal, no significant Day × Age × Drinking History interaction was found upon deconstruction of the significant 4-way interaction along the Age factor [ANOVA: $p = 0.524$, $\eta^2p = 0.019$]. However, a Day x Age interaction was observed [$F(4.00, 175.76) = 2.18$, $p = 0.074$, $\eta^2p = 0.047$], that reflected a trend toward more reference memory errors committed by adult versus adolescent males on day 6 of training only (Figures 7B, D; $p = 0.061$).

For mice tested in later withdrawal (Figures 7E–H), a significant Day × Age interaction [$F(5, 440) = 2.72$, $p = 0.020$, $\eta^2p = 0.030$] was detected. However, *post hoc* analyses indicated that this interaction reflected more reference memory errors committed by adults vs. adolescents only on day 4 of training ($p = 0.041$) and thus, this interaction is not depicted.

Working memory correct errors

Analyses of the data from the mice tested in early withdrawal identified a significant Day × Sex × Age × Drinking History interaction for the number of working memory correct errors during the first week of testing (Figures 7I–L) [$F(4.48,394.13) = 2.43$, $p = 0.041$, $\eta^2p = 0.027$]. While deconstruction along the Sex factor indicated no significant interactions [ANOVA for females, p's > 0.212; ANOVA for males, p's > 0.162], deconstruction along the Age factor revealed a significant Day x Sex interaction for the adolescent-onset mice [$F(4.31,189.61) = 2.76$, $p = 0.026$, $\eta^2p = 0.059$], that reflected a greater number working memory correct errors in males versus females only on day 3 of radial arm maze training (Figure 7M; $p = 0.044$, all other p's > 0.065). In contrast, no interactions were detected in adult-onset mice, with all mice exhibiting a progressive reduction in working memory correct errors with training (Figure 7N) [Day effect: $F(4.24,186.56) = 4.89$, $p < 0.001$, $\eta^2p = 0.100$].

Analyses of the data from mice tested in later withdrawal failed to indicate a significant 4-way interaction [Figures 7O–R; Day × Sex × Age × Drinking History ANOVA: $p = 0.168$, $\eta^2p = 0.064$]. However, a significant Day x Drinking History interaction was detected [$F(4.429,389.719) = 6.02$, $p < 0.001$ $\eta^2p = 0.064$] that reflected *fewer* working memory correct errors

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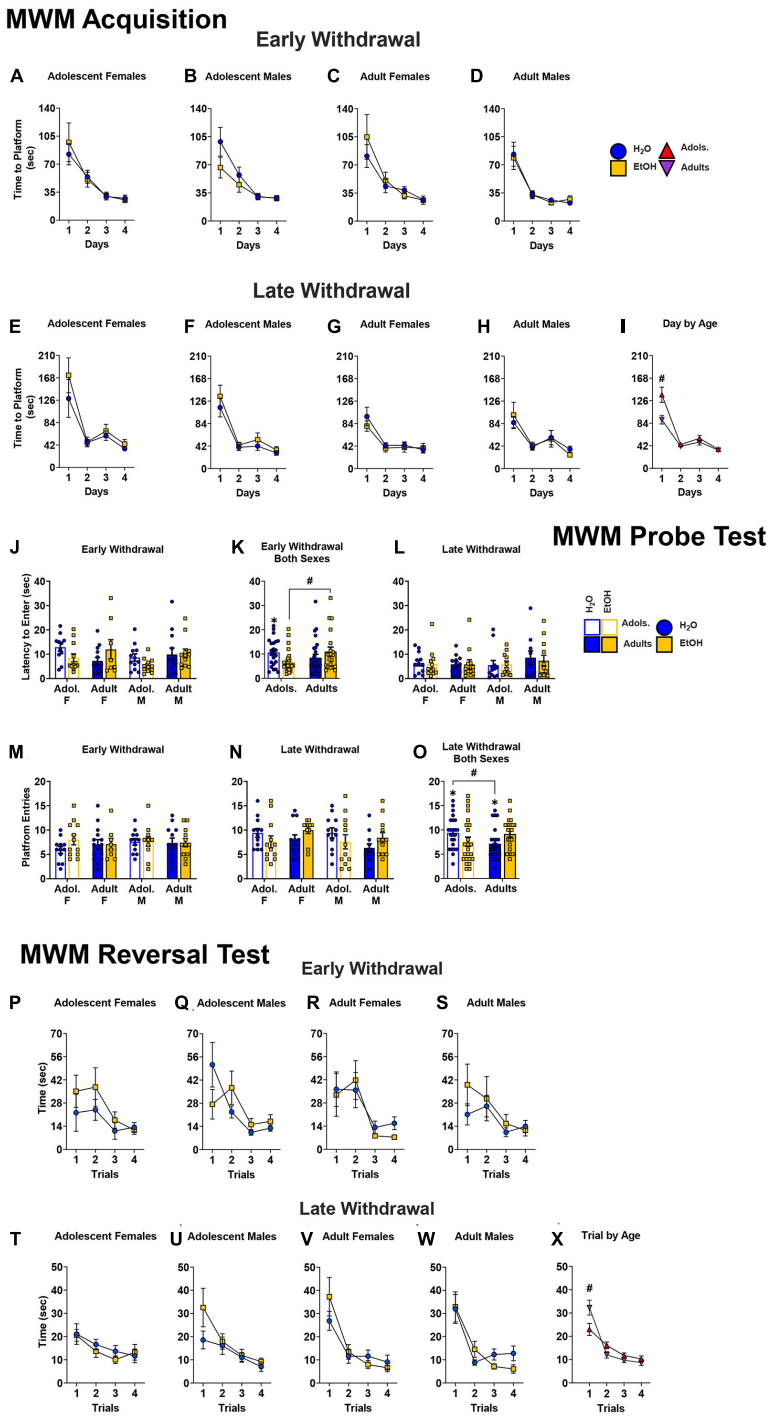

FIGURE 6

Depiction of the results of the Day × Sex × Age × Drinking History mixed-model ANOVAs evaluating spatial learning during the different phases of testing in the Morris water maze. **(A–D)** No group differences were noted for the average time taken by mice tested in early alcohol withdrawal to locate the hidden platform during Morris maze acquisition. The sample sizes for mice tested on WD1 are the following: **(A)** H2O (n = 9), EtOH (n = 12); **(B)** H2O (n = 11), EtOH (n = 12); **(C)** H2O (n = 15), EtOH (n = 8); **(D)** H2O (n = 12), EtOH (n = 12) **(E–H)** For mice trained during later withdrawal, we detected no significant Day by Sex by Age by Drinking History interaction. The sample sizes for mice tested on WD are the following); **(E)** H2O (n = 12), EtOH (n = 11); **(F)** H2O (n = 12), EtOH (n = 9); **(G)** H2O (n = 12), EtOH (n = 12); **(H)** H2O (n = 12), EtOH (n = 11). **(I)** However, a significant Day by Age interaction was detected that reflected a longer time taken by adolescent versus adult mice to locate the platform on the first day training [adolescents (n = 44), adults (n = 47)]. **(J)** When tested in early alcohol withdrawal, no significant 3-way interaction was detected for the latency to enter the platform's former location [females: adolescent H2O (n = 9); adolescent EtOH (n = 12); adult H2O (n = 11); adult EtOH (n = 12); males: adolescent H2O (n = 15); adolescent EtOH (n = 8); adult H2O (n = 12); adult EtOH (n = 12)]. **(K)** On the probe test, an Age by Drinking History interaction indicated that adolescent-onset mice exhibited a shorter latency to enter the platform's former location in the NE quadrant compared to their age-matched water control counterparts and the adult-onset mice [adolescents: H2O (n = 24); EtOH (n = 20); adults: H2O (n = 23); EtOH (n = 24). **(L)** No significant group differences were found for this measure in mice tested in later withdrawal [females: adolescent

(Continued)

FIGURE 6 (Continued)
H2O (n = 12); adolescent EtOH (n = 11); adult H2O (n = 12); adult EtOH (n = 19); males: adolescent H2O (n = 12); adolescent EtOH (n = 12); adult H2O (n = 12); adult EtOH (n = 12)]. **(M)** We also did not detect group differences on WD1 with regards of the number of entries to the former site of the platform [samples sizes same as panel **(A)**]. **(N)** However, on WD30, a significant Age by Drinking History interaction was observed [sample sizes same as Panel **(C)**]. **(O)** This interaction reflected trends for more entries by adolescent EtOH versus adolescent H2O mice, as well as fewer entries by adult EtOH versus adult H2O mice. Additionally, adolescent H2O mice made significantly more entries than adult H2O mice [adolescents (n = 44), adults (n = 47)]. For the data from the reversal learning phase of the study, Trial by Sex by Age by Drinking History ANOVAs revealed no significant group differences for the time taken to locate the repositioned platform during the reversal test when mice were tested in either early **(P–S)** or late withdrawal **(T–W)**. Sample sizes are the following: **(P)** H2O (n = 10), EtOH (n = 12); **(Q)** H2O (n = 12), EtOH (n = 12); **(R)** H2O (n = 15), EtOH (n = 8); **(S)** H2O (n = 11), EtOH (n = 11); **(T)** H2O (n = 12), EtOH (n = 10); **(U)** H2O (n = 11), EtOH (n = 10); **(V)** H2O (n = 11), EtOH (n = 12); **(W)** H2O (n = 12), EtOH (n = 11). **(X)** However, a significant Trial by Age interaction was observed for the mice tested in late withdrawal that reflected a longer latency of adult-onset versus adolescent-onset mice to locate the repositioned platform on the first reversal trial [adolescents (n = 43), adults (n = 46)]. The data represent the means ± SEMs for the number of mice indicated above. $^{\#}p < 0.05$, adolescents vs. adults.

committed by binge- versus water-drinking mice on the first two days of radial arm maze training (Figure 7S; $p < 0.001$)–a result suggestive of better working memory performance in binge- versus water-drinking mice. However, it is notable that the time-course of working memory errors committed by binge-drinking mice during later withdrawal was relatively flat (Figure 7S); in fact, binge-drinking mice committed significantly *more* working memory correct errors later during training than at the start of training (Figure 7S; day 2 vs. days 3–5, all p's < 0.027). In contrast, the number of working memory correct errors committed by water-drinking mice declined progressively over the course of training, indicative of intact learning (Figure 7S; day 2 vs. subsequent days, all p's < 0.046).

Working memory incorrect errors

No significant Day × Sex × Age × Drinking History interaction was detected for the number of working memory incorrect errors committed by the mice tested in early withdrawal (Figures 7T–W; 4-way ANOVA: $p = 0.588$, $\eta^2p = 0.008$). However, a significant Day × Age x Drinking History interaction was found for this time-point [$F(4.26,374.68) = 2.76$, $p = 0.018$, $\eta^2p = 0.030$]. Deconstruction of this interaction along the Age factor indicated a significant Day x Drinking History interaction for both age groups [ANOVA for adolescent-onset: $F(4.31,198.12) = 2.84$, $p = 0.017$, $\eta^2p = 0.058$; ANOVA for adult-onset: $F(4.03,185.41) = 2.91$, $p = 0.014$, $\eta^2p = 0.060$]. On days 2, 4, and 5, adolescent-onset binge-drinking mice made more working memory incorrect errors versus their water controls (Figure 7X; Day 2: $p = 0.005$; Day 4: $p = 0.023$; Day 5: $p = 0.034$). In contrast, adult-onset binge-drinking mice committed fewer working memory incorrect errors than water controls but only on day 3 (Figure 7Y; $p = 0.014$). As depicted in Figures 7X, Y, the number of working memory incorrect errors declined progressively in both water- and binge-drinking mice, indicative of learning in all groups when tested at the earlier time-point.

For the mice tested in later withdrawal, no significant Day × Age × Sex × Drinking History interaction was found for the number of working memory incorrect errors [Figures 7Z–C'; 4-way ANOVA $p = 0.267$, $\eta^2p = 0.014$]. However, a significant Day x Drinking History interaction [$F(4.16,365.85) = 2.68$, $p = 0.030$, $\eta^2p = 0.029$] was detected that reflected a lower number of working memory incorrect errors in binge- versus water-drinking mice, but only on day 2 of training (Figure 7D'; $p < 0.001$, all other p's > 0.092). Consistent with the data for the number of working memory correct errors, water-drinking controls tested in later withdrawal exhibited a progressive decline in the number of working memory incorrect errors with training (Figure 7D'; days 2 and 3 vs. 4–7, all p's < 0.041), while the time-course of behavior was flat in binge-drinking animals (Figure 7D'; day 2 < day3, $p = 0.032$), indicative of little to no learning.

Chaining behavior

The Day × Sex × Age × Drinking History ANOVA for the mice tested in early withdrawal indicated in no significant four-way interaction for chaining behavior [Figures 8A–D; 4-way ANOVA: $p = 0.184$, $\eta^2p = 0.017$]. However, a significant Day × Sex × Drinking History interaction was observed [$F(4.26,374.80) = 3.02$, $p = 0.016$, $\eta^2p = 0.033$]. Deconstruction of this interaction along the Sex factor yielded a significant Day × Drinking History interaction for the female mice (Figure 8E) [$F(3.69,169.50) = 3.96$, $p = 0.005$, $\eta^2p = 0.079$]. As illustrated (Figure 8E), binge-drinking females exhibited more chaining behavior than their water controls on day 4 ($p = 0.002$) and day 5 ($p = 0.008$) of training. No significant interactions were detected for the male mice tested in early withdrawal (Figure 8F) [ANOVA: $p = 0.416$, $\eta^2p = 0.021$]. As illustrated (Figure 8F), all males exhibited a training-dependent reduction in the amount of chaining behavior [Day effect: $F(4.01,184.40) = 21.63$, $p < 0.001$, $\eta^2p = 0.320$; *post-hoc* tests, days 2 and 3 versus days 4–7, all p's < 0.010].

The analyses of the data for the mice tested in later withdrawal failed to detect a significant Day × Age × Sex × Drinking History interaction [Figures 8G–J; 4-way ANOVA, $p = 0.338$, $\eta^2p = 0.010$]. However, a significant Day x Sex interaction was observed [$F(4.16,365.77) = 2.57$, $p = 0.036$, $\eta^2p = 0.028$] that reflected more chaining episodes in females versus males on day 2 of training, while males exhibited more chaining episodes on day 4 [Figure 8K; Day 2: $p = 0.053$; Day 4: $p = 0.026$]. As illustrated in Figure 8K, male mice exhibited a progressive decline in the amount of chaining across the first week of testing, indicative of a shift from non-spatial to spatial learning strategies [Day 2 vs., Days 4 –6: p's < 0.033]. While chaining behavior declined early during training in the females tested in later withdrawal (Figure 8K; days 2 and 3 vs. days 5–7; all p's < 0.003), this behavior plateaued, with females exhibiting more chaining on day 6, relative to day 4 ($p = 0.032$) and day 7 (Figure 8K; $p = 0.037$).

Time to complete the maze

No significant interactions between Day × Sex × Age × Drinking History were detected for the

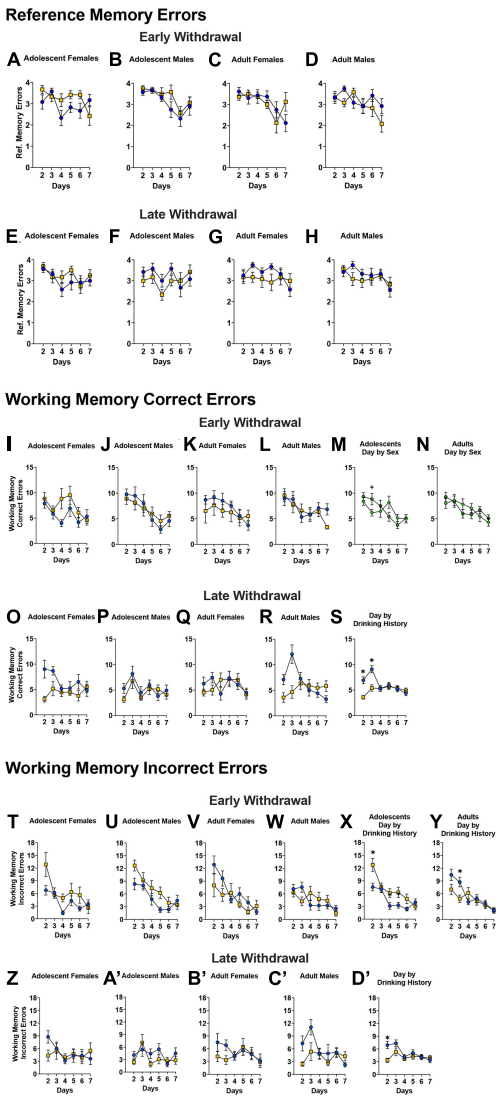

FIGURE 7

Depiction of the results of the Day × Sex × Age × Drinking History mixed-model ANOVAs evaluating reference memory, working memory correct and incorrect errors in the Radial Arm Maze. **(A–D)** For mice tested in early withdrawal (top), a significant Day by Sex by Age by Drinking History interaction was detected for the number of reference memory errors during the first week of radial arm maze training testing. **(A,C)** In female mice, a significant Day by Age by Drinking History interaction was found and follow up analyses indicated a significant Day by Drinking History interaction for adolescent females. However, no statistically significant drinking history differences were noted for the adolescent females on any of the training days [females: adolescent H2O (n = 12); adolescent EtOH (n = 12); adult H2O (n = 16); adult EtOH (n = 8)]. **(B,D)** For male mice, a Day by Age interaction was observed, reflecting more errors by adult versus adolescent males on day 6 of training only irrespective of drinking history [males: adolescent H2O (n = 12); adolescent EtOH (n = 12); adult H2O (n = 12); adult EtOH (n = 12)]. **(E–H)** For the mice tested in later withdrawal, a significant Day by Age interaction was found on day 4 of training, with more errors by adults than adolescents. For WD30, sample sizes were the following: **(E)** H2O (n = 12), EtOH (n = 12); **(F)** H2O (n = 12), EtOH (n = 12); **(G)** H2O (n = 12), EtOH (n = 12); **(H)** H2O (n = 12), EtOH (n = 12). Note that interactions that do not include Drinking History as a factor have not been included in panels **(A–H)**. **(I–L)** For mice tested in early withdrawal, there was a significant Day by Sex by Age by Drinking History interaction for working memory correct errors committed in the radial arm maze. The samples sizes are the same

(Continued)

FIGURE 7 (Continued)

as panels **(A–D)**. When collapsed along the Age factor, **(M)** a significant Day by Sex interaction for adolescent mice indicated that males committed more errors on day 3 of training [females (n = 24), males (n = 24)]. **(N)** However, only a main effect of Day was observe for adult mice [females (n = 24), males (n = 24)]. **(O–S)** For WD30 mice, no significant 4-way interaction was found. The samples sizes are the same as panels **(E–H)**. **(S)** There was a significant Day by Drinking History interaction during late withdrawal that indicated binge-drinking mice committed fewer errors on the first two days [H2O (n = 48), EtOH (n = 48)]. **(T–W)** No significant Day by Sex by Age by Drinking History interaction was detected for the number of working memory incorrect errors committed by the mice tested in early withdrawal. The sample sizes are the same as panels **(A–D)**. However, deconstruction of the significant Day by Age by Drinking History interaction along the Age factor indicated that **(X)** adolescent-onset binge-drinking mice made more errors on certain days [H2O (n = 24), EtOH (n = 24)], while **(Y)** adult-onset binge-drinking mice committed fewer errors only on day 3 [H2O (n = 28), EtOH (n = 20)]. **(Z–C')** For the mice tested in later withdrawal, no significant Day by Age by Sex by Drinking History interaction was found. The sample sizes are the same as panels **(E–H)**. **(D')** However, a significant Day by Drinking History interaction was detected that reflected a progressive decline in working memory incorrect errors in water-drinking animals versus the relatively flat time-course of errors exhibited by binge-drinking mice [H2O (n = 48), EtOH (n = 48)]. The data represent the means ± SEMs of the number of mice indicated above. *$p < 0.05$, EtOH vs. H2O; $^{+}p < 0.05$, Female vs. Male.

total time taken to find all the platforms in the radial arm maze when the mice were tested in early withdrawal [Figures 8L–O); all ANOVA p's > 0.147]. All mice exhibited a progressive decline in the amount of time taken to complete the maze [Day effect: $F(4.15, 364.98) = 42.03$, $p < 0.001$, $\eta^2p = 0.323$; *post-hoc* tests for all groups, all p's < 0.030].

No significant 4-way interaction was observed with respect to the time taken by mice to complete the radial arm maze during later withdrawal [Figures 8P–S; Day × Sex × Age × Drinking History ANOVA: $p = 0.206$, $\eta^2p = 0.018$). However, a significant Day x Group interaction [$F(4.08, 358.22) = 4.96$, $p = 0.001$, $\eta^2p = 0.053$] was found that reflected a shorter time taken by binge- versus water-drinking mice on days 2 and 3 of training [Figure 8T; Day 2 $p < 0.001$; Day 3 $p = 0.052$). As illustrated in Figure 8T, the WD30 water-drinking mice exhibited a progressive decline in the time taken to complete the maze, consistent with learning (day 2 vs. days 5–7; all p's < 0.002). In contrast, the time-course for this variable exhibited an inverted U-shape in the binge-drinking mice tested in later withdrawal, with the longest latency to complete the maze observed on day 4 of training (Figure 8T; all p's < 0.043).

Replicate testing for alcohol withdrawal-induced negative affect

An analysis of the average total alcohol consumed over the 2-week drinking period indicated a significant Sex × Age interaction [$F(1,23) = 6.33$, $p = 0.021$; $\eta^2p = 0.240$]. In this replicate study, the interaction reflected higher alcohol intake by male adolescent mice versus their adult controls [$t(10) = 6.28$, $p < 0.001$], with no age difference detected for the relatively high alcohol intake exhibited by female subjects (Figure 9A; t-test, $p = 0.858$).

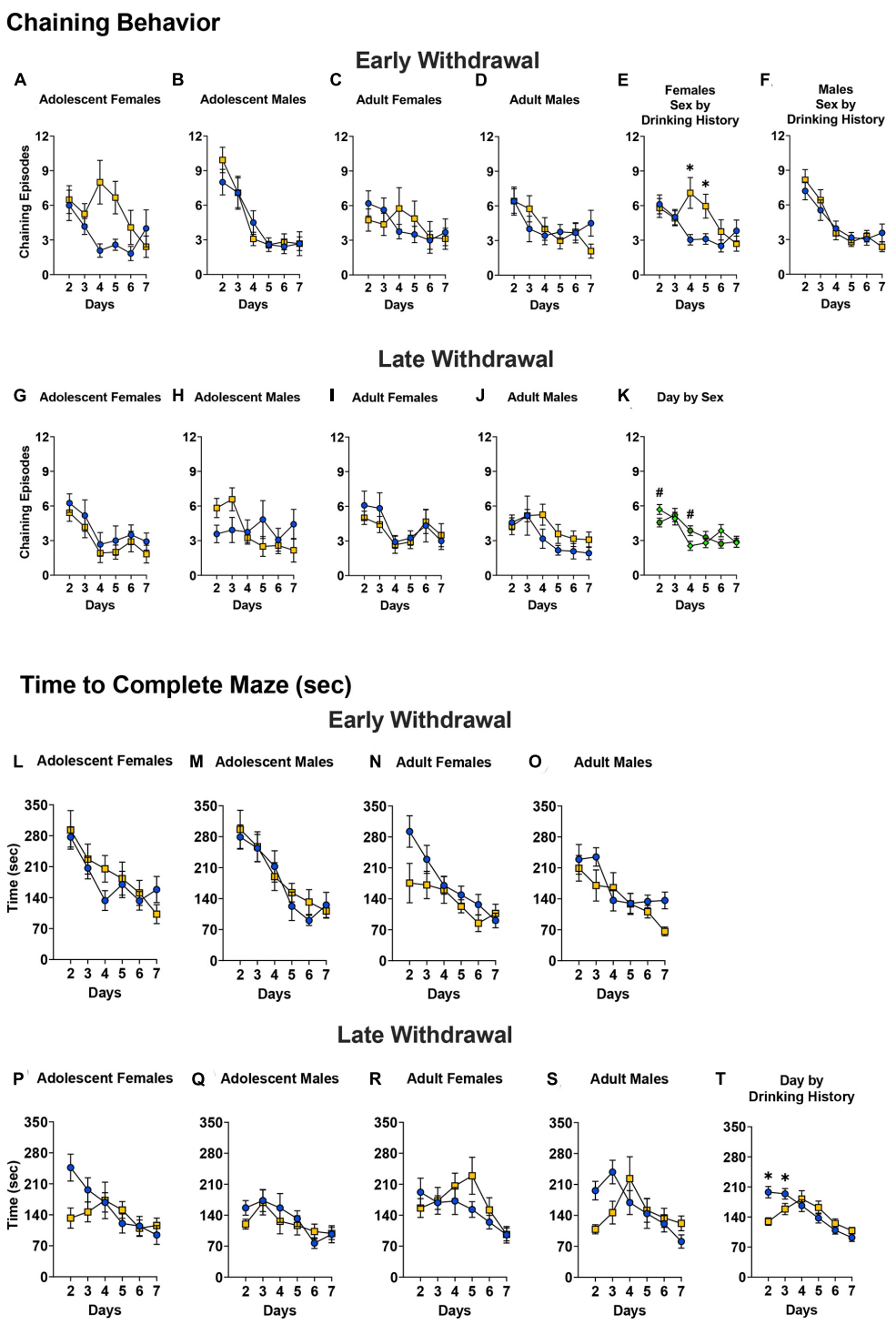

FIGURE 8
Depiction of the results of the Day × Sex × Age × Drinking History mixed-model ANOVAs evaluating non-spatial navigation (chaining episodes) and time taken to navigate the Radial Arm Maze. **(A–D)** No significant 4-way interaction in mice tested in early withdrawal. For early withdrawal, the sample sizes were as follows: **(A)** H2O (n = 12), EtOH (n = 12); **(B)** H2O (n = 12), EtOH (n = 12); **(C)** H2O (n = 16), EtOH (n = 8); **(D)** H2O (n = 12), EtOH (n = 12). **(E)** However, a significant Day by Sex by Drinking History interaction was detected that reflected more chaining behavior by binge-drinking females than water controls on days 4 and 5 [H2O (n = 28), EtOH (n = 20)]. **(F)** No significant interaction was detected for males tested in early withdrawal [H2O (n = 24), EtOH (n = 24)]. **(G–J)** In mice tested in later withdrawal, no significant 4-way interaction was found. For late withdrawal, the sample sizes were as follows: **(G)** H2O (n = 12), EtOH (n = 12); **(H)** H2O (n = 12), EtOH (n = 12); **(I)** H2O (n = 12), EtOH (n = 12); **(J)** H2O (n = 12), EtOH (n = 12). **(K)** However, a significant Day by Sex interaction was detected that reflected sex differences in chaining on day 2 and 4 of training [females (n = 48), males (n = 48)]. The data represent the means ± SEMs for the number of mice indicated above. **(L–O)** For the mice tested in early withdrawal, there were no significant Day by Sex by Age by Drinking History interactions on the total time to complete the maze, and all mice showed improvement in maze completion over time. The sample sizes are the same as for panels **(A–D)**. **(P–S)** For the mice tested in later withdrawal, no significant 4-way interaction was detected. The sample sizes are the same as for panels **(G–J)**. **(T)** However, a significant Day by Group interaction was noted, which reflected a shorter latency to complete the maze on days 2 and 3 by binge-drinking mice [H2O (n = 48), EtOH (n = 48)]. The data represent the means ± SEMs for the number of mice indicated above. $^{*}p < 0.05$, EtOH vs. H2O; $^{\#}p < 0.05$, adolescents vs. adults.

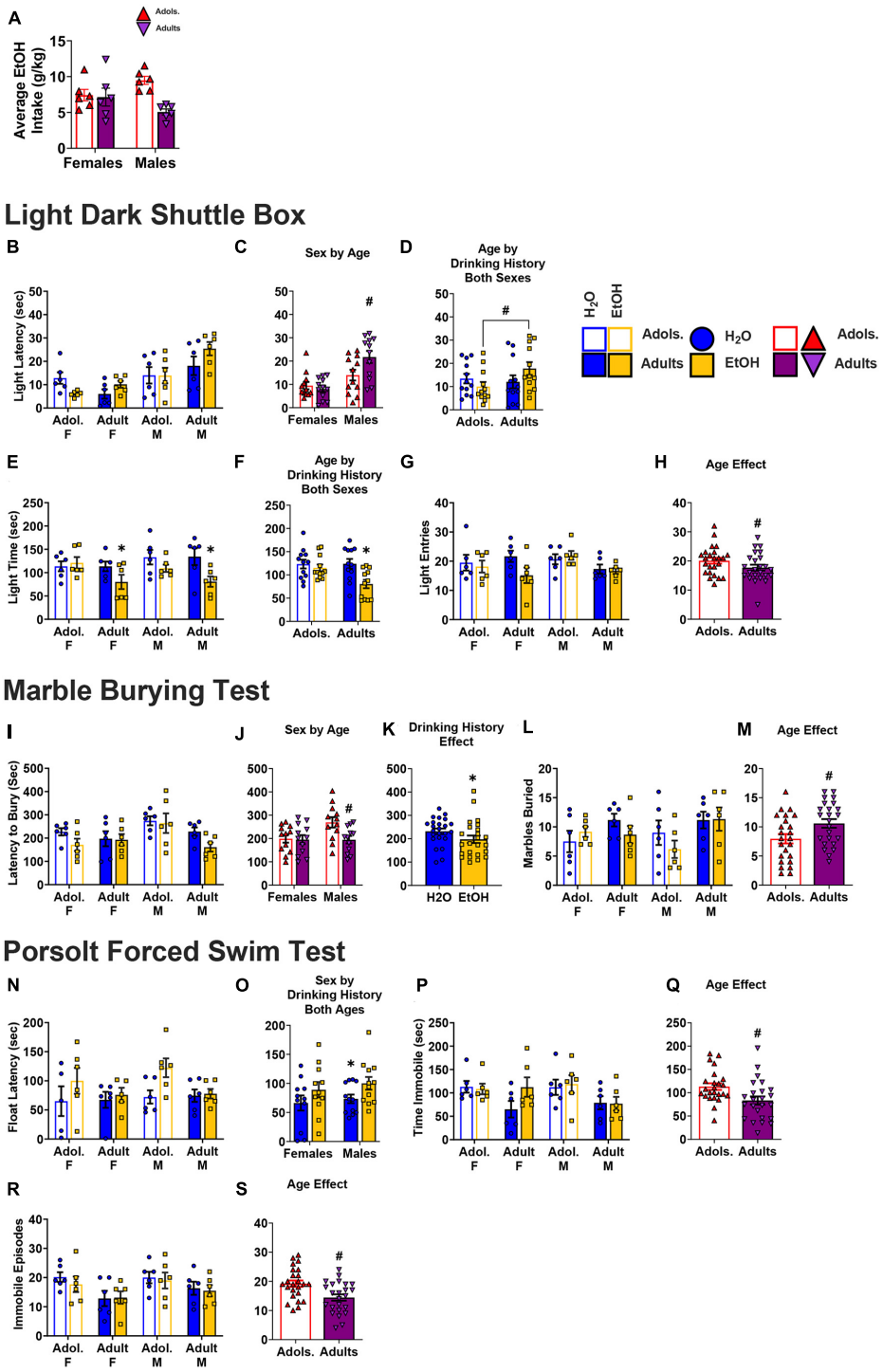

FIGURE 9
Depiction of the results from Study 2. **(A)** In the replicate study, a significant age x sex interaction was detected for the amount of alcohol consumed (n = 6/sex/age), that reflected more alcohol intake by adolescent versus adult males. **(B)** Summary of the data for the latency to first enter the light-side of the light-dark shuttle box on WD 1 (n = 6/sex/age/drinking history). The ANOVA conducted on this variable revealed a Sex by Age interaction [**(C)**; n = 12/sex/drinking history] and an Age by Drinking History interaction [**(D)**; n = 12/age/drinking history]. **(E)** Summary of the data for the time spent in the light side (in sec), highlighting a main drinking history effect in adult mice (n = 6/sex/age/drinking history). **(F)** The ANOVA conducted on this variable indicated also an Age × Drinking History interaction that reflected H2O-EtOH differences in adult mice (n = 12/age/drinking history). **(G)** Summary of the number of entries into the light side of the shuttle box (n = 6/sex/age/drinking history). **(H)** The ANOVA indicated fewer light-side entries by adults vs. adolescents (n = 24/age). **(I)** Summary of the data for the latency to begin marble-burying (n = 6/sex/age/drinking history). The ANOVA indicated a Sex × Age interaction [**(J)**; n = 12/sex/age], as well as a main Drinking History effect [**(K)**; n = 24/drinking history]. **(L)** Summary of the data for the number of marbles buried (n = 6/sex/age/drinking history). **(M)** The ANOVA indicated that adults buried more marbles than adolescent mice (n = 24/age). **(N)** Summary of the data for the latency to first floatin in the forced swim test (n = 6/sex/age/drinking history) [females: adolescent-H20 (n = 5); adolescent-EtOH (n = 6); adult-H2O (n = 6); adult-EtOH (n = 5); males:

(Continued)

FIGURE 9 (Continued)
n = 6/age/drinking history]. **(O)** The ANOVA revealed a Sex × Drinking History inaction, but no specific H2O-EtOH differences were detected [female-H2O (*n* = 11); female-EtOH (*n* = 11); male-H2O (*n* = 12); male-EtOH (*n* = 12]. **(P)** Summary of the data for the time spent immobile (*n* = 6/sex/age/drinking history). **(Q)** The ANOVA indicated less time immobile in adult versus adolescent mice (*n* = 24/age). **(R)** Summary of the data for the number of immobile episodes (*n* = 6/sex/age/drinking history), the ANOVA for which indicated fewer immobile episodes in adult versus adolescent mice [**(S)**; *n* = 24/age]. The data are presented as the means ± SEMs for the respective number of mice indicated above. $^{*}p < 0.05$ H2O vs. EtOH; $^{\#}p < 0.05$, adolescents vs. adults (main Age effect).

Light-dark shuttle box

Latency to enter the light-side

Under these more insulated testing conditions, we detected two significant interactions with respect to the latency to first enter the light-side of the light-dark shuttle box (Figure 9B). As illustrated in Figure 9C, a Sex × Age interaction [$F(1,47) = 5.57$, $p = 0.023$; $\eta^2p = 0.122$] reflected a shorter latency of adolescent versus adult males to enter the light-side [$t(22) = 2.24$, $p = 0.035$], with no age difference observed in females (*t*-test, $p = 0.516$). We also detected a significant Age X Drinking interaction for this variable (Figure 9D) [$F(1,47) = 5.59$, $p = 0.023$; $\eta^2p = 0.123$]. Although inspection of Figure 9D suggested that this interaction reflected specifically an alcohol-induced increase in the latency of adult mice to first enter the light-side, water-alcohol differences were not detected for either age group (*t*-tests, *p*'s > 0.158). Rather, the Age × Drinking interaction reflected a longer latency to enter the light side by alcohol-experienced adults versus their adolescent counterparts [$t(22) = 2.28$, $p = 0.032$], with no age difference noted for water controls (Figure 9D; *t*-test, $p = 0.697$).

Light side time and entries

A summary of the data for the time spent on the light side is depicted in Figure 9E. A significant Age × Drinking interaction was also detected for this variable [$F(1,47) = 3.63$, $p = 0.064$; $\eta^2p = 0.083$], which reflected less time spent by alcohol-experienced adults versus their water controls [$t(22) = 3.14$, $p = 0.055$] with no water-alcohol differences detected in adolescent mice (Figure 9F; *t*-test, $p = 0.499$). Although it appeared that adult female alcohol-experienced mice entered the light-side fewer times than their water controls (Figure 9G), we detected only an overall effect of age with respect to this variable, with adults spending less time in the light-side than adolescents (Figure 9H) [Age effect: $F(1,47) = 2.93$, $p = 0.095$; $\eta^2p = 0.068$; other *p*'s > 0.133; η^2p's < 0.056].

Marble-burying

Latency to bury

A summary of the data for the latency to begin marble burying is provided in Figure 9I. Under the more insulated testing conditions, we detected a significant Age × Sex interaction for the latency to begin marble burying [$F(1,47) = 3.68$, $p = 0.062$; $\eta^2p = 0.084$] that reflected a longer latency of adolescent versus adult males [$t(22) = 2.71$, $p = 0.013$], with no age difference noted for females (Figure 9J; *t*-test, $p = 0.885$). We also detected an overall Drinking effect [$F(1,47) = 3.46$, $p = 0.070$; $\eta^2p = 0.080$] that reflected a shorter latency to bury in alcohol-experienced mice versus water controls, irrespective of the animals' age or sex (Figure 9K; Drinking interactions, all *p*'s > 0.149; η^2p's < 0.052).

Marbles buried

In contrast, we detected only an overall Age effect with respect to the number of marbles buried (Figure 9L) [$F(1,47) = 5.482$, $p = 0.024$; $\eta^2p = 0.121$; other *p*'s > 0.117; η^2p's < 0.061], that reflected more marbles buried by adult versus adolescent mice (Figure 9M).

Forced swim test

Latency to first immobile episode

As depicted in Figure 9N, there was considerable variability in the latency to first float in the forced swim test even when extreme outliers were removed. However, we did detect a significant Sex × Drinking History interaction (Figure 9O) [$F(1,45) = 70.15$, $p = 0.050$; $\eta^2p = 0.825$]. This interaction reflected a longer latency to float by alcohol-experienced males versus their water controls [$t(22) = 2.022$, $p = 0.056$], with no significant alcohol-water difference detected in females (*t*-test, $p = 0.235$). No Age effect or interactions were detected for this variable (*p*'s > 0.208; $\eta^2p < 0.650$).

Number and duration of immobility

In contrast to the latency to float, we detected no alcohol or sex effects for the time spent floating (Figure 9P; *p*'s > 0.187; $\eta^2p < 0.044$) or the number of floating episodes (Figure 9R; *p*'s > 0.282; $\eta^2p < 0.029$) or in the forced swim test. Instead, we detected only main Age effects for both variables (Figures 9O, S) [for float episodes, Age effect: $F(1,47) = 8.73$, $p = 0.005$; $\eta^2p = 0.179$; for float time (sec), Age effect: $F(1,47) = 6.86$, $p = 0.012$; $\eta^2p = 0.146$] that reflected less floating-related behavior in adult vs. adolescent mice.

Discussion

The present study was designed to expand upon a recent report from our group describing weak interactions between a sub-chronic (i.e., 2 week) history of binge-drinking, the age of drinking-onset and sex in the affective consequences of alcohol assayed at 1 versus 70 days withdrawal (Jimenez Chavez et al., 2020). The results of this prior study (Jimenez Chavez et al., 2020) contrasted with earlier reports of robust, age-dependent, effects in the marble-burying, light-dark box and forced swim tests (Lee et al., 2016, 2017a,b, 2018a,b; Szumlinski et al., 2019). As these latter studies employed a single sex and tested for negative affect at 1 versus 30 days withdrawal, herein, we segregated the testing of our male and female mice on WD1 and WD30 to reduce the influence of chemosensory social stimuli from the opposite sex

on behavior. Based on a recent study of older mice (>6 months of age) indicating sex differences in alcohol-induced cognitive impairment (Jimenez Chavez et al., 2022), as well as published work from other groups indicating that a history of alcohol-drinking during adolescence can accelerate the onset of cognitive decline (e.g., Ledesma et al., 2021; Van Hees et al., 2022), we also tested for interactions between our subject factors with respect to spatial learning and memory in the Morris water maze, as well as reference and working memory in the radial arm maze. Although we detected some affective and cognitive effects of binge-drinking, the group differences were not as robust as in prior work when a single sex was tested. Thus, we also conducted an additional study to best mimic the procedural conditions of our prior work (i.e., Lee et al., 2016, 2017b, 2018a), in which we single-housed water controls during drinking procedures and behavioral testing was conducted in series in distinct procedural rooms.

Robust binge-drinking for 2 weeks elicits relatively few effects on negative affect during alcohol withdrawal

A summary of the effects of alcohol withdrawal on our behavioral measures from our two studies is presented in **Table 6**. As expected (Finn et al., 2010; Strong et al., 2010; Wilsnack et al., 2018; Szumlinski et al., 2019; Jimenez Chavez et al., 2020, 2022), the female mice in the larger study binge-drank more alcohol than males and exhibited higher BACs (**Figure 2B**). Also as expected (Moore et al., 2010; Melón et al., 2013; Lee et al., 2016, 2017b, 2018a; Szumlinski et al., 2019; Jimenez Chavez et al., 2020), adolescents consumed more alcohol and attained higher BACs than their adult counterparts (**Figure 2A**). Moreover, BACs on the day of sampling were at or above the NIAAA 80 mg/dL criterion for binge-drinking (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2004) and BACs correlated with alcohol intake, with adult males exhibiting the lowest intakes/BACs, and adolescent females exhibiting the highest intakes/BACs (**Figure 2C**). However, in the smaller scale study (n = 6/sex/age/group), the sex and age differences were less robust, owing to the relatively high alcohol intake of the adolescent males (**Figure 9A**).

However, as observed in our prior large study of sex by age interactions in alcohol withdrawal-induced negative affect (Jimenez Chavez et al., 2020), we detected very few alcohol or -age-related differences in negative affect in either of the studies presented herein (see summary in **Table 6**). Thus, we twice failed to replicate the robust alcohol by age by withdrawal interactions detected for the majority of our dependent variables in our earlier studies employing a single sex (Lee et al., 2016, 2017b, 2018a,b; Szumlinski et al., 2019). As chemosensory social stimuli from females can affect anxiety-like behavior in males (Aikey et al., 2002; Fernández-Guasti and Martínez-Mota, 2005; Frye et al., 2008), both of the experiments herein tested males and females on different days to mitigate this influence. Thus, gonadal pheromones from mice of the opposite sex during testing cannot readily account for the relatively weak effects of alcohol withdrawal upon our measures of negative affect in the present studies. Likewise, as female mice have historically been housed in the same colony room as male mice, either under ventilated or filter-top-type caging over the years that we have been conducting binge-drinking studies in mice, it is also unlikely that gonadal pheromones from mice of the opposite sex in the colony room can account for the relatively weak effects of alcohol observed in the present studies.

It is interesting to note that we detected more male-selective effects of alcohol withdrawal in the present large-scale study (**Table 6**), compared to that previous employing concurrent testing of male and female subjects (Jimenez Chavez et al., 2020). As highlighted in **Table 6**, male-selective alcohol-water differences were noted for the entries into the light-side in the light-dark shuttle box test (WD1), the time spent immobile in the forced swim (WD1), and the number of immobile episodes (both WD1 and WD30), while female-selective alcohol-water differences were noted for the number of immobile episodes (WD1) and the number of marbles buried (WD30) (**Table 6**). Further, the fact that some sex by age interactions for our measures of negative affect were observed when male and female mice are segregated during testing for negative affect indicates that a segregation strategy may prove more fruitful for detecting such interactions be more optimal for detecting sex-selective effects than concurrent testing of both sexes. Admittedly, the smaller scale replicate study was likely insufficiently powered to detect sex by alcohol interactions as we detected only trends for sex-selective alcohol effects (**Figure 9**). This being said, Sex by Age interactions were noted for the latency to enter the light-side of the light-dark shuttle box (**Figure 9C**) and the latency to being burying marbles (**Figure 9J**), in which males exhibited the age-related difference in behavior. However, the simple fact remains that three of our sex differences studies to date (Jimenez Chavez et al., 2020; present study) have yielded less robust and consistent alcohol effects on anxiety- and depressive-like behaviors than our earlier single-sex studies. While it might be argued that the group-housing procedure employed for water control mice in the present larger scale study and that previous (Jimenez Chavez et al., 2020) may have confounded their results, age by alcohol interactions were apparent in earlier single-sex studies using comparable group-housed water-drinking procedures (Lee et al., 2018a; Szumlinski et al., 2019). Moreover, individually housing both the water- and alcohol-drinking mice in the follow-up study herein did not improve experimental outcomes (see **Table 6**), despite the study being sufficiently powered to detect alcohol by age interactions (n = 12/age/drinking history).

At the time we completed the larger scale study herein, we considered two additional procedural factors that might account for the discrepancy across our sex difference (Jimenez Chavez et al., 2020; present study) versus single-sex studies to date (e.g., Lee et al., 2016, 2017a,b, 2018a,b; Szumlinski et al., 2019): (1) the research personnel conducting the study and (2) the location of the behavioral laboratory. However, as both studies of one or both sexes are labor-intensive, they have always been conducted by teams of researchers such that the mice are handled by multiple, different, researchers throughout drinking and are only tested for negative affect by individuals familiar to the mice, with the goal of minimizing experimenter-induced anxiety-like behavior. We followed a similar "team" approach in the larger scale study herein, while both the drinking and behavioral testing procedures employed in the smaller scale study was conducted by a single researcher. Thus, it would not appear that our "team approach" is a major driver of our failure to detect age by alcohol interactions when both sexes are studied.

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TABLE 6 Summary of the effects of a 2-week history of binge-drinking upon our measures of negative affect and cognition.

Dependent variable	Study 1: WD 1 and 30		Study 2: WD1 only
Binge drinking			
Average Total Intake	**adolescent** > **adults**females > males		**adolescents** > **adults** (males only)
BACs	adolescent > adultsfemales > males		ND
	Early Withdrawal	**Late Withdrawal**	**Early Withdrawal**
Tests for negative affect			
Latency to enter the light side	EtOH = H2O	EtOH = H2O	EtOH = H2O
Time spent in the light side	EtOH > H2O (adolescents only) **EtOH < H2O (adults only)**	EtOH = H2O	**EtOH < H2O (adults only)**
Entries into the light side	EtOH = H2O	EtOH = H2O	EtOH = H2O
Latency to bury marbles	ND	ND	EtOH < H2O
Number of marbles buried	EtOH = H2O	EtOH = H2O	EtOH = H2O
Latency to immobility	EtOH > H2O	EtOH = H2O	EtOH = H2O
Time spent immobile	EtOH > H2O (adolescent males only) EtOH < H2O (adult males only)	EtOH = H2O	EtOH = H2O
Immobile Episodes	EtOH > H2O (adult females only) EtOH > H2O (adolescent males only)	EtOH < H2O (adolescents only) EtOH < H2O (males only)	EtOH = H2O
Morris water maze			
Latency to platform during the flag test	EtOH = H2O	EtOH = H2O	
Latency to platform during acquisition	EtOH = H2O	EtOH = H2O	
Latency to platform during probe test	EtOH < H2O (adolescents only)	EtOH = H2O	
Entries to platform location during probe test	EtOH = H2O	EtOH < H2O (adolescents only) EtOH > H2O (adults only)	
Time spent in the NE quadrant	EtOH = H2O	EtOH = H2O	
Latency to new platform location	EtOH = H2O	EtOH = H2O	
Radial arm water maze			
Reference memory errors	EtOH = H2O	EtOH = H2O	
Working memory correct errors	EtOH = H2O	Days 2 and 3: EtOH < H2O	
Working memory incorrect errors	Days 2, 4 and 5: EtOH > H2O (adolescents only) Day 3: EtOH < H2O (adults only)	Day 2: EtOH < H2O	
Chaining episodes	Days 4 and 5: EtOH > H2O (females only)	EtOH = H2O	
Time to locate all platforms	EtOH = H2O	Days 2 and 3: EtOH < H2O	

EtOH-Water differences in behavior that were consistent across the two studies and/or that align with prior published studies by our group are bolded. ND indicates not determined. The mice in Study 2 were only assayed for negative affect.

A more plausible explanation relates to the locations of the colony rooms in which mice consumed alcohol/water and the procedural space employed for behavioral testing. The mice in all our earlier studies (Lee et al., 2016, 2017a,b, 2018a,b; Szumlinski et al., 2019) were housed and drank alcohol in a small satellite vivarium, with testing conducted in several, small, distinct procedural rooms dedicated to a specific behavioral test that were located outside of the vivarium. While the same behavioral equipment and procedures for assaying negative affect continue to be employed, the three most recent studies from our group examining for age by sex interactions in alcohol withdrawal-induced anxiety (Jimenez Chavez et al., 2020, 2022; present study) were all conducted in the main campus vivarium, in large procedural rooms housing multiple apparati, during which groups of mice undergo different tests concurrently in the same room (i.e., tests for marble-burying conducted on the bench along the right side of the room, with tests for light-dark box conducted on the bench along the left side of the room). To minimize the noise associated with daily vivarium routines, we only tested mice for negative affect on weekends when vivarium staff was minimal and the general vivarium traffic low. However, the modular nature of our current behavioral testing space may not be ideal for testing anxiety- and depressive-like behavior in mice. To probe this possibility, each behavioral assay in the smaller, follow-up, study was conducted in distinct rooms within the main campus vivarium and the mice underwent the behavioral procedures in series. As illustrated in **Figure 9**, the procedural modifications in the second study were sufficient to unmask age differences and/or age by sex interactions for our light-dark shuttle-box and forced swim measures that were not apparent in the larger scale study (see **Figures 3**, **5**, respectively). However, as highlighted in **Table 6**, we detected fewer alcohol-related effects in the follow-up study than the larger original study. Unfortunately, as our small satellite vivarium no longer exists, we cannot directly compare outcomes from experiments conducted in the main versus satellite vivaria. Given this, we can conclude that segregating the sexes during behavioral testing and sample size, but not necessarily the involvement of a single versus a team of experimenters, the employ of single versus group-housing of water controls and serial versus concurrent behavioral testing appear to influence the manifestation of negative affect during alcohol withdrawal.

Robust binge-drinking for 2 weeks elicits a few signs of mild cognitive impairment during alcohol withdrawal

The extant human (e.g., Squeglia et al., 2009, 2011a,b; Novier et al., 2015; Cservenka and Brumback, 2017; Huang et al., 2018; Ledesma et al., 2021) and rodent (Salling et al., 2016; Grifasi et al., 2019; Hoffman et al., 2019; Jimenez Chavez et al., 2022; Van Hees et al., 2022) literature indicates that a history of excessive drinking can accelerate cognitive decline and associated neuropathology, with adolescent female binge-drinking humans exhibiting greater neurocognitive anomalies than their male counterparts (e.g., Squeglia et al., 2009, 2011a,b). Given the robust sex- and age-related differences in alcohol intake and BACs observed in the present study (**Figure 1**), we predicted that adolescent female mice would exhibit the most robust deficits in cognitive function, potentially exhibiting cognitive anomalies as young adults. However, as summarized in **Table 6**, only one variable across our Morris water maze procedures exhibited alcohol-dependent effects - the number of entries into the former platform location, a measure of spatial recall. These alcohol effects were observed only in later withdrawal (i.e., approximately 60 days following the last drinking day), were of medium effect size (*d*'s~0.5) and reflected poorer spatial recall by adolescent-onset binge-drinkers, but better spatial recall by adult-onset binge-drinkers (**Figure 6N**). No other cognitive measure exhibited an alcohol effect that was selective for adolescent-onset binge-drinkers (**Table 6**). Thus, while non-dependence drinking can alter the expression of Alzheimer's Disease-related genes in both adolescent and adult B6 mice (Salling et al., 2016; Hoffman et al., 2019), it may be that a 2-week history of binge-drinking under our 2-h procedures during adolescence is insufficient to accelerate cognitive decline. Alternatively, 3.5 months of age may be too early to detect signs of alcohol-induced cognitive decline in mice with a history of adolescent-onset binge-drinking. Arguing in favor of the former (and against the latter) possibly, Van Hees et al. (2022) recently showed that 10 days of binge-drinking during adolescence under 4-h DID procedures [during which alcohol intakes were approximately double those observed in the present study; see Figure 2C in Van Hees et al. (2022)] is sufficient to induce a deficit in novel object recognition when mice are tested 40 days later. It is also possible that the Morris water maze is less sensitive than other cognitive tasks for the detection of alcohol-induced cognitive decline. Indeed, in our prior study of mature adult and aged mice, we detected very few alcohol-related effects in the Morris water maze, while several measures in the radial arm maze were consistently negatively impacted by an alcohol-drinking history (Jimenez Chavez et al., 2022).

Consistent with this, we detected more alcohol effects in the radial arm maze than in the Morris water maze in the present study (**Table 6**). However, in contrast to older mice (Jimenez Chavez et al., 2022), the alcohol-water differences observed in adolescent- and adult-onset binge-drinking mice were not systematic across maze acquisition. For some variables, alcohol effects were observed for 1–2 days during early learning, for other variables they appeared during the middle of the first week of training and no obvious pattern of effect is apparent from the results of specific alcohol-water comparisons as presented in **Table 6**. However, a comparison of the shapes of the time-courses for both working memory correct (**Figure 6S**) and incorrect errors (**Figure 6D'**) committed by the binge-drinking mice in later withdrawal argues that a binge-drinking history impairs between-session learning in a manner that is independent of both sex and age of drinking-onset. To the best of our knowledge, this study is the first to examine the effects of a history of binge-drinking during adolescence or younger adulthood on radial arm maze performance. As we know that a month of binge-drinking under our 2-h DID procedures is sufficient to induce sex- and age-selective deficits in radial arm maze performance in older mice (Jimenez Chavez et al., 2022), while binge-drinking large amounts of alcohol (6–8 g/kg/day) over a 10-day period during adolescence is sufficient to induce

cognitive deficits in early adulthood (Van Hees et al., 2022), future work seeks to determine the relationship between cumulative alcohol intake and cognitive outcomes, with a focus on how individual differences, such as sex and age of drinking-onset, modify this relationship. As a history of alcohol-drinking during adolescence/early adulthood induces microglial activation (Grifasi et al., 2019), as well as increases the expression of markers of Alzheimer's disease-related neuropathology (e.g., Salling et al., 2016; Hoffman et al., 2019), future work also seeks to relate alcohol-induced cognitive anomalies, even those mild signs observed herein, to indices of neuropathology.

Conclusion

Herein we show that a 2-week history of binge-drinking by male and female, adult and adolescent, B6 mice induces relatively few signs of negative affect, some of which were sex-selective. Further, this binge-drinking history is sufficient to induce some signs of mild cognitive impairment in both adolescent- and adult-onset binge-drinkers that persist for greater than 1 month following the cessation of drinking.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was reviewed and approved by the Institutional Animal Care and Use Committee of the University of California Santa Barbara.

Author contributions

KS and CJ: conceptualization, supervision, formal analysis, writing—original draft preparation, writing—review and editing, and visualization. KS: project administration. CJ, ED, GS, ER, JT-G, JH, SK, AG, CJED, and MC: investigation and writing—review and editing. KS, CJ, and ED: funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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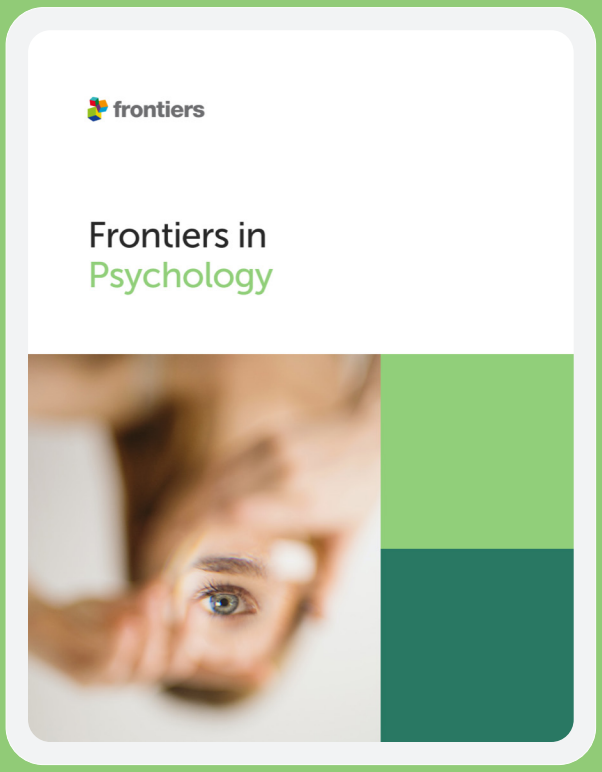

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