Universidade do Minho
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Neurocognitive Mechanisms of Alcohol-Related Memory Processes Across the Spectrum of Alcohol Use

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Rui Rodrigues

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“ (...) my life, pretty much imploded before my eyes. I mean, my grades plummeted. I got grounded. I had to stay home every weekend doing chores. But then one day, I was cleaning bat shit out of my parents’ garage, and I found this 8-millimeter film reel. You know? And it was just from this silly movie that I made in fourth grade, but I got it up on the projector, and all of a sudden, I was looking at this little version of myself. And that little me, I could hardly recognize her. You know, she was so carefree and, like, fearless. She just loved every part of herself. And that’s when it hit me. (...) It was always just about me. I was looking for answers in somebody else, but... I had all the answers. I just needed to stop being so goddamn scared. Scared of... who I really was. Once I did that, oh, I felt so free. It’s like I could fly, you know? Like, I could finally be... “

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Mecanismos Neurocognitivos de Processamento de Memórias Relacionadas com Álcool no Espectro do Consumo de Álcool

O consumo problemático de álcool constitui uma importante preocupação de saúde pública, estando associado a alterações nos processos de controlo cognitivo, de incentivo e nos mecanismos de memória. Modelos neurocognitivos da adição sugerem que o consumo repetido de álcool enviesar progressivamente os sistemas cognitivos e de incentivo em direção a estímulos relacionados com o álcool, reforçando memórias associativas e aumentando a sua influência no comportamento. Estes processos contribuem para o *craving*, a manutenção do consumo e o risco de recaída. No entanto, os mecanismos neurocognitivos através dos quais os processos de memória relacionados com o álcool interagem com o controlo cognitivo e a saliência motivacional ao longo das diferentes fases do consumo problemático permanecem pouco explorados. A presente tese teve como objetivo investigar de que forma diferentes padrões de consumo, desde o *binge drinking* até à perturbação do uso de álcool (PUA), influenciam os processos de memória e os seus correlatos neurais, bem como a sua relação com o *craving* e a gravidade do consumo. Para tal, foram conduzidos quatro estudos complementares, recorrendo a metodologias comportamentais, eletroencefalográficas e de neuroimagem. O primeiro estudo consistiu na validação portuguesa do *Alcohol Craving Questionnaire – Short Form – Revised*. O segundo analisou os efeitos do *binge drinking* na atenção e na memória de trabalho através de eletroencefalografia, evidenciando alterações nos potenciais evocados associados ao processamento atencional e mnésico, apesar de desempenho comportamental preservado. O terceiro utilizou ressonância magnética funcional para investigar a recuperação de memórias associativas em *binge drinkers*, revelando maior ativação em regiões percetuais e subcorticais. Por fim, o quarto estudo recorreu a uma versão adaptada do paradigma *Think/No-Think* para examinar a supressão intencional de memórias relacionadas com o álcool em indivíduos com PUA, evidenciando alterações na conectividade funcional. Globalmente, os resultados sugerem que o consumo problemático de álcool está associado a alterações neurais nos processos de memória que podem emergir antes de défices cognitivos evidentes. As memórias relacionadas com o álcool parecem adquirir maior relevância motivacional, envolvendo sistemas de saliência e recompensa. Estes resultados contribuem para a compreensão dos mecanismos neurocognitivos da adição e destacam os processos de memória como potenciais alvos de intervenção.

Palavras-chave: Álcool; Memória; Controlo Cognitivo; Eletroencefalografia; Neuroimagem.

Neurocognitive Mechanisms of Alcohol-Related Memory Processes Across the Spectrum of Alcohol Use

Alcohol misuse represents a major public health concern and has been associated with alterations in cognitive control, motivational processing, and memory mechanisms. Contemporary neurocognitive models of addiction suggest that repeated alcohol consumption progressively biases cognitive and motivational systems toward alcohol-related stimuli, strengthening alcohol-related memories and increasing their influence on behavior. These processes are thought to contribute to craving, the persistence of alcohol use, and relapse risk. However, the neurocognitive mechanisms through which alcohol-related memory processes interact with cognitive control and motivational salience across different stages of alcohol misuse remain poorly understood. The present thesis aimed to investigate how alcohol consumption, ranging from hazardous binge drinking to alcohol use disorder (AUD), affects memory processes and their neural correlates, and how these processes relate to craving and alcohol use severity. To address this aim, four complementary studies combining behavioral, electrophysiological, and neuroimaging approaches were conducted. The first study provided the Portuguese validation of the Alcohol Craving Questionnaire – Short Form – Revised, establishing a reliable and valid instrument for assessing acute alcohol craving in Portuguese-speaking populations. The second study examined the effects of binge drinking on attention and working memory using electroencephalography, revealing alterations in event-related potentials associated with attentional allocation and memory-related processing despite largely preserved behavioral performance. The third study used functional magnetic resonance imaging to investigate associative memory retrieval for alcohol-related information in binge drinkers, demonstrating increased activation in perceptual and subcortical regions during retrieval of alcohol-related associations. Finally, the fourth study employed an adapted Think/No-Think Alcohol paradigm to examine the neural mechanisms underlying intentional suppression of alcohol-related memories in individuals with AUD, showing altered functional connectivity patterns during memory suppression. Overall, the findings suggest that alcohol misuse is associated with neural alterations in memory-related processes that may emerge before overt cognitive deficits become evident. Alcohol-related memories appear to acquire increased motivational relevance, engaging salience- and reward-related neural systems during both retrieval and regulation. These results contribute to a better understanding of the neurocognitive mechanisms underlying alcohol misuse and highlight memory-related processes as potential targets for intervention.

Keywords: Alcohol; Memory; Cognitive Control; Electroencephalography; Neuroimaging.

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Abbreviations, Acronyms and Symbols

ACC - Anterior cingulate cortex

ACQ - Alcohol Craving Questionnaire

ACQ-SF-R - Alcohol Craving Questionnaire – Short Form – Revised

AF - Anterior Frontal

Ag - Silver

AgCI - Silver chloride

AHSS - Alcohol Hangover Severity Scale

AIC - Akaike information criterion

ANOVA - Analysis of variance

AUD - Alcohol use disorder

AUDIT - Alcohol Use Disorders Identification Test

AUQ - Alcohol Urge Questionnaire

BAC - Blood Alcohol Concentration

BD - Binge Drinking

BDs - Binge Drinkers

BIS11 - Portuguese version of Barratt Impulsiveness Scale 11

BOLD - Blood-oxygenation-level-dependent

C - Central

CFI - Comparative Fit Index

CI - Confidence Interval

CMS - Common Mode Sense

CP - Centro-Parietal

CPT - Continuous performance task

DAQ - Desires for Alcohol Questionnaire

df - Degrees of freedom

dL - deciliter

DS - Dorsal striatum

DS - dorsal striatum

DSM - Diagnostic and Statistical Manual of Mental Disorders

EEG - Electroencephalography

EFA - Exploratory Factorial Analysis

EPI - echo-planar imaging

ERP - Event-related potential

EU - European Union

F - Factor

F - F-ratio

F - Frontal

FA - Flip Angle

fMRI - Functional magnetic resonance imaging

FoV - Field of View

Fp - Fronto-polar

FWE - Family-Wise Error

FWEc - Family-Wise Error corrected

FWHM - Full Width at Half Maximum

g - grams

GABA - Gamma-aminobutyric acid

GFI - Goodness-of-Fit Index

Hz - Hertz

I - Inion

ICA - Independent Component Analysis

ICD - International Classification of Diseases

IL-6 - Interleukin-6

iRISA - Impaired Response Inhibition and Salience Attribution

ISI - Interstimulus interval

JCR - Journal citation reports

k - cluster size

KMO - Kaiser Meyer Olkin

LPC - Late positive component

M – Mean

mm - Milimeters

MNI - Montreal Neurological Institute

MRI - magnetic resonance imaging

ms - miliseconds

mV - Millivolts

N - Number of participants

NFI - Normed Fit Index

NIAAA - National Institute on Alcohol Abuse and Alcoholism

NMDA - N-methyl-D-aspartate

P - Parietal

p - Probability value

P3 - Positive 300 ms

PACS - Penn Alcohol Craving Scale

PCA - Principal component analysis

PFC - Prefrontal cortex

PO - Parieto-Occipital

POPORO - Pool of Pairs of Related Objects

r - Correlation coefficient

RMSEA - Root Mean Square Error of Approximation

RTs - Reaction Times

s - Seconds

SCL-90-R - Symptom Checklist-90 Revised

SD - Standard deviation

SICAD - Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências

SPM - Statistical Parametric Mapping

SPSS - Statistical Package for Social Sciences

t - t-value

TBI - Traumatic Brain Injury

TE - Echo Time

TF - Temporal factor

TNF - Tumor necrosis factor

TNT - Think/No-Think

TR - Repetition Time

ULS - Unweighted least squares

USA - United States of America

vmPFC - Ventromedial prefrontal cortex

WHO - World Health Organization

μV - Microvolts

$\chi 2$ - Chi-Square

Chapter I

General Introduction

1. Introduction

1.1. Alcohol Consumption and Neurobiological Consequences

Alcohol is humanity's most prevalent yet harmful psychoactive substance. Worldwide, harmful alcohol use leads to roughly 2.6 million deaths per year and about 4.7% of the global burden of disease, being in fact the leading risk factor for premature death (World Health Organization [WHO], 2024a). In European countries, alcohol is a leading cause of preventable mortality (roughly 8000 deaths per year), ranging from car accidents to homicides and suicides (WHO Regional Office for Europe, 2024a). Among adolescents, alcohol accounts for about one-quarter of injury-related deaths (WHO Regional Office for Europe, 2024b). Moreover, alcohol misuse generates substantial social and economic burdens, ranging from higher healthcare expenditures, lost productivity, and increased rates of domestic violence, traffic injuries, and crime, impacting individuals, families, and communities (Moss, 2013). From an economic standpoint, alcohol misuse is estimated to cost roughly 2–3% of gross domestic product annually in health care, lost productivity, and law enforcement (Manthey et al., 2023).

In Portugal, recent estimates indicate that approximately 62% of the population reported alcohol use in the past year, and alcohol-related causes account for around 2% of all deaths (Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências [SICAD], 2023). Among younger populations, 59% of adolescents and youth aged 15 to 24 reported consuming alcohol in the past month (SICAD, 2023). Similarly, around 60% of 18-year-olds reported monthly alcohol use, with more than one episode of intoxication in the past year (Carapinha et al., 2024).

1.1.1. Effects of alcohol on the brain

Given alcohol´s long history of use in human societies and its wide impact across ages and cultures, the effects of alcohol consumption on the body and the brain have been extensively investigated. Evidence shows that even a single episode of heavy drinking can have detrimental effects, impacting multiple systems and organs, including the gastrointestinal and pulmonary systems (Vonghia et al., 2008), as well as inducing neuronal and behavioral alterations (Kong et al., 2012; Zoethout et al., 2010). Consequently, alcohol intoxication has been associated with significant adverse health effects and appears to be particularly harmful to the brain (Hua et al., 2020; Moss, 2013). Additionally, it is also linked to a range of acute social and health consequences, including physical injuries, sexual assault, alcohol overdose, memory blackouts, and death (McPeake et al., 2016; White et al., 2014).

Notably, ethanol, the primary psychoactive component of alcoholic beverages, acts as a central nervous system depressant (Mukherjee, 2013). Following ingestion, ethanol is rapidly absorbed from the gastrointestinal tract into the bloodstream and freely crosses the blood–brain barrier, allowing direct interaction with neuronal membranes, ion channels, and neurotransmitter receptors. This interaction alters synaptic transmission by enhancing GABAergic inhibitory signaling and inhibiting NMDA-mediated glutamatergic excitation, thereby increasing overall inhibitory tone in the brain (Costardi et al., 2015; Lovinger et al., 2023). Together, these mechanisms contribute to sedation, impaired coordination (ataxia), memory disruption, and reduced behavioral inhibition (D'Angelo et al., 2022; Rose et al., 2007) Similarly, ethanol's action on limbic reward circuits (including increased dopamine release in the mesolimbic pathway) contributes to its euphoric and reinforcing effects of drinking (Söderpalm et al., 2009; You et al., 2018). In parallel to its rapid effects on the central nervous system, ethanol also undergoes systemic metabolism following absorption. Following ingestion, it is transported via the bloodstream to the liver, where alcohol dehydrogenase converts ethanol into acetaldehyde, a highly reactive and toxic metabolite (Zakhari, 2006). The accumulation of acetaldehyde in the body promotes cellular damage and inflammation, thereby contributing to alcohol's toxic effects (Setshedi et al., 2010).

Beyond the acute effects of intoxication, short-term residual consequences may persist even as blood ethanol levels return to zero. One of the most well-characterized manifestations of these post-intoxication effects is alcohol hangover, defined as a set of adverse mental and physical symptoms emerging after a drinking episode, once blood alcohol concentration declines towards zero. These symptoms typically begin several hours after heavy drinking (often 6–8 hours later) and may extend into the following day (Verster et al., 2010). Clinically, the hangover state encompasses somatic discomfort (e.g., headache, nausea, gastrointestinal upset, thirst, muscle aches, and sensory hypersensitivity) together with cognitive alterations ranging from fatigue and drowsiness to impairments in attention, memory, and concentration (Penning et al., 2012). Furthermore, these symptoms are frequently accompanied by affective disturbances, including irritability, tension and negative mood (Alford et al., 2020).

Such short-term effects reflect multiple interacting biological processes occurring as ethanol is metabolized. In particular, the accumulation of alcohol metabolites, particularly acetaldehyde and acetate, promotes oxidative stress and inflammatory activation, with circulating biomarkers such as IL-6, TNF-α, and C-reactive protein correlating with symptom severity (van de Loo et al., 2020). Concurrent homeostatic

disturbances, including dehydration, electrolyte imbalance, and sleep disruption further exacerbate discomfort and cognitive slowing (Verster, 2008; Wiese et al., 2000). In parallel, the waning of ethanol-induced GABAergic potentiation may lead to a transient glutamatergic rebound and relative hyperexcitability, contributing to anxiety, restlessness and headaches during hangover (Palmer et al., 2019; Turner et al., 2024).

Behaviorally, these physiological disturbances translate into several cognitive alterations. Specifically, hangover has been consistently associated with reduced sustained attention, slower psychomotor speed, and impairments in working memory, episodic encoding, and higher-order executive functions (e.g., planning, decision-making, and cognitive flexibility) (Gunn et al., 2020; Ling, 2010; Scholey et al., 2019; Verster et al., 2003). Accordingly, individuals experiencing a hangover exhibit slower reaction times, increased attentional lapses, poorer working memory updating and higher error rates on tasks requiring cognitive control (Ayre et al., 2022; Devenney et al., 2019; Wolff et al., 2018).

Over time, repeated episodes of intoxication and hangover can cumulatively alter brain structure and function. Although epidemiological findings regarding light-to-moderate alcohol consumption remain mixed, sustained heavy alcohol use has been consistently associated with accelerated cognitive decline (Fernández-Solà, 2015; Jani et al., 2021; Rehm et al., 2021). In line with this, recurrent exposure to acetaldehyde, oxidative stress, and inflammatory signaling over months or years is thought to contribute to progressive neurodegeneration (Anand et al., 2022; Baliño et al., 2019; Kamal et al., 2020; Wu et al., 2003). Consequently, long-term heavy drinkers often display subtle cognitive impairments even when sober, including deficits in visuospatial processing, episodic and short-term memory, as well as executive functioning (Ioime et al., 2018; Stavro et al., 2012; Woods et al., 2016). Similarly, at a neuronal level, prolonged alcohol exposure has also been associated with persistent brain alterations, including reduced gray matter volume, metabolic disruption, and widespread neurotransmitter dysregulation (Bühler et al., 2011; Zahr et al., 2017).

With increasing frequency, intensity, and chronicity of alcohol exposure, neurobiological disruptions may lead to alcohol use disorder, producing profound and often irreversible brain damage (Zahr & Pfefferbaum, 2017). Long-term alcoholism is linked to widespread neuronal loss, particularly within frontal brain circuits (executive functions), limbic regions (memory, reward, and emotion), and the cerebellum (motor coordination) (Oscar-Berman et al., 2007). In this sense, these structural alterations underlie the classical neuropsychological profile of alcohol use disorder, that is, marked executive dysfunction, impaired memory,

slowed processing speed, and ataxia (Fama et al., 2021; Galandra et al., 2020; Maharjan et al., 2022; Mistarz et al., 2024). At an emotional level, alcohol use disorder individuals may exhibit generalized dysregulation, including aggression, anxiety, and reduced distress tolerance, reflecting limbic system disruptions (Garofalo et al., 2017; Stellern et al., 2022; Wołyńczyk-Gmaj et al., 2022; Zaorska et al., 2023).

1.1.2. Alcohol and the Young Brain

From a developmental perspective, alcohol consumption has been shown to exert more severe effects when initiated earlier in life (McCambridge et al., 2011), particularly during adolescence, a critical neurodevelopmental period characterized by substantial brain maturation, that extends into early adulthood (Lebel et al., 2019; Mills et al., 2016). At a structural level, the cortex reaches its maximal volume in early adolescence and thereafter undergoes synaptic pruning -the elimination of excess connections (Selemon, 2013)-, and myelination -the insulation of neural pathways (Corrigan et al., 2021)- throughout the teen years and beyond. Importantly, these maturational processes do not occur uniformly across brain regions but instead follow differential developmental trajectories, such that higher-order associative areas do not reach full structural and functional maturation until early adulthood. Limbic and subcortical regions involved in reward and emotion processing (e.g., the striatum, amygdala, nucleus accumbens) mature earlier and become highly reactive during early development (Foulkes et al., 2016), whereas the prefrontal cortex (PFC) -critical for planning, decision-making, and impulse control- matures later, typically into the mid-20s (Blakemore, 2012; Galvan et al., 2006). This developmental asynchrony gives rise to a neurobiological imbalance (Casey et al., 2010), in which reward-driven and socio-emotional systems are relatively mature before cognitive control systems are fully established (Steinberg, 2009).

In practical terms, adolescents exhibit heightened sensitivity to reward and novelty (Wahlstrom et al., 2010; Walker et al., 2017), while their top-down regulatory mechanisms are still developing (Casey et al., 2013) (Figure 1). This developmental profile is associated with an increased propensity for adolescent risk-taking, including experimentation with substances such as alcohol (Feldstein et al., 2006; LaSpada et al., 2020). Hence, the adolescent brain is primed to seek rewards and peer-related stimuli while its executive control system is immature (Albert et al., 2013). Given the substantial maturational changes occurring in the brain during this developmental stage, infrequent episodes of heavy alcohol use may have heightened effects on the developing brain during adolescence (Marshall, 2014; Zeigler et al., 2005). Accordingly, a single episode of heavy drinking has been shown to disrupt hippocampal function and impair memory consolidation

(Weafer et al., 2016; White, 2003). When such episodes are recurrent during adolescence or the transition to adulthood, they may interfere with synaptic refinement and white matter integrity, resulting in deviations from typical cortical maturation (Anton-Toro et al., 2024; Cservenka et al., 2017; Tetteh-Quarshie et al., 2023).

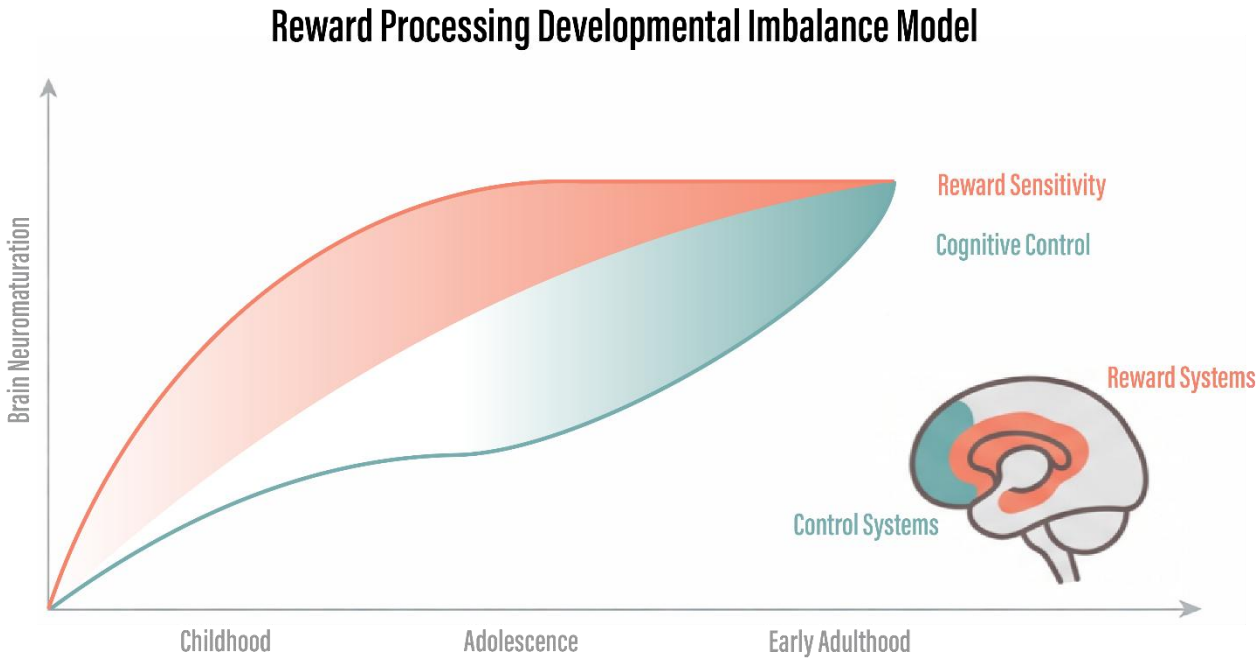


Figure 1. Developmental trajectories of reward sensitivity and cognitive control. Reward sensitivity increases rapidly from childhood and remains elevated during adolescence, whereas cognitive control develops more gradually into early adulthood. The imbalance between heightened reward sensitivity and still-maturing cognitive control during adolescence may contribute to increased risk taking.

In parallel, due to the heightened reward sensitivity and immature control systems, adolescence is also the developmental stage when alcohol use typically begins -ranging from casual experimentation to more hazardous patterns (Kuntsche et al., 2011)-. Notwithstanding, it is deeply embedded in youth culture, particularly during the transition to adulthood, where university settings often provide a social backdrop for heavy drinking (Siqueira et al., 2015; Weitzman et al., 2003). Social events (i.e., parties, sports games, and student traditions) frequently reinforce a culture in which excessive consumption is not only accepted but expected (Buettner et al., 2011; Marzell et al., 2015). Consequently, what often begins as sporadic, high-intensity consumption in social settings (for example, weekend heavy alcohol drinking) can gradually shift into more frequent and hazardous use (Addolorato et al., 2018). As tolerance develops and alcohol becomes a strategy for emotional coping, these patterns may extend beyond the social sphere and increase the risk of

progressing towards heavier patterns of consumption and, ultimately, alcohol use disorder over time (Herrero-Montes et al., 2022; Prince et al., 2019).

1.2. From Binge Drinking to Addiction

1.2.1. Binge Drinking

During adolescence and early adulthood, heavy or episodic drinking becomes especially evident. Among these, binge drinking represents one of the most prevalent forms of alcohol misuse in adolescents and young adults (Goings et al., 2019; Saldanha et al., 2025). In the literature, this pattern of alcohol consumption is commonly defined as recurrent episodes of heavy drinking, typically occurring once or more per month, interspersed with periods of abstinence. During these episodes, blood alcohol concentration typically reaches ≥ 0.08% following the consumption of at least five standard drinks for males (four or more for females) within a short period (typically within two hours), resulting in a subjective sense of intoxication (Maurage et al., 2020; Siqueira et al., 2015).

In the United States, binge drinking prevalence rises sharply throughout secondary school, reaching its highest levels during the college years. Several reports from the Monitoring the Future initiative indicate past-two-week binge drinking rates of approximately 2% for 8th-graders, 5.4% for 10th-graders, and 10.2% for 12th-graders (Miech et al., 2024). Among young adults, national data show that roughly 46.3% of full-time college students consumed alcohol in the past month, and approximately 27.9% reported past-month binge drinking (Center for Behavioral Health Statistics and Quality, 2023). Similarly, in Europe, recent surveys show that approximately 42% of high-school students consumed alcohol in the past month, with 30–37% reporting at least one episode of heavy drinking during that period, roughly double the rate observed among adults in many countries (European Union Drugs Agency, 2025). Eurostat (2021) further reported that, in 2019, about 22.3% of adults with upper-secondary to post-secondary education engaged in heavy episodic drinking at least once per month, with men (26.3%) being considerably more likely than women (11.4%). Highlighting the concerning impact of alcohol consumption, a recent study in the Portuguese population (Saldanha et al., 2025) provided a comprehensive description of alcohol consumption in university students, showing that more than 45% were hazardous drinkers, of whom roughly half were binge drinkers. Furthermore, this study highlighted that 1.5% of the students already fulfilled criteria for alcohol dependence.

Consequently, research on alcohol consumption during adolescence and youth has increasingly focused on binge drinking patterns and how the development of a systematic pattern of consumption might impact brain functioning. Neuroimaging studies have shown atypical gray matter metrics (i.e., volume and/or cortical thickness) in prefrontal and subcortical limbic regions of young binge drinkers (Howell et al., 2013; Infante et al., 2022; Lisdahl et al., 2013; Sousa et al., 2017, 2020), suggesting potential disruptions in self-control, emotional regulation, and reward sensitivity, a combination that can reinforce risky drinking patterns (Martín-Pérez et al., 2022; Murphy et al., 2012; Tang et al., 2015).

Functionally, young binge drinkers exhibit altered brain activity during cognitive tasks (e.g., attention, working memory, and response inhibition) as well as during resting-state conditions, indicating widespread dysregulation of both task-evoked and intrinsic networks (Affan et al., 2018; Antón-Toro et al., 2021; Correas et al., 2019; Folgueira-Ares et al., 2017; Holcomb et al., 2019; Lannoy et al., 2020; Molnar et al., 2018; Campanella et al., 2013). Notably, several studies describe a pattern of neurocompensation, whereby binge drinkers -despite comparable behavioral performance- recruit greater neural resources to achieve similar cognitive outcomes as non- or low-drinking peers, suggesting early or latent neural inefficiency (Correas et al., 2021; Jones et al., 2018; López-Caneda et al., 2012). Importantly, this compensatory pattern appears to depend on task demands, with hyperactivation typically reported in tasks with substantial executive demands, suggesting increased recruitment of executive control processes (Gil-Hernandez et al., 2017; Kashfi et al., 2017; López-Caneda et al., 2012). In contrast, tasks placing lower demands on executive functioning -such as those involving emotional or reward processing- are more often associated with attenuated neural responses, even in the absence of behavioral differences (Cohen-Gilbert et al., 2017; Cservenka et al., 2015; Maurage et al., 2013). In addition, young binge drinkers consistently exhibit heightened attentional bias toward alcohol-related cues (Almeida-Antunes et al., 2022; Cservenka et al., 2017; Petit et al., 2012), as well as increased BOLD activation to alcohol stimuli in regions involved in visual processing, pointing to heightened motivational salience of these cues (Nguyen-Louie et al., 2018).

1.2.2. The continuum hypothesis

Concurrently, these neural correlates may evolve with the escalation of consumption (Jones et al., 2018), alongside emerging structural alterations (Tetteh-Quarshie et al., 2023). Eventually, as alcohol use becomes more severe and pathological, neurocompensatory mechanisms appear to diminish, while hypoactivation and behavioral deficits become more prominent, accompanied by more pronounced structural

changes (Cao et al., 2023; Galandra et al., 2018; Roberge et al., 2025). For instance, heavy drinkers make more errors and show reduced frontal brain activation during Go/No-Go tasks compared to light drinkers (Ahmadi et al., 2013). Similarly, binge drinkers exhibit attenuated theta and delta oscillations during motor inhibition tasks, reflecting neural deficits in response inhibition akin to those seen in alcohol-dependent patients (López-Caneda et al., 2017). Impaired response inhibition is considered a core feature of alcohol use disorder (Gerhardt et al., 2021), and, from this perspective, the literature supports the notion of a continuum between binge drinking and alcohol use disorder in terms of brain alterations.

The continuum hypothesis is used in two related ways to describe links between binge drinking and severe alcohol use disorders (Figure 2). First, it denotes a continuum of consumption patterns, that is, binge drinking is seen as placing individuals at greater risk of progressing toward more severe, dependence-like drinking than light or moderate use (Lowe, 2019). Second, it denotes a continuum of impairments, particularly, binge drinkers may show qualitative cognitive, emotional, and neural deficits that resemble those observed in people with severe alcohol use disorder (Gowin et al., 2021; MacKillop et al., 2022; Waszkiewicz et al., 2018), notwithstanding whether their drinking pattern ultimately escalates to dependence per se (King et al., 2021; Patrick et al., 2021). In fact, binge drinkers´ consumption cycle between high consumption and withdrawal has been shown to have a significant impact on cognitive and neurofunctional levels, similar to those observed in alcohol use disorder (Arienzo et al., 2020; Maurage et al., 2012; Waszkiewicz et al., 2018). Some behavioral findings even suggest premature aging of specific cognitive capacities in young binge drinkers, consistent with the notion that binge patterns accelerate decline in processes that are central to addiction vulnerability (Hermens et al., 2013; Luciana, 2020). Overall, these data support the idea that binge drinking does not simply produce temporary impairments that can be recovered, but rather that it can lead to lasting deficits that situate it within the broader spectrum of alcohol-related brain alterations.

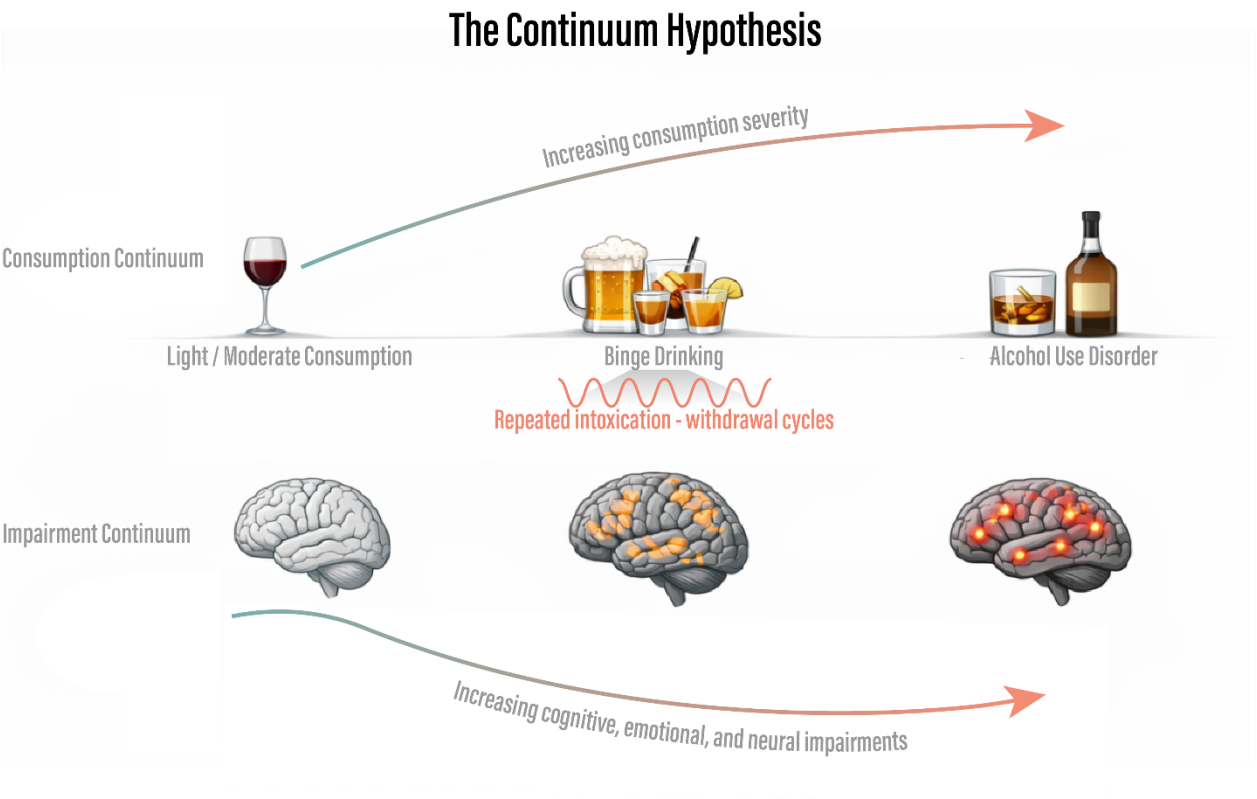


Figure 2. The Continuum Hypothesis. Schematic representation of the progression from light/moderate alcohol consumption to binge drinking and alcohol use disorder. Increasing consumption severity is accompanied by repeated intoxication–withdrawal cycles and increasing cognitive, emotional, and neural impairments.

1.2.3. Alcohol Use Disorder

At the extreme end of this continuum of alcohol consumption lies alcohol use disorder, a clinical syndrome that encompasses the most impairing and persistent forms of alcohol misuse. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), alcohol use disorder is defined as a problematic pattern of alcohol use leading to clinically significant impairment or distress (American Psychiatry Association [APA], 2013). This disorder is diagnosed based on multiple criteria (e.g., loss of control, tolerance) and can be mild, moderate, or severe, depending on the number of symptoms present. The DSM-5 combined the prior abuse and dependence categories into a single alcohol use disorder diagnosis, requiring at least 2 of 11 symptoms within a 12-month period (Agabio et al., 2023). Key criteria include impaired control (e.g., drinking larger amounts or longer than intended, persistent desire or unsuccessful efforts to cut down), social/occupational impairment (failure to fulfill major role obligations), risky use (recurrent drinking in

physically hazardous situations), and pharmacological criteria (tolerance and withdrawal) (Agabio et al., 2023; APA; 2013; Volkow et al., 2023).

From a functional approach, repeated alcohol use dysregulates reward and stress pathways (Blain et al., 2012; 2016; Cavicchioli et al., 2018; Koob et al., 2023). Specifically, alcohol initially boosts dopamine signaling and opioidergic activity whitin mesolimbic circuits, thereby reinforcing drinking behavior (Nutt, 2014; Söderpalm et al., 2011; Volkow et al., 2019). Over time, however, reward system function becomes blunted (Arias et al., 2021; Tunstall et al., 2017), and brain stress systems become increasingly overactive (Anthenelli, 2012; Guinle et al., 2020; Koob et al., 2023). These dysregulations in both the reward circuitry and stress regulation, together with a maladaptive association between alcohol consumption and negative affect relief, promote further consumption and deepen dependency (Stasiewicz et al., 2013; Guinle et al., 2020; Wang et al., 2022). As a result, chronic alcohol use may lead to widespread neurocognitive deficits and alterations in brain function (Pervin et al., 2021; Sullivan et al., 2023; Wang et al., 2023). In this vein, neuropsychological studies consistently show that individuals with alcohol use disorder exhibit multiple cognitive impairments, particularly in executive functions, episodic memory, and visuospatial abilities, reflecting alterations in frontal, temporal, and cerebellar circuits (Fama et al., 2021; Maharjan et al., 2022; Pandey et al., 2018; Rice et al., 2024). For instance, alcohol abuse leads to shrinkage of the PFC and hippocampal volume, reducing working memory, planning, and inhibitory control (Bernardin & Maheut-Bosser, 2014). Moreover, these cognitive deficits seem to be maintained even during early abstinence (Kopera et al., 2012; Stavro et al., 2013), with many showing poor executive functioning, affecting problem-solving and learning (Burhanoglu et al., 2014; La Berre et al., 2017; Martelli et al., 2017). This not only emphasizes alcohol's impact on the brain, but also the everlasting markers this chronic problem leaves behind.

Despite the significant cognitive and neurobiological consequences outlined above, available treatments for alcohol use disorder remain limited in their overall effectiveness (Heilig et al., 2024). Relapse rates remain worrying, with approximately half of patients relapsing within the first year of treatment and close to 70% doing so within three years (Witkiewitz et al., 2021). Concurrently, one of the major factors contributing to relapse is alcohol craving, which is widely recognized in the literature as a hallmark of alcohol abuse and addiction (Hormes, 2017; Ray et al., 2018; Schneekloth et al., 2012; Seo et al., 2014).

1.2.3.1. Craving as a hallmark of alcohol addiction

Alcohol craving is typically defined as a powerful urge or desire to consume alcohol (Sinha, 2013). It has been described as a multidimensional phenomenon encompassing cognitive, emotional and physiological components (Noël et al., 2013). Cognitively, craving involves intrusive alcohol-related thoughts and attentional biases toward alcohol cues; emotionally, it is often elicited by stress, anxiety, or negative affect and can be reinforced by expectations of pleasure or relief; physiologically, craving is accompanied by autonomic arousal (e.g. increased heart rate, sweating) and withdrawal-like sensations reflecting homeostatic dysregulation (Bernard et al., 2021; Field et al., 2013; Heinz et al., 2009; Seo et al., 2014; Verheul et al., 1999). These components interact dynamically, such that attentional bias and expectancy processes amplify subjective urge (Ciccarelli et al., 2022; Field et al., 2008; Jones et al., 2012), stress system activation increases motivational drive (Belujon et al., 2011; Koob, 2009; Sinha et al., 2009), and bodily arousal reinforces the craving experience (Naqvi et al., 2009; Wang et al., 2019). Consequently, alcohol craving tends to reinforce cognitive disruptions, giving emphasis to perception bias and attentional allocation toward alcohol stimuli, as well as undermining inhibitory control towards the consumption itself (Bernard et al., 2021; Christiansen et al., 2016; Flaudias et al., 2019).

At the neural level, craving consistently engages reward and salience-related regions and their regulation by prefrontal control systems (Tanabe et al., 2019). Alcohol cues reliably activate mesocorticolimbic structures, including the ventral striatum, anterior cingulate cortex, and ventromedial prefrontal cortex, which encode incentive value and motivational relevance (Alba-Ferrara et al., 2016; Koopmann et al., 2019; Schacht et al., 2013; Vollstädt-Klein et al., 2012). In addition, the insula is also consistently implicated, reflecting its role in integrating interoceptive signals and linking subjective urge to bodily states (Campbell et al., 2021; Jakubczyk et al., 2020; Huang et al., 2018). Consequently, theoretical models have sought to explain how these processes give rise to persistent craving and compulsive alcohol use.

One of the most influential models is the Incentive-Sensitization Theory (Figure 3a), proposed by Robinson and Berridge (1993; Berridge & Robinson,1998), suggests that repeated exposure to addictive substances produces long-lasting sensitization of mesolimbic dopamine systems. This sensitization selectively enhances the attribution of incentive salience (“wanting”) to alcohol-related cues, even as the hedonic effects (“liking”) of alcohol diminish with repeated use (Berridge & Robinson, 1998; Berridge et al., 2007). Within this framework, craving reflects the amplification of cue-triggered motivation. That is, alcohol-associated

stimuli acquire excessive motivational value, becoming powerful elicitors of approach behavior and subjective urge, independent of actual reward. Importantly, incentive sensitization explains why craving can persist after prolonged abstinence and why craving may be dissociated from conscious pleasure or positive reinforcement (Robinson & Berridge, 2025). Accordingly, neuroimaging findings showing heightened striatal and insular responses to alcohol cues in individuals with alcohol misuse are consistent with this theory (Koopmann et al., 2019; Vollstädt-Klein et al., 2012).

Building on these motivational mechanisms, the Impaired Response Inhibition and Salience Attribution (iRISA) model (Figure 3b; Goldstein & Volkow, 2002; Zilverstand et al., 2018) emphasizes the interaction between exaggerated salience attribution and impaired cognitive control. According to this model, chronic alcohol use leads to enhanced valuation of alcohol-related cues, reduced valuation of alternative non-drug rewards, and deficits in inhibitory control processes (Acuff et al., 2024; Bickel et al., 2014; Hildebrandt et al., 2021). Subsequently, neuroimaging studies have supported this imbalance, showing increased reactivity to alcohol cues in limbic and prefrontal regions alongside reduced engagement of inhibitory control regions during tasks requiring inhibition or executive control (Garavan et al., 2007; Hester et al., 2009; Kaufman et al., 2003; Nestor et al., 2011). Meta-analytic evidence further indicates persistent under-activation of prefrontal regions, including the middle and superior frontal gyri and dorsal anterior cingulate cortex, as well as dysregulated striatal responses during reward processing in individuals with alcohol use disorder, even following abstinence (Roberge et al., 2025). Moreover, disrupted functional connectivity between the ventral striatum and ventromedial prefrontal cortex has also been reported, suggesting weakened integration between bottom-up reward signals and top-down valuation (Dugré et al., 2023). Thus, in the iRISA framework, craving reflects both heightened motivational pull of alcohol cues and reduced capacity to regulate that pull. The subjective urge to drink is therefore intensified not only by salience attribution but also by impaired executive control over alcohol-seeking behavior.

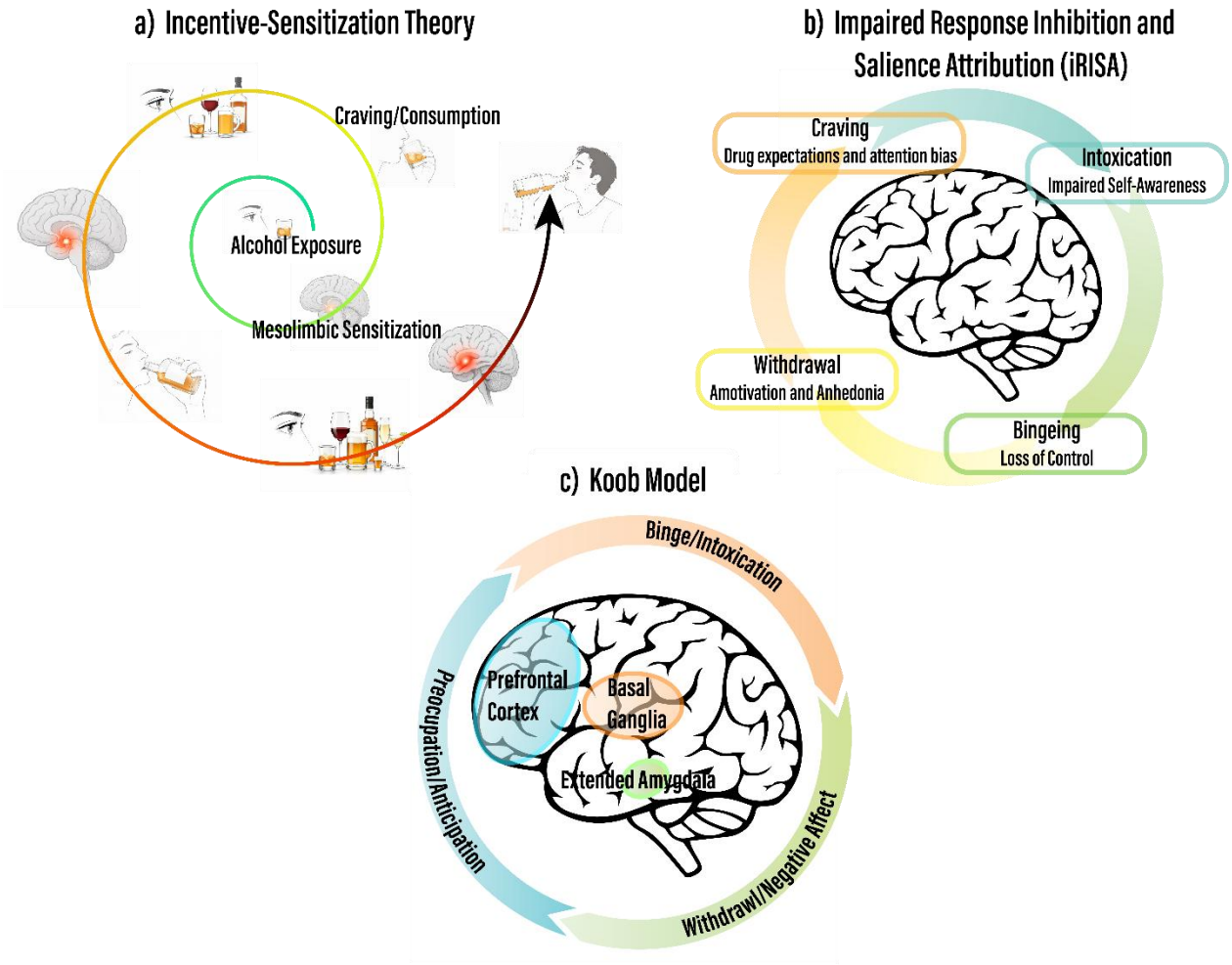


Figure 3. Theoretical models of alcohol craving and alcohol use disorder. a) Incentive-Sensitization Theory: repeated alcohol exposure is depicted as leading to mesolimbic sensitization, which increases the motivational impact of alcohol-related cues. In the model, alcohol exposure, craving/consumption, and sensitization form a recurring cycle, illustrating how alcohol cues may progressively amplify craving and further alcohol use; b) Impaired Response Inhibition and Salience Attribution (iRISA) model: the iRISA model is shown as a cycle linking drug-cue expectations and attention bias, intoxication and impaired self-awareness, bingeing and loss of control, and withdrawal/anhedonia. The figure emphasizes the interaction between heightened salience of alcohol-related cues and impaired regulatory processes in the maintenance of alcohol use; c) Koob model. Koob's model is presented as a three-stage addiction cycle comprising binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. The figure maps these stages onto basal ganglia, extended amygdala, and prefrontal cortex systems, illustrating how reward, negative affect, and anticipatory processes contribute to recurring alcohol use.

More recent models proposed by Koob and colleagues extend these accounts by situating craving within a broader cycle of neuroadaptation involving reward and stress systems (Figure 3c; Koob & Le Moal, 1997; Koob, 2009; Koob et al., 2016). From an allostatic framework, it describes addiction as a progressive shift from positive reinforcement toward negative reinforcement. That is, repeated alcohol use leads to

downregulation of reward circuitry and recruitment of stress-related systems, including the extended amygdala, resulting in a chronic dysphoric state during withdrawal and abstinence. In this context, craving increasingly reflects the motivation to alleviate negative affect and stress rather than to obtain pleasure. Koob and collegues (2016) describe two interacting systems, a subcortical reward/salience circuit, involving dopaminergic projections to the ventral striatum and extended amygdala, and a cortical control circuit, comprising prefrontal regions and the anterior cingulate cortex that normally regulate urges via top-down control. Concurrently, chronic alcohol use weakens this control network, while stress responsivity becomes sensitized, particularly during withdrawal (Quadros et al., 2016; Vendruscolo et al., 2020). As a result, craving is strongly provoked by negative emotional states and stress, consistent with clinical observations of relapse during periods of distress (Sinha et al., 2009).

Although differing in emphasis, these models converge on a shared account of craving as the central driver of alcohol addiction. Incentive-sensitization highlights the amplification of cue-driven motivation, iRISA emphasizes the failure of inhibitory control over salient alcohol cues, and the allostatic model situates craving within stress-related negative reinforcement and dysregulated homeostasis. Empirical findings in alcohol misuse support this convergence, showing increased attentional bias toward alcohol cues alongside deficits in inhibitory control and heightened stress sensitivity (Bollen et al., 2021; Carbia et al., 2025; Grieder et al., 2022). Taken together, these frameworks position craving as the key mechanism through which alterations in reward processing, cognitive control, and stress regulation translate into compulsive alcohol use.

1.3. Memory, alcohol, and forgetting

Inhibitory control may both predict alcohol consumption and be impaired as a consequence of it (Antón-Toro et al., 2023; López-Caneda et al., 2013). A similar bidirectional relationship has been proposed for memory processes. Indeed, different memory subsystems are closely linked to alcohol use, both through impairments in short-term memory or through more complex interactions between episodic memories, alcohol craving, and the reinforcement of subsequent consumption (Carbia et al., 2017; Finn et al., 2004; Goldfarb et al., 2020; Meda et al., 2018; Peeters et al., 2014).

Memory encompasses multiple systems organized by timescale and function, extending from the initial sensory registers to more durable memory encoding (Atkinson et al., 1968; Squire, 2004). Sensory memory holds information for brief moments, particularly, visual inputs are briefly retained in iconic memory

for a fraction of a second, while auditory inputs can persist in echoic memory for a few seconds (Darwin et al., 1972; Irwin et al., 2008; Kinukawa et al., 2019). These sensory memories have high fidelity but decay rapidly unless attention selects them for further processing (Sligte et al., 2010). After sensory processing, attended information enters short-term memory, which maintains a limited amount of information for brief periods (typically seconds) enabling conscious access to current information but remaining inherently transient without sustained neural activity (Jonides et al., 2008). This temporary maintenance is commonly conceptualized within the framework of working memory, which not only sustains but also actively manipulates and updates information in short-term storage (Atkinson et al., 1971; Cowan, 2012), and has been described as comprising subsidiary components such as a phonological loop for verbal information and a visuospatial sketchpad for visual data (Baddeley, 2006; Baddeley et al., 2019).

Neurobiologically, working memory is mediated by a distributed network anchored in the PFC (Curtis & D'Esposito, 2003; Markowitz et al., 2015). In particular, the dorsolateral PFC is critically involved in the active maintenance and manipulation of information (Barbey et al., 2013), whereas ventrolateral and polar PFC regions contribute to the controlled updating and gating of memory content (Passingham et al., 2004; Segal et al., 2023). Posterior parietal cortex and the anterior cingulate are also engaged, providing attentional regulation, cue-based manipulation and organization, as well as response monitoring and error correction, respectively (Berryhill, 2012; Rushworth et al., 2003).

Once consolidated, long-term memory stores information over extended periods of time, being divided into implicit (non-declarative) memory -procedural skills and habits, such as riding a bicycle-, and explicit (declarative) memory which can be semantic (general facts and knowledge, e.g. knowing that Paris is the capital of France) or episodic (personal experiences, e.g. recalling a trip to Paris or a specific moment spent there) (Squire et al., 1992). Among explicit memory types, episodic memory refers to the recollection of personal experiences tied to specific times and places, enabling an individual to mentally re-experience past events with vivid detail and a sense of personal perspective (Tulvig, 1972; 1983). Basic models implicate the hippocampus as critical for episodic memory formation because it binds together the various elements of an experience (e.g., time, place, and people) into a coherent memory trace (Eichenbaum, 2017; Rolls, 2010; Tulvig et al., 1998). But, equally important, the PFC -particularly, the dorsolateral PFC- contributes by guiding strategic retrieval and monitoring of these memories (Eichenbaum, 2017; Van der Linden et al., 2000).

Ultimately, declarative memory may be understood as inherently associative. Through semantic memory, associations are formed between concepts —e.g., word-word pairings based on category (e.g. Dog-Cat; Apple-Pear) or part-whole relationships (e.g., Engine-Car; Leaf-Tree). In contrast, episodic memory supports the binding of contextual information/stimuli related to past events (e.g., remembering that plates are stored in a particular cabinet; associating an object with a particular emotional state; or linking events to dates). Accordingly, associative memory has been defined as a subsystem of declarative memory that binds two or more memories/items, such that the recall or recognition of one element can trigger retrieval of the entire representation (Mayer et al., 2007).

1.3.1. Working memory and alcohol use

Working memory relies on prefrontal and frontoparietal control networks which, as previously described, are particularly vulnerable to the effects of alcohol (Abernathy et al., 2010; López-Caneda & Martínez, 2013). This cognitive function supports active maintenance, updating, and manipulation of task-relevant information and plays a central role in higher-order cognitive control by enabling individuals to maintain goal representations, resist distraction, and flexibly adjust behavior (Baddeley, 2012; D'Esposito & Postle, 2015; Miller & Cohen, 2001). Consequently, alcohol-related impairments in working memory may not only reflect underlying neural dysfunction but may also reduce the capacity to regulate intrusive alcohol-related thoughts and urges, thereby facilitating craving-driven behavior (Brewin et al., 2010; May et al., 2015).

Research has consistently shown that even moderate levels of alcohol intoxication impair working memory performance, particularly when tasks place high demands on executive function and continuous updating rather than simple maintenance (Cofresí et al., 2021; Spinola et al., 2022). These effects are thought to reflect diminished top-down control efficiency and reduced attentional stability, compromising the ability to sustain and update representations over time (Miller & Cohen, 2001; Gazzaley & Nobre, 2012). Beyond acute intoxication, alcohol-related cognitive alterations can persist into post-intoxication states. Studies of next-day performance following heavy drinking indicate that cognitive functioning may remain impaired during the hangover state, even after blood alcohol concentration has returned to zero (Gunn et al., 2018; Prat et al., 2008; Scholey et al., 2019; Verster, 2008). Impairments in executive functioning and working memory have been reported during hangover, with poorer performance correlating with hangover severity (Scholey et al., 2019), alongside slowed processing speed and reduced executive control (Gunn et al., 2018). Consequently, hangover-related attentional lapses and cognitive slowing may reduce working

memory updating capacity, weakening cognitive control in everyday situations requiring regulation of behavior and mental content.

In individuals who engage in systematic and hazardous alcohol consumption, working memory alterations are more often evident at the neurofunctional level than in overt behavioral performance. In particular, neuroimaging studies frequently report compensatory or inefficient recruitment patterns during working memory tasks, whereby hazardous drinkers show increased activation in prefrontal and parietal regions despite comparable task accuracy (Campanella et al., 2013). Complementary electrophysiological evidence similarly indicates enhanced neural activity during working memory processing in hazardous drinkers, consistent with reduced processing efficiency rather than preserved function (Schroder et al., 2019), aligning with the notion of neurocompensation. Moreover, binge drinkers have been shown to exhibit altered activation profiles alongside reduced functional differentiation between task conditions during working memory tasks (Crego et al., 2009, 2010; López-Caneda et al., 2013).

Importantly, developmental and longitudinal research in adolescents and young adults has indicated that brain responses during working memory tasks change over time as a function of drinking patterns, supporting the notion that alcohol use may interfere with the typical developmental refinement of frontoparietal control networks (Squeglia et al., 2012). As alcohol use becomes more severe and persistent, working memory alterations extend beyond changes in activation magnitude to involve broader disruptions in the organization and integration of control networks. In alcohol use disorder, neuroimaging studies indicate altered engagement of working memory regions and disrupted functional connectivity between prefrontal and parietal areas, consistent with a reorganization of frontoparietal control systems (Park et al., 2010; Pfefferbaum et al., 2001; Tapert et al., 2006). Comparisons across the drinking continuum further suggest that working memory capacity limits and load-dependent neural recruitment differ between controls, non-dependent heavy drinkers, and individuals with alcohol use disorder, indicating a progressive reduction in the efficiency of working memory networks as alcohol misuse escalates (Wesley et al., 2017).

Finally, working memory is not only affected by alcohol use but can also influence alcohol-related memory processes. Experimental evidence indicates that imposing high working memory load prior to memory retrieval can interfere with the reconsolidation of alcohol-related memories in heavy drinkers, highlighting the close interaction between cognitive control resources and alcohol-memory dynamics (Kaag et al., 2017). This bidirectional relationship underscores the relevance of working memory within broader

models of addiction, in which compromised executive control both results from and contributes to the persistence of maladaptive alcohol-related thoughts and behaviors (Hofmann et al., 2008; Thush et al., 2008).

Taken together, these findings indicate that alcohol-related alterations in working memory reflect broader disruptions in cognitive control systems that regulate access to internal mental content. However, impairments in control mechanisms alone are insufficient to explain the persistence of alcohol-related thoughts, craving, and relapse risk. Equally important is the nature of the memory representations themselves, particularly how alcohol-related information is encoded, bound, and retrieved. Thus, beyond deficits in working memory and executive control, it is necessary to consider how alcohol use alters associative memory processes that link alcohol-related cues, contexts, and outcomes.

1.3.2. Associative memory and alcohol use

Beyond deficits in executive control, research has begun to highlight the relevance of memory associations in alcohol use; however, the way these associative memory processes shape the encoding and retrieval of drinking-related experiences remains less clearly characterized. Research has shown that acute alcohol consumption impairs memory recall, while alcohol-related stimuli tend to be more resistant to this impairment (Nguyen-Louie et al., 2016; Ray et al., 2006). Moreover, evidence suggests that alcohol intoxication impairs associative memory significantly more than item memory (Maylor et al., 2018), but little is known about how hazardous drinkers remember drinking episodes when sober, and what emotional valence these memories carry. Nonetheless, recent research suggests that individuals with alcohol use disorder show impaired free and associative recall compared to moderate drinkers; however, this impairment appears to be attenuated when the associations are alcohol-related (Goldfarb et al., 2020), aligning with research indicating a prioritization of drug-related memories in addiction (Robbins et al., 2008). Concurrently, as previously described, classic models such as the incentive-sensitization theory propose that drug-associated cues acquire motivational salience through repeated pairing with alcohol's effects, such that encountering these cues can trigger the retrieval of alcohol-related memories and elicit a powerful motivational state, namely craving (Robinson et al., 1993, 2025).

Craving in alcohol use can be understood from a memory-based perspective, whereby alcohol-related cues (e.g., contexts, sights, smells, or thoughts) automatically reactivate learned associations between drinking and its rewarding or relieving outcomes (Pickering et al., 2003; Rose et al., 2013; Verheul et al.,

1999). In this view, craving arises when alcohol-related memories evoke episodic representations of drinking (e.g., celebrating with friends), activating reward circuitry and "wanting" systems (Berridge et al., 2016; Franken et al., 2003). Consequently, persistent alcohol-related memories are thought to sustain the cycle of substance use through unintentional recall upon exposure to associated cues, triggering craving that leads to further consumption and, in turn, strengthens the link between the cue and alcohol intake (Lüscher et al., 2020; Milton et al., 2012; Wise et al., 2014).

Thus, if craving arises largely from the spontaneous retrieval of alcohol-related memories, it becomes essential to examine the extent to which individuals with addictive behaviors -including binge and hazardous drinking- are able to suppress such memories. Understanding this ability, along with the cognitive and neural mechanisms that support it, offers a more integrated framework for explaining how certain mental contents can be maintained, attenuated, or blocked, and how these processes shape the emergence of craving and vulnerability to drinking.

1.3.3. Memory Inhibition and Alcohol Use

Memory inhibition, also referred to as memory suppression, is defined as the intentional process of preventing unwanted memories from entering conscious awareness, thereby leading to subsequent impairments in recall (Anderson & Hulbert, 2021). This ability, which has been proposed to draw on mechanisms similar to those involved in motor inhibition (Wessel & Anderson, 2024), is commonly investigated using the Think/No-Think (TNT) paradigm (Anderson & Green, 2001), a memory adaptation of the classical Go/No-Go task typically used to study the suppression of motor responses (Huster et al., 2013). In this task, participants first learn cue-target associations (e.g., words or images), after which cues are presented under either a "Think" or "No-Think" condition. During Think trials, participants are instructed to retrieve the associated target, whereas during No-Think trials they must actively prevent the target from entering awareness. Critically, items that are repeatedly suppressed in No-Think trials are later recalled less accurately than baseline items, a phenomenon known as suppression-induced forgetting (Anderson & Green, 2001; Marsh & Anderson, 2022). This effect has been robustly replicated across numerous studies, highlighting the capacity to voluntarily exert control over memory retrieval and thus modulate the accessibility of unwanted memories (Anderson et al., 2025; Anderson & Levin, 2009).

At the neural level, the ability to suppress memories and thoughts has been linked to top-down regulatory mechanisms. Neuroimaging studies consistently show that prefrontal regions, particularly the

dorsolateral PFC and inferior frontal cortex, exert inhibitory influences over memory-related areas such as the hippocampus and posterior cortical regions, thereby limiting the retrieval of unwanted representations (Aron, 2007; Detre et al., 2013; Dieler et al., 2010). In this sense, memory suppression appears to recruit neural mechanisms analogous to those involved in motor inhibition, engaging a "stop signal"-like process that interrupts ongoing retrieval (Castiglione et al., 2019; Wessel & Anderson, 2023). Importantly, these neural dynamics have been observed across different types of material, extending beyond neutral word lists to emotionally salient images and autobiographical events (De Vito et al., 2017; Dieler et al., 2010; Lambert et al., 2010; López-Caneda et al., 2019; Murray et al., 2011; Simeonov et al., 2022). Taken together, these findings suggest that memory suppression relies on domain-general control systems that may be particularly relevant for mental health, especially in contexts involving intrusive or maladaptive thoughts (Nørby, 2015, 2018).

Notably, deficits in memory suppression have been documented in clinical conditions, particularly those characterized by intrusive and recurrent thoughts (Stramaccia et al., 2021). For example, individuals with post-traumatic stress disorder, depression or obsessive-compulsive disorder show reduced suppression of negative memories (Catarino et al., 2015; Demeter et al., 2014; Geraerts et al., 2007; Joorman et al., 2005; Sullivan et al., 2019). In this context, and given the central role of intrusive, substance-related memories in addiction (Bernard et al., 2021; Moss et al., 2015), there is growing interest in whether similar alterations in memory suppression mechanisms may also be present in substance use disorders. To date, however, this question remains relatively underexplored. Theoretical accounts suggest that deficits in memory inhibition may exacerbate addictive behaviors, as a reduced ability to suppress intrusive alcohol-related thoughts could facilitate craving and increase the risk of relapse (Almeida-Antunes et al., 2024; Bernard et al., 2021; López-Caneda & Almeida-Antunes, 2025).

In line with this, neurobiological models of addiction (e.g., the Koob-Volkow three-stage model; Koob & Volkow, 2016) propose that the anticipation stage is characterized by heightened salience of drug-related memories and impaired executive (prefrontal) control. During this stage, drug cues strongly engage hippocampal memory systems and limbic regions such as the amygdala, while top-down regulatory prefrontal control is weakened (Koob et al., 2016; Kutlu et al., 2016, Lüscher et al., 2020). Empirical evidence further shows that alcohol-related cues reliably elicit brain responses in memory- and control-related brain regions in

heavy drinkers (Kreusch et al., 2015; Ray et al., 2018) and can involuntarily trigger alcohol-related memories that contribute to craving (Kohen et al., 2023; Pina et al, 2016; Witteman et al., 2015).

Despite this growing body of work, the role of memory suppression in alcohol use remains poorly understood (Almeida-Antunes et al., 2024). While previous research has extensively examined executive control deficits and cue-reactivity in addiction, far less attention has been paid to the ability to intentionally regulate alcohol-related memories (van der Plas et al., 2008; Witteman et al., 2015). This gap is particularly relevant given that intrusive, substance-related memories are thought to play a central role in craving and relapse (Vafaie & Kober et al., 2022). Accordingly, investigating whether individuals with problematic alcohol use show alterations in memory suppression processes may provide novel insights into the cognitive mechanisms underlying addiction and inform the development of targeted interventions.

In this context, López-Caneda et al. (2019) adapted the TNT paradigm to alcohol-related content, developing the Think/No-Think Alcohol task. This paradigm examines whether individuals can exert top-down control specifically over alcohol-related memories by cuing alcohol versus non-alcohol representations and instructing participants either to retrieve or suppress them. Conceptually, the Think/No-Think Alcohol extends the suppression-induced forgetting effect observed with neutral stimuli to motivationally salient content, such as alcohol-related cues. Consistent with this, electrophysiological markers associated with successful suppression (e.g., reduced late parietal positivity and enhanced frontal slow-wave activity) suggest decreased conscious recollection and increased engagement of control processes when alcohol memories are successfully inhibited (López-Caneda et al., 2019).

More recently, Almeida-Antunes and colleagues (2024) applied the Think/No-Think Alcohol paradigm to examine memory inhibition in young binge drinkers. Compared to light drinkers, binge drinkers showed impaired suppression of non-alcohol-related memories alongside altered brain functional connectivity. Specifically, when trying to suppress neutral (non-alcohol) pairs, binge drinkers exhibited reduced alpha-band connectivity between the anterior cingulate cortex and the fusiform gyrus, accompanied by a failure to forget these items. In contrast, when suppressing alcohol-related pairs, binge drinkers showed increased gamma-band connectivity between the inhibitory-control network and medial temporal memory regions (namely, hippocampus, parahippocampus, and fusiform gyrus), suggesting increased cognitive effort in response to highly salient alcohol cues, possibly reflecting heightened attention to intrusive alcohol-related memories and compensatory attempts to overcome control deficits.

In summary, converging evidence highlights the central role of memory processes in alcohol use, encompassing alterations in executive control, working memory, and episodic associative memory, particularly in the context of alcohol-related cues. These processes are closely linked to the salience and persistence of alcohol-related memories, which can contribute to craving and the maintenance of maladaptive consumption patterns. Emerging findings further suggest that the ability to exert control over such memories through suppression mechanisms may also be altered in individuals with hazardous drinking patterns. However, despite these advances, important questions remain regarding how these memory processes interact across different stages and states of alcohol use, from binge drinking and acute post-intoxication states (hangover) to alcohol use disorder, and how factors such as the emotional and motivational valence of alcohol-related memories influence their accessibility and regulation. Addressing these issues is critical for advancing our understanding of the cognitive and neurobiological mechanisms underlying alcohol misuse.

1.4. The Present Work

1.4.1. Aims of the Present Thesis

Taken together, these considerations establish a clear rationale for studying the impact of alcohol on memory processes and brain function across the continuum of alcohol use. Accordingly, the objective of the present work is to advance understanding of how different patterns of alcohol consumption, ranging from binge drinking and hangover states to alcohol use disorder, affect and modulate working memory (both short-term and long-term), associative episodic memory in alcohol-related contexts, and the capacity for intentionally suppressing alcohol-related memories. By examining the neural mechanisms supporting these processes, this work aims to clarify how altered memory dynamics interact with subjective alcohol craving to sustain and perpetuate hazardous alcohol consumption.

Taking into account the body of literature reviewed in this chapter, several research questions were identified, and the following specific aims were formulated to address them. These aims are examined across the empirical studies presented in Part III (Empirical Studies) of this dissertation.

Specific Aims:

1. To develop and validate a measure of acute alcohol craving for the Portuguese population. (Chapter 3)

2. To investigate the short-term impact of alcohol intoxication in executive functioning, particularly working memory processes, and to distinguish these effects from longer-term alterations associated with the neurotoxic effects of alcohol consumption. (Chapter 4)
3. To examine and compare the neurofunctional mechanisms underlying alcohol-related memory processing in healthy controls and binge drinkers, and to determine how these mechanisms interact with alcohol consumption. (Chapter 5)
4. To evaluate how alcohol use disorder affects memory inhibition processes and to characterize the associated neurofunctional signature of alcohol-related memory suppression. (Chapter 6)

1.4.2. Hypotheses of the Present Thesis

Based on the literature reviewed above, the present thesis was guided by a set of hypotheses concerning alcohol-related memory processes across the continuum of alcohol use. Overall, it was hypothesized that alcohol misuse would be associated with alterations in memory and cognitive control, especially in the context of alcohol-related or motivationally salient information.

1. The Portuguese version of the Alcohol Craving Questionnaire – Short Form – Revised would show adequate psychometric properties, preserving a multidimensional structure and demonstrating satisfactory reliability and validity, thereby constituting an appropriate instrument for the assessment of acute alcohol craving in Portuguese-speaking samples.
2. Acute post-intoxication effects and habitual binge drinking would be associated with alterations in attentional allocation and working memory processing. In particular, it was expected that these alterations would be detectable at the electrophysiological level (P3 and LPC) even in the absence of behavioral performance alterations, consistent with the notion of early neurofunctional disruption and compensatory recruitment.
3. Alcohol-related associative memory retrieval would differentially engage neural systems involved in salience, reward, and memory processing, particularly in binge drinkers. Specifically, it was expected that alcohol-related associations would show enhanced motivational relevance and recruit these systems more strongly in binge drinkers than in control participants.
4. Alcohol use disorder would be associated with impairments in the intentional suppression of unwanted memories, particularly when those memories were alcohol-related. Along with these behavioral alterations, it was hypothesized that individuals with alcohol use disorder would show

altered neurofunctional connectivity in networks supporting inhibitory control, salience/reward processing, and memory regulation, including altered coupling between prefrontal control regions and memory-related medial temporal areas, reflecting reduced efficiency in the suppression of alcohol-related memories.

In sum, these hypotheses reflect the broader expectation that alcohol-related memories become progressively more salient, more strongly encoded in motivationally relevant neural systems, and more difficult to regulate as alcohol misuse becomes more severe.

1.4.3. Structural Organization of the Thesis

The first part of the present thesis (Part I: Introduction) provides the theoretical framework that underpins the dissertation and establishes the general and specific aims guiding the empirical work. This section reviews the relevant literature on alcohol use, memory, craving, and associated neurocognitive mechanisms, thereby defining the conceptual basis and research questions addressed in the subsequent chapters.

The second part of the current thesis (Part II: Method) summarizes the methodologies employed throughout this thesis to explore the aims defined above. The characteristics of each population studied are defined, tasks used are briefly described, and neurocognitive tools used across the studies are presented. Additionally, the neurofunctional techniques employed are briefly described (Chapter 2: General Methodology).

Following the methodological introduction, the third part of this dissertation (Part III: Empirical Studies) comprises four empirical studies conducted during my doctoral training, which, as outlined previously, are designed to address and provide empirical answers to the specific aims enumerated above. Although alcohol craving has been widely studied, there remains a lack of validated instruments assessing acute subjective alcohol craving in the Portuguese population. Chapter 3 addresses this gap by presenting a translation and validation of a questionnaire that assesses acute alcohol craving (Chapter 3: *Portuguese Validation of the Alcohol Craving Questionnaire – Short Form – Revised*). Given that alcohol craving is systematically described as being a cornerstone on addiction, and a strong predictor of relapse in alcohol use, this study aimed to develop a culturally adapted and psychometrically sound instrument capable of capturing fluctuations in acute craving. Hence, the hypothesis was that the translated scale would replicate

the original multidimensional factor structure, show good internal consistency and validity, and correlate positively with established measures of hazardous drinking and impulsivity, thereby providing the practical tool needed to test links between subjective craving and neural measures in subsequent chapters.

The second empirical study aimed to explore both the short and long-term effects of binge drinking on executive functioning, with a particular focus on working memory and attention (Chapter 4: *The Day After Binge: Electrophysiological correlates of attention and working memory processing the day after hazardous alcohol intake*). The primary aim of this study was to characterize short-term neurocognitive alterations associated with hangover and to contrast them with more stable alterations related to habitual binge drinking. Using electrophysiological measures, this chapter tested the hypothesis that hangover would be associated with reduced P3/LPC amplitudes and slower behavioral performance, reflecting alterations in attention and working memory, whereas habitual binge drinking would be associated with altered baseline event-related potential (ERP) profiles consistent with compensatory neural activity. It was further hypothesized that both acute and longer-term electrophysiological alterations would be associated with higher levels of subjective alcohol craving and greater indices of hazardous alcohol use.

The third empirical study investigated the neurofunctional underpinnings of associative memory in alcohol-related contexts (Chapter 5: *Associative memory in alcohol-related contexts: An fMRI study with young binge drinkers*). The aim of this study was to examine how associative memory retrieval differs between binge drinkers and alcohol-abstainers when recalling alcohol-related and neutral information. Specifically, the study tested the hypothesis that associative recall of alcohol-related items would preferentially engage reward- and memory-related neural networks in binge drinkers, including striatal and medial temporal regions, relative to abstainers. It was further hypothesized that the magnitude of alcohol-related associative memory activation would be positively associated with measures of consumption severity.

The final experimental study focused on memory inhibition processes in individuals with alcohol use disorder (Chapter 6: *Forgetting Alcohol: Brain connectivity and memory suppression capacity in Alcohol-Dependent Patients*). The primary aim of this study was to examine how alcohol dependence affects the ability to intentionally suppress unwanted memories and whether these impairments are exacerbated for alcohol-related content. It was hypothesized that individuals with alcohol use disorder would show reduced behavioral suppression-induced forgetting and diminished prefrontal control over memory-related regions, particularly reduced downregulation of hippocampal and medial temporal lobe activity during memory

suppression. Furthermore, it was predicted that impairments in memory suppression and fronto-hippocampal connectivity would be associated with greater clinical severity and heightened alcohol craving, supporting the role of deficient memory inhibition in intrusive alcohol memories and relapse vulnerability.

The chapters presented above are formatted as standalone articles in accordance with the submission and publication guidelines of the respective scientific journals. As such, each chapter includes its own theoretical introduction, methodology, results and discussion. At the start of each chapter, we indicate the target or publishing journal (with JCR and Scopus impact factors and quartile) and list any scientific symposia or meetings where the work was presented.

Lastly, the present thesis concludes with a general discussion (Part IV: Discussion; Chapter 7: General Discussion), in which the body of work will be fully integrated, discussing the main findings and how these further our knowledge on the matters of alcohol abuse, memory, and craving. In that integrative chapter, we explicitly return to the main objective of this dissertation and explore the interaction between alcohol craving and alcohol related memories and draw insights on the relevance of alcohol related memories on the development, perpetuation and escalation of alcohol consumption. Synthesizing how the identification of alcohol-biased associative memory activation in binge drinkers, the delineation of acute and chronic electrophysiological disruptions in attention and working memory, and the demonstration of impaired memory suppression in alcohol use disorder collectively test the core hypotheses linking memory reactivity, deficient memory inhibition, and craving to hazardous consumption. Furthermore, the main limitations found through the studies that make this thesis are mentioned, with considerations for future research as well as possible considerations for practical implications of the findings discussed in this dissertation. The conclusion of this work presents an overall summary highlighting the main findings presented.

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Chapter II

General Methodology

2. General Methodology

This dissertation aims to elucidate how alcohol consumption alters memory and executive control processes across the spectrum of drinking behaviors, and how alcohol-related memories interact with subjective craving to promote the development, maintenance, and escalation of hazardous drinking. Specifically, the thesis integrates behavioral, electrophysiological, and neuroimaging approaches to examine short-term and chronic effects of alcohol on working and episodic associative memory, as well as on the capacity to intentionally inhibit alcohol-related memories, while identifying the neural mechanisms underlying these alterations.

To that end, four empirical studies were conducted: first, the development and Portuguese validation of a psychometrically robust measure of acute alcohol craving, providing a critical tool to assess moment-to-moment motivational states; second, an electroencephalography (EEG) investigation of the acute (hangover) and longer-term effects of binge drinking on attention and working memory, and their relationship with craving; third, a functional magnetic resonance imaging (fMRI) study comparing the neural substrates of alcohol-related and neutral associative memory retrieval in binge drinkers and abstainers, and their association with craving and consumption severity; and fourth, a fMRI connectivity study in individuals with alcohol use disorder examining impairments in intentional forgetting, particularly for alcohol-related memories, and their links to craving and clinical severity. Collectively, these studies seek to clarify how maladaptive memory dynamics and craving mutually reinforce each other at behavioral and neural levels, thereby contributing to the persistence and relapse of harmful alcohol use.

The specific methods employed in each study will be described below.

2.1. Study 1 — Portuguese validation of the Alcohol Craving Questionnaire – Short Form – Revised (Chapter 3)

Participants. The validation sample included 591 Portuguese-speaking young adults. Participants were recruited from the University of Minho and data were collected between October 2018 and October 2019 through questionnaire administration in a classroom setting. Undergraduate students were invited to participate during scheduled classes, following verbal consent from both lecturers and students. Inclusion criteria were being a native Portuguese speaker and aged between 18 and 30 years; no exclusion criteria were applied. Participants completed the translated questionnaire alongside established measures, including

the Alcohol Use Disorders Identification Test (AUDIT) and the Penn Alcohol Craving Scale, to allow the assessment of concurrent and convergent validity.

Procedure. The measure was translated and back-translated following standard cross-cultural adaptation procedures, piloted for comprehension, and then subjected to psychometric analysis. Factor analyses were used to examine structure, internal consistency metrics were estimated, and correlations with external measures served to establish convergent validity.

Data Analyses. Psychometric evaluation combined exploratory and confirmatory factor analysis to test whether the original multidimensional model was replicable. Internal consistency for the new model was assessed with Cronbach's alpha and inter-item consistency, and convergent validity was assessed by correlating questionnaire scores with AUDIT totals and trait/long term alcohol craving. Model fit indices and factor loadings are reported in Chapter 3.

2.2. Study 2 — The Day After Binge: Electrophysiological correlates of attention and working memory processing the day after hazardous alcohol intake (Chapter 4)

Participants. Participants were university students aged between 18 and 24 years, recruited through a widespread online screening questionnaire at the University of Minho (Braga, Portugal). The final sample comprised 52 participants, including 24 binge drinkers and 28 Controls. Participants were allocated to the binge drinking group if they reported consuming five or more standard drinks (four or more for women) within a two-hour period, reaching an estimated blood alcohol concentration of 0.08 g/dL or higher, at least once per month over the previous year. Control participants were required to report no lifetime binge drinking episodes and to score below 4 on the AUDIT. For both groups, inclusion required normal or corrected-to-normal sensory functioning and the absence of neurological disorders, traumatic brain injury, alcohol use disorder, regular cannabis use, other illicit drug use, major psychopathology, or a family history of severe psychiatric disorders.

Procedure. Binge participants were tested both on a non-drinking day to capture baseline/chronic effects and during hangover to characterize short-term impairments; control participants were tested on non-drinking days. EEG was recorded while participants performed a visual one-back continuous-performance task.

During the task abstract shapes were presented briefly and the participant responded when the current stimulus matched the immediately preceding one. Matching trials comprised 20% of trials.

Data Analyses. Behavioral outcomes included hit rates, false alarms and reaction times. Event-related potentials were computed, and principal component analysis (PCA) was applied to multichannel ERP waveforms to isolate latent temporal components and reduce bias in peak selection. Neural outcomes focused on ERP amplitudes of components classically associated with attention and memory processing (notably P3 and the late positive component) derived from the PCA component scores. Statistical analyses compared groups and conditions (hangover vs non-drinking day) using repeated-measures models. Correlation analysis explored interaction between ERP measures, behavioral scores, craving, drinking variables, and impulsivity scores (derived from the Baratt Impulsivity Scale).

2.3. Study 3 — Associative memory in alcohol-related contexts: An fMRI study with young binge drinkers (Chapter 5)

Participants. Participants were university students aged between 18 and 23 years, recruited via an online screening survey and subsequently assessed through a structured clinical interview. The final sample comprised 36 participants, including 20 binge drinkers and 16 alcohol-abstinent controls. Inclusion in the binge drinking group required a consistent binge drinking pattern, defined as the consumption of five or more standard drinks for men (four or more for women) within a two-hour period, reaching an estimated blood alcohol concentration of at least 0.08 g/dL, occurring at least once per month during the preceding 10 months. The control group consisted exclusively of alcohol-abstinent individuals who reported no lifetime alcohol consumption and, consequently, no history of binge drinking episodes.

For both groups, inclusion required right-handedness, normal or corrected-to-normal sensory functioning, and the absence of neurological disorders, traumatic brain injury, alcohol use disorder, regular cannabis use, other illicit drug use, major psychopathology, a family history of neurological or psychiatric disorders, or any contraindications for magnetic resonance imaging.

Procedure. During an initial session participants encoded ninety object–scene pairs in which neutral objects were paired with social scenes that depicted either alcohol-drinking or non-alcohol studying contexts. fMRI data was acquired during a retrieval session one day after encoding. 135 object images (90 old, 45 new) were presented individually and participants indicated for each old object whether it had been paired with an alcohol or a no-alcohol context; new items required no response.

Data Analyses. Behavioral measures included correct context retrieval and reaction times. fMRI data preprocessing included motion correction, co-registration to a high-resolution T1, normalization and spatial smoothing. First-level GLMs modelled retrieval-related responses for alcohol-paired items, no-alcohol items, and new items, and second-level analyses contrasted these conditions between groups using whole-brain analysis. Correlation analyses were run to assess interaction between brain activation and alcohol related behavioral scores.

2.4. Study 4 — Forgetting alcohol: memory suppression and connectivity in alcohol-dependent patients (Chapter 6)

Participants. Participants aged between 26 and 65 years were recruited through a widespread online screening questionnaire, physical advertisements displayed at the University of Minho campus, and collaboration with drug and alcohol rehabilitation facilities located in the districts of Braga, Viana do Castelo, and Porto (Portugal). The final sample comprised 41 individuals, including 26 participants with alcohol use disorder and 15 healthy controls.

Inclusion in the clinical group required a prior clinical diagnosis of alcohol use disorder, current participation in a rehabilitation program, and a minimum abstinence period of six weeks at the time of assessment. Participants in the clinical group were additionally required to report no past or current dependence on other substances. The control group consisted of individuals with no lifetime history of alcohol abuse or dependence, no consumption of illicit drugs, and no history of psychiatric or neurological disorders.

For both groups, inclusion criteria comprised normal or corrected-to-normal sensory functioning, absence of neurological disease, major psychopathology, or other substance use disorders, and no contraindications for magnetic resonance imaging. Groups were matched for sex and years of education. All participants provided written informed consent prior to participation.

Procedure. Participants completed an adapted version of the Think/No-Think Alcohol paradigm to assess intentional memory suppression for alcohol-related and non-alcohol-related material. During an initial encoding phase, participants learned 24 cue–target pairs in which neutral object cues were paired with images depicting either alcoholic or non-alcoholic beverages. To accommodate the clinical characteristics of the alcohol use disorder sample, encoding was implemented using a simplified, criterion-based procedure to ensure adequate learning prior to the experimental phase.

Following successful encoding, participants underwent fMRI acquisition while performing the Think/No-Think phase. During this phase, previously learned cue images were presented with colored borders indicating whether participants should actively retrieve the associated beverage image (Think condition) or suppress its retrieval (No-Think condition). A subset of encoded cues was not presented during this phase and served as a Baseline condition.

After the Think/No-Think phase, participants completed a final recall test outside the scanner. All encoded cues were presented, and participants were asked to recall the associated beverage information.

Data Analyses. Behavioral analyses focused on encoding performance, conditionalized recall accuracy, and suppression-induced forgetting. Encoding performance was defined as the proportion of correctly learned cue–target pairs. Final recall accuracy was conditionalized on successful encoding and expressed as the percentage of correctly recalled items for each condition (Think, No-Think, Baseline) and stimulus type (Alcohol, No-Alcohol). Suppression-induced forgetting was computed as the difference in recall accuracy between Baseline and No-Think conditions.

Behavioral data were analyzed using mixed repeated-measures models with Condition (Think, No-Think, Baseline) and Stimulus (Alcohol, No-Alcohol) as within-subject factors and Group (Alcohol use Disorder, Control) as a between-subject factor. Complementary analyses examined the contribution of individual differences in encoding performance. Correlational analyses explored associations between behavioral indices of memory suppression and subjective alcohol craving.

fMRI analyses examined task-modulated functional connectivity during memory retrieval and suppression. Seed-based connectivity analyses targeted brain regions implicated in inhibitory control, memory processing, and reward. Connectivity patterns were compared between groups for each experimental condition and between conditions within each group. Finally, within the clinical group, exploratory correlations assessed relationships between functional connectivity measures, behavioral performance, and craving severity.

Chapter III

Portuguese Validation of the Alcohol Craving Questionnaire – Short Form – Revised

The work presented in Chapter 3 was published in PLOS One.

The reference style used in this Chapter is in accordance with the published paper.

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3.1. Abstract

Alcohol craving has been described as a strong subjective desire to drink, being considered highly valuable in clinical practice, as it is recognized as a strong predictor of alcohol relapse in alcohol-dependent individuals. However, to date, there is not a multifactorial questionnaire available for assessing short-term acute craving experience in Portugal. The aim of the present study was to validate a swift and efficient tool for the assessment of acute alcohol craving in a sample of Portuguese citizens. For that purpose, the Alcohol Craving Questionnaire – Short Form – Revised (ACQ-SF-R) was translated into European Portuguese and administered to a sample of 591 college participants with ages between 18 and 30 years. Results suggested that a three-factor model (i.e., Emotionality, Purposefulness, and Compulsivity) proved to be most suitable for the Portuguese sample. Overall, the ACQ-SF-R exhibited good psychometric properties, having a good internal consistency both for the general craving index (Cronbach's α = 0.85) and each subscale (Cronbach's α = 0.66 - 0.83), as well as an appropriate convergent validity with the Penn Alcohol Craving Scale (r=0.65, p<0.001), suggesting a good construct validity. In addition, the ACQ-SF-R also showed a good concurrent validity with the Alcohol Use Disorders Identification Test (r=0.57, p<0.001), indicating that risky alcohol use patterns are associated with increased craving scores in the ACQ-SF-R. Collectively, these findings suggest that the Portuguese version of the ACQ-SF-R can accurately measure alcohol craving at a multifactorial level, being a valid and reliable tool to use in Portuguese samples in research settings.

3.2. Introduction

Alcohol craving has been classically described as a strong subjective desire to drink, being considered a hallmark of alcohol dependence [1,2]. As such, it has been suggested that craving for alcohol is involved in the development and maintenance of severe alcohol use disorder (AUD), facilitating the emergence of alcohol-related obsessive thoughts and compulsive approach behaviors, despite repeated efforts to stop the consumption [3]. Therefore, craving conceptualization is considered highly valuable in clinical practice, as it is recognized as a strong predictor of alcohol relapse in alcohol-dependent individuals [4]. In addition, reduction of alcohol craving can lead to several benefits throughout rehabilitation, ultimately preventing relapses and boosting natural treatment outcomes [5], becoming one of the main targets for intervention in alcohol addiction [6, 7]. Indeed, the International Classification of Diseases (ICD-10 and ICD-11) [8, 9], as well as the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) [10] considered craving as a major criterion in the diagnosis of alcohol dependence and AUD, respectively.

The urge to drink or the intense and recurrent thoughts about alcohol, typically linked to alcohol craving, have often been associated with physiological and environmental cues [11]. Accordingly, specific environmental contexts (e.g., seeing/smelling alcohol) and physiological signals (i.e., bodily perceptions such as those linked to withdrawal symptoms) are known inducers of craving [3, 12-14]. Craving levels may also be time persistent, remaining low for long periods and still having high peak occurrences after weeks or months [11]. In this sense, it has been proposed that craving measures may be included within two main categories with respect to their timeframe: the state measures, which focus on the "here-and-now" craving status; and the global measures, which reflect the craving experience over the course of days, weeks or longer periods [1]. Additionally, recent investigation has described craving in terms of a triadic model, considering the craving experience as the interplay between three subcomponents: *cognitive craving*, associated with reduced efficiency in high-level cognitive abilities (e.g., inhibitory control); *automatic craving*, which represents the cue reactivity and the attentional bias to addiction-related cues; and *physiological craving*, expressed by body signals caused by a homeostatic imbalance such as stress or sleep deprivation [15].

The complexity of the craving phenomenon has led to the development of different questionnaires in order to capture the temporal nature of this experience as well as the potential sub-components or dimensions of craving. Specifically, two of the most commonly used questionnaires for assessing craving, namely the Alcohol Urge Questionnaire (AUQ) [16] and the Alcohol Craving Questionnaire (ACQ) [17], are

measures of short-term acute craving experience. On the other hand, the Penn Alcohol Craving Scale (PACS) [18] and the Desires for Alcohol Questionnaire (DAQ) [19] retroactively assess past level of craving in the midterm. Concerning the dimensionality of these questionnaires, AUQ and PACS are characterized by having a unidimensional -single factor- structure, whereas ACQ and DAQ comprise multiple sub-scales or factors, thus being considered multidimensional.

Accordingly, as craving is often described as being composed of multiple subcomponents [1, 15], it is likely to be beneficial to use multifactorial scales for measuring craving, since these can have different predictive utility and offer contrasting treatment targets [20]. However, this type of scale usually has a great number of items, which has a negative effect on respondents' willingness to accurately complete them [21, 22]. Aiming to overcome these limitations, several short forms of multifactorial alcohol craving questionnaires have been developed and validated, including the six-item version of the DAQ (DAQ-6) [23] and the short form of the ACQ (ACQ-SF-R) [24]. Whereas DAQ-6 has six items divided into only two factors (i.e., "expectancy of negative reinforcement" and "strong desires and intentions to drink or use drugs"), the ACQ-SF-R is more comprehensive and comprises 12 items divided into four factors (i.e., Compulsivity, Expectancy, Purposefulness and Emotionality). This latter questionnaire has already been adapted and validated to the Brazilian and Spanish populations [25, 26], and it is considered a valuable and reliable measure widely used both in research and clinical settings to assess acute alcohol craving [27-29].

In Portugal, as far as we know, the PACS is the only alcohol craving measure that has been translated and validated to European Portuguese speakers [30]. However, this questionnaire simply allows assessing the craving levels retrospectively (during the past week) and as a single factor disregarding the individual's current craving and the potential multidimensional nature of this phenomenon [15, 31]. With the intention of providing a swift and more efficient tool for the assessment of acute alcohol craving to researchers working with a sample of European Portuguese speakers, the objective of the present study was to develop and validate the Portuguese version of the ACQ-SF-R.

3.3. Methods

3.3.1. Participants

The initial sample included a total of 842 students from the University of Minho (Portugal). Data was collected between October 2018 and October 2019 by administering the questionnaires in a classroom setting. From the initial sample, 162 participants were excluded for not completing all questions of both questionnaires (ACQ-SF-R and PACS) and 89 for not meeting the age criteria (ages between 18-30 years

old), which besides being Portuguese was the only inclusion criteria. There were no exclusion criteria. Thus, the final sample included 591 participants (67.3% female; see Table 1), of which eight did not complete the Alcohol Use Disorders Identification Test (AUDIT). Additionally, the sample was divided in two groups based on alcohol use pattern, i.e., non/low-risk drinkers (AUDIT < 8) and risky drinkers (AUDIT ≥ 8).

Table 1. Age and alcohol consumption by Gender and Alcohol Use Pattern

	Age *M(SD)*	**AUDIT *M(SD)***	**PACS *M(SD)***	**ACQ-SF-R *M(SD)***
Gender				
Men (N=193)	20.65 (2.16)	4.68 (4.35)	2.40 (3.45)	2.18 (1.00)
Women (N=398)	20.23 (1.64)	5.11 (5.47)	1.73 (3.35)	1.80 (0.86)
Alcohol Use Pattern				
Risky Drinkers (N=129)	20.29 (1.60)	12.88 (5.47)	5.08 (5.04)	2.73(1.10)
Non/low Risk Drinkers (N=454)	20.43 (1.89)	2.59 (2.20)	1.07 (2.06)	1.70(0.73)
Total Sample (N=591)	20.37 (1.84)	4.97 (5.13)	1.95 (3.40)	1.93(0.93)

Note: M, mean; SD, standard deviation; AUDIT, Alcohol Use Disorders Identification Test; PACS, Penn Alcohol Craving Scale; ACQ-SF-R, Alcohol Craving Questionnaire – Short Form – Revised.

3.3.2. Measures

The Alcohol Craving Questionnaire – Short Form – Revised (ACQ-SF-R) [24]. This questionnaire is a self-report measure consisting of 12 items derived from the 47-item Alcohol Craving Questionnaire (ACQ-Now) [17] and was designed to provide a brief screening method to be used in research and clinical practice to assess current craving for alcohol. Items are rated in a 7-point Likert-scale, from "totally disagree" (1) to "totally agree" (7), with the items 3, 8, and 11 being inversely scored, and a general craving index may be derived by summing all items and dividing by 12.

According to Singleton [24], the factor analysis of the ACQ-SF-R supported the same four factors as the ACQ-Now, with a good internal consistency (Cronbach's α ranged between 0.77 and 0.86). These factors measure different dimensions of craving for alcohol: *Compulsivity,* related to the loss of control over drinking; *Expectancy*, concerned with the positive benefits of drinking; *Purposefulness*, associated with the intention and plan to drink; and *Emotionality*, linked to the relief from withdrawal/negative affect [32].

Penn Alcohol Craving Scale (PACS) [18]. The PACS is a self-report measure with five questions, each one with seven answer options (from 0 to 6). The first three questions range from different levels of intensity, frequency and duration of alcohol-related thoughts. The fourth question concerns the alcohol consumption

restraint capacity and the last one focuses on the levels of craving in the past week. This scale has been translated and validated for European Portuguese speakers, and presents good psychometric properties [30]. *Alcohol Use Disorders Identification Test* (AUDIT) [33]. The AUDIT is a self-report measure with ten questions, used to identify current harmful and hazardous drinking. This test has been validated to assess alcohol-related problems and/or AUD [34] and has become the world's most widely used alcohol screening instrument, including in Portugal [35]. AUDIT scores < 8 reveal low risk of alcohol use; scores between 8 and 15 represent a risky consumption; scores from 16 to 19 are considered a harmful intake pattern; and scores ≥ 20 indicate very high risk for alcohol dependence and warrant further diagnostic evaluation for alcohol dependence [33, 36, 37]. In the present study, we used the European Portuguese translated version of the AUDIT [37].

3.3.3. Procedure

The study consisted of three phases: (1) scale translation; (2) questionnaire administration; and (3) analysis of validity and reliability.

In the first phase, ACQ-SF-R was independently translated from the English version into European Portuguese by four Portuguese native researchers with a high level of proficiency in English and, subsequently, compared and discussed in a small group of expert researchers in the topic. This version was then back translated into English by an independent researcher with English as first language and compared with the original English questionnaire. After verifying the equality of contents between the original and the final translation as well as the proper understanding of all items, the final version was created (see Appendix A).

In the second phase, the two alcohol craving measurements (ACQ-SF-R and PACS) were administered, along with the AUDIT, to college students at University of Minho in a classroom context, with the professor and students' verbal consent and the agreement of the Ethical Committee of Social and Human Sciences of the University of Minho.

During the third phase, statistical analyses of validation and reliability of the Portuguese version of ACQ-SF-R were performed. The guidelines of the General Data Protection Regulation (EU 2016/679) and the Declaration of Helsinki [38] were followed to guarantee the confidential treatment of the data and to ensure compliance with international standards of ethical research involving human beings.

3.3.4. Data Analysis

Firstly, an Exploratory Factorial Analysis (EFA) with a Varimax rotation was conducted to identify the factorial structure of the scale. The method of extraction used was unweighted least squares (ULS), and factors with eigenvalue below one were excluded. Kaiser Meyer Olkin (KMO) and Bartlett's Test were performed as a preliminary step to determine the properties of the inter-item correlation matrix and to measure the strength of the relationship between factors. The items were checked for double loading to a factor (i.e., having a loading > 0.60 to more than one factor). Subsequently, a Confirmatory Factor Analysis was completed by the Maximum Likelihood method to test the Portuguese three-factor model and the original four-factor model. To this extent, we considered the following fit indexes: Relative Chi-Square ($x2/df$); Normed Fit Index (NFI); Comparative Fit Index (CFI); Goodness-of-Fit Index (GFI); and Root Mean Square Error of Approximation (RMSEA). In accordance, commonly accepted fit indices and acceptable limits for model fit are presented in Table 2 [39, 40]. Akaike information criterion (AIC) was also considered for the comparisons between different models, where smaller values represent the best model.

Table 2. Goodness of fit indices and acceptable limits

Indices	Acceptable limits
$\chi 2/df$	≤ 5 acceptable fit, ≤ 2 perfect fit
RMSEA	0.10 – 0.08 weak fit, ≤ 0.08 good fit, ≤ 0.06 perfect fit
GFI	0.85–0.89 acceptable fit, ≥ 0.90 good fit, ≥ 0.95 perfect fit
CFI	≥ 0.90 acceptable fit, ≥ 0.95 good fit, ≥ 0.97 perfect fit
NFI	≥ 0.90 acceptable fit, ≥ 0.95 good fit

Note: χ^2, chi-Square; *df*, degrees of freedom; RMSEA, Root mean square error of approximation; GFI, Goodness-of-fit statistic; CFI, Comparative fit index; NFI, Normed-fit index.

The internal consistency of the full scale and each factor was calculated using the Cronbach's α coefficient and the mean inter-item correlation was calculated to confirm if each individual item provides a consistent and appropriate measurement of the construct. Furthermore, Pearson's correlations were conducted to assess convergent validity using PACS data as reference, and concurrent validity using AUDIT scores. Additionally, in order to compare ACQ-SF-R scores for participants in the two levels alcohol risk (see Table 1), a repeated measures ANOVA was conducted with one between-subjects factor with two levels (alcohol use pattern: risk and non/low risk) and one within-subjects factor with three levels (ACQ-SF-R: Emotionality, Purposefulness and Compulsivity) to evaluate potential differences in the craving levels between these two groups.

Finally, configurational invariance across gender was also explored. Specifically, EFA, KMO and Bartlett's Test, as well as the Cronbach's α coefficient and mean inter-item correlation, were conducted separately within each gender.

3.4. Results

3.4.1. Exploratory Factor Analysis (EFA)

Results of the Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett's test of sphericity were appropriate for factor analysis (KMO = 0.87; $\chi 2 = 2429.56$; $p < 0.001$). Three different factors, which together accounted for 60.64% of the total variance were extracted (see Table 3). Factor 1, Emotionality, explained 38.58% of the variance and it was comprised of items 6, 7, 9, 10 and 12. Factor 2, Purposefulness, explained 12.03% of the variance and it included the items 3, 8 and 11. Factor 3, Compulsivity, explained 10.03% of the variance and encompassed items 1, 2, 4 and 5. None of the items were double loaded on any factor.

Table 3. Total explained variance from the exploratory factor analysis

	Initial Eigenvalues			Extraction Sums of Squared Loading			Rotation Sums of Squared Loadings		
		Variance	Cumulative		Variance			Variance	Cumulative
Factor	Total	%	%	Total	%	Cumulative %	Total	%	%
1	4.628	38.567	38.567	4.628	38.567	38.567	3.037	25.312	25.312
2	1.453	12.107	50.674	1.453	12.107	50.674	2.381	19.842	45.153
3	1.201	10.011	60.685	1.201	10.011	60.685	1.864	15.532	60.685
4	0.762	6.350	67.035						
5	0.710	5.913	72.948						
6	0.624	5.198	78.146						
7	0.585	4.879	83.025						
8	0.538	4.487	87.512						
9	0.456	3.803	91.315						
10	0.413	3.444	94.759						
11	0.360	3.001	97.760						
12	0.269	2.240	100.000						

3.4.2. Confirmatory Factor Analysis

In conformity with the Maximum Likelihood method, the three-factor model and the original four-factor model were tested. The three-factor model reached the following fit indices: *x2/df* = 4.98, NFI = 0.90, CFI = 0.92, GFI = .94, RMSEA = 0.08, while the four-factor model reached the following fit indices: *x2/df* = 6.50, NFI = 0.87, CFI = 0.89, GFI = 0.91, RMSEA = 0.10. Each model scored 307.72 and 372.14 for AIC, respectively. The upper-mentioned indices and AIC indicated a better model fit for the three-factor model (see Figure 4 and, Tables 2 and 4).

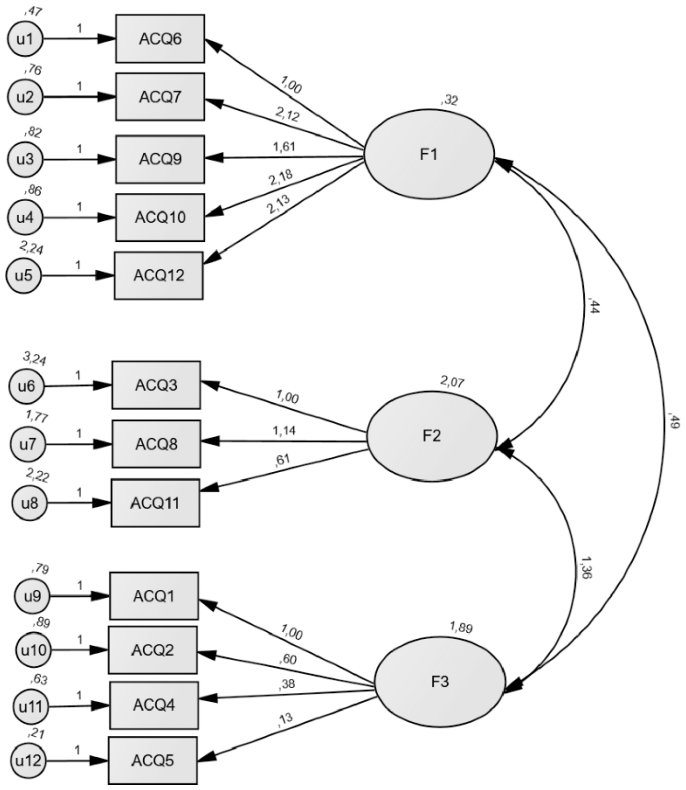


Figure 4. Confirmatory factor analysis for the ACQ-SR-N Portuguese Version: F1 -Emotionality- includes items 6, 7, 9, 10, and 12; F2 -Purposefulness- includes items 3, 8, and 11; F3 – Compulsivity includes items 1, 2, 4, and 5 (N = 591).

Table 4. Model fit indices

Model	χ^2	df	χ^2/df	NFI	CFI	GFI	RMSEA	AIC
Three-factor	253.72	51	4.98	0.90	0.92	0.94	0.08	307.72
Four-factor	312.14	48	6.50	0.87	0.89	0.91	0.10	372.14

Note: $\chi 2$ – Chi-Square; *df* – degrees of freedom; NFI – Normed Fit Index; CFI – Comparative Fit Index; GFI – Goodness-of-Fit Index; RMSEA – Root Mean Square Error of Approximation; AIC – Akaike Information Criterion.

3.4.3. Reliability

Both the total scale (α = 0.85) and the three factors (F1, α = 0.83; F2, α = 0.66; F3, α = 0.70) showed good internal consistency values [41]. Calculation of the mean inter-item correlation also showed good internal consistency for the full scale (0.32) and the three factors (F1 = 0.32; F2 = 0.40; F3 = 0.37) [42]. Finally, the reliability of the scale did not improve by removing any of the items.

3.4.4. Validity

A significant correlation was found when PACS was compared with the full-scale score of the ACQ-SF-R (r = 0.65, p < 0.001), indicating good convergent validity. Furthermore, a significant correlation was also observed between ACQ-SF-R and AUDIT (r = 0.57, p < 0.001), indicative of appropriate concurrent validity. Additionally, comparisons between risky drinkers and non/low risk drinkers showed significant differences regarding their craving scores (F (1, 581) = 155.86, p < 0.001). Specifically, risky drinkers reported higher scores of alcohol craving for all three subscales in comparison with non/low risk drinkers (F (2, 1655 = 16.91, p < 0.001) (Table 5).

Table 5. Craving scores across alcohol use pattern groups

	Non/Low Risk Drinkers M(SD)	**Risky Drinkers** M(SD)
	N = 454	N = 129
F1 - Emotionality	1.60 (0.91)	2.56 (1.40)
F2 - Purposefulness	2.35 (1.45)	3.83 (1.57)
F3 - Compulsivity	1.34 (0.58)	2.11 (1.21)
ACQ-SF-R – Full Scale	1.70 (0.73)	2.72 (1.10)

Note:

ACQ-SF-R, Alcohol Craving Questionnaire – Short Form – Revised; M, mean; SD, standard deviation.

3.4.5. Factorial invariance and reliability across gender

When conducting EFAs separately within each gender, results of both female (KMO = .84; $\chi 2$ = 1638.29, p < 0.001) and male groups (KMO = 0.84; $\chi 2$ = 799.69, p < 0.001) were appropriate. EFA showed that males and females had identical factor loadings in all the subscales as the main exploratory analysis, except for item 1 which had a higher factor loading on F2 (Purposefulness) than F3 (Compulsivity) for

females. Additionally, the three factors explained similar amounts of variance, namely F1, F2 and F3 explained 38.49%, 12.49% and 9.50% of the variance for males, and 37.42%, 12.93% and 9.92% for females.

Furthermore, good internal consistency values in the total scale and the three subscales were expressed for both males (Total scale: α = 0.84; F1: α = 0.81; F2: α = 0.60; F3: α = 0.72) and females (Total scale: α = 0.83; F1: α = 0.81; F2: α = 0.69; F3: α = 0.64). Likewise, mean inter-item correlations also showed good internal consistency in the full scale and the three factors, in both male (Total scale: α = 0.31; F1: α = 0.49; F2: α = 0.33; F3: α = 0.42) and female (Total scale: α = 0.30; F1: α = 0.50; F2: α = 0.42; F3: α = 0.32) groups.

3.5. Discussion

The ACQ-SF-R is a widely used screening instrument to assess craving in both clinical and non-clinical populations. However, there are no studies to date assessing the psychometric properties of this questionnaire in Portugal. Thus, the main objective of the present study was to adapt and validate a version of the ACQ-SF-R for European Portuguese speakers. The findings of the present study suggest that the ACQ-SF-R possesses good psychometric properties and is a valid and reliable measure to assess acute alcohol craving in three complementary dimensions: Emotionality, Purposefulness, and Compulsivity. Additionally, the instrument showed good convergent and concurrent validity and showed cohesiveness within each gender, with good internal consistency of the scale for both males and females.

Regarding instrument reliability, results revealed good internal consistency values (α = 0.85), with similar values to the original version of the ACQ-SF-R (α range between 0.77 and 0.86; Singleton, 1997) as well as the Spanish (α = 0.87; Gálvez et al., 2016) and the Brazilian (α = 0.91; Girelli et al., 2019) validations. Similarly, the Portuguese version of the ACQ-SF-R showed good convergent validity with the PACS, with a higher relationship strength than the Spanish ACQ-SF-R validation [25]. Thus, the present study seems to complement the psychometric results found for the Portuguese version of the PACS, which to date is the only questionnaire assessing alcohol craving validated in European Portuguese. Furthermore, and contrary to the PACS, ACQ-SF-R also allows the assessment of different dimensions of alcohol craving, which can be useful to differentiate how this phenomenon is expressed in different populations (e.g., light drinkers, binge drinkers, alcohol dependent individuals).

Additionally, Pearson's correlations showed satisfactory concurrent validity between the ACQ-SF-R and the AUDIT (r = 0.57), reflecting an interaction between alcohol craving and alcohol consumption. In a related vein, levels of alcohol craving were significantly higher in risky drinkers when compared to non/low risk drinkers. Indeed, alcohol craving has often been associated with higher detrimental patterns of alcohol use [3, 43, 44]. Consequently, ACQ-SF-R may be a useful tool for clinical practice, being able to help to detect risky drinking, and future research could determine whether this questionnaire will be useful in predicting risk for relapse and other treatment outcomes.

According to Singleton [24], the English version of ACQ-SF-R is a four-factor measure, however, in our study, the confirmatory factor analysis showed better fit indices for the three-factor model when compared to the original model. Nonetheless, with the number of factors reduced to three, the Portuguese version of the ACQ-SF-R still presented a good construct validity [45] with a total explained variance of 60.6%. Concerning the overall structure of the scale, in the Portuguese version the Expectancy factor was removed, and its items merged into the Emotionality and Compulsivity factors. Furthermore, item 6, which previously loaded on the Compulsivity factor, was included in the Emotionality factor. Thus, the Emotionality dimension included five items (i.e., 6, 7, 9, 10, 12) that paired abstinence from alcohol with feelings of irritability, tension, and restlessness together with the anticipation of some benefits of drinking (e.g., on mood); the Compulsivity factor was composed of four items (i.e., 1, 2, 4, 5) reflecting the urges and desires to drink along with the ability to refrain from consuming alcohol; and, finally, the Purposefulness factor remained identical to the original scale, characterized by three items (i.e., 3, 8, 11) reflecting the intention and plan to drink alcohol.

Consistent with the present study, both the Spanish and Brazilian validations [25, 26] suggested better fit with a smaller number of factors than the original version of the ACQ-SF-R, i.e., three factors for the Spanish validation and two factors for the Brazilian one. With regard to the latter, there are a number of differences between the Brazilian version and the current validation that are worth mentioning. Participants of the Brazilian study were patients recently admitted into a detoxification facility, therefore they had high motivation to change [46] and, consequently, scored low on the scale of purposefulness in regard to drinking. In addition, prior to the craving assessment, these patients were exposed to two pictures of alcoholic beverages, which could lead to incremental changes in craving levels [14] and might have increased both the positive alcohol expectancies and the compulsive tendencies to approach alcohol [47, 48]. Thus, it could

be suggested that this previous exposure to alcohol cues may have led to this co-occurrence, causing items associated with expectancies, compulsivity, and emotionality to have higher correlation, which may entail a bigger loading to the same factor [49]. Therefore, these methodological differences might have led to the structural differentiation between the Brazilian and the Portuguese validations.

Finally, the present study has some limitations that deserve consideration. While a strength of the study was that the sample size was higher than previous validation studies of the scale [25, 26], the nature of the sample (young college students) may limit the generalization of the results to the adult population or population without higher education. In the same vein, although part of the sample had a risky consumption pattern, participants cannot be considered a clinical population. As such, results from this validation should not be generalized to clinical populations (e.g., patients with AUD). Moreover, only students from a single public university completed the questionnaire, hence external validity concerning the sociodemographic characteristics of the population might be limited. In addition, the fact that this study presents a significantly higher number of females than males (67.3% vs 32.7%), might be affecting our results. Lastly, all variables analyzed were self-reported, which makes it difficult to determine possible underestimation/overestimation of the levels of alcohol consumption. Thus, additional studies trying to equate the number of each gender and include a general adult population should be conducted in order to validate the present results.

In conclusion, the Portuguese version of the ACQ-SF-R showed good psychometric properties, i.e., revealing good internal consistency and satisfactory convergent validity with the PACS and concurrent validity with the AUDIT. Furthermore, despite having a shorter length, it allows assessment of different dimensions of alcohol craving (i.e., Emotionality, Purposefulness and Compulsivity). Collectively, these findings suggest that this version of the ACQ-SF-R can accurately measure acute alcohol craving at a multifactorial level, being a valid and reliable tool to use in Portuguese samples in research settings.

3.6. Acknowledgements

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Chapter IV

The Day After Binge: Electrophysiological correlates of attention and working memory processing the day after hazardous alcohol intake

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4.1. Abstract

Binge drinking (BD) is a prevalent pattern of alcohol consumption among young adults, with significant cognitive and neural implications. While its long-term effects on executive function and memory have been widely studied, less is known about the short-term consequences of the hangover state. This study investigates the impact of BD and alcohol hangover on working memory and attention. Fifty-two university students (24 Binge drinkers [BDs]; 28 control) participated in an EEG-based continuous performance task (CPT). BD participants were assessed on a non-drinking day and during hangover state, while controls completed a single assessment. The P3 and late positive component (LPC) event-related potentials were analyzed to examine attentional and memory-related processes. While no significant behavioral differences were observed, neurophysiological analyses revealed altered cognitive processing associated with both the long-term consequences of BD behavior and its short-term effects (i.e., during the hangover state). Specifically, during hangover, BDs P3 and LPC amplitudes were significantly reduced in both conditions, indicating impairments in attentional resource allocation and memory processing. In contrast, BDs exhibited larger LPC amplitudes for both conditions on a non-drinking day than controls, suggesting the engagement of compensatory neural mechanisms. Additionally, in the hangover state, reduced P3 correlated with increased alcohol craving, while lower LPC amplitudes in hangover state were associated with greater alcohol intake during BD episode in the preceding day. These findings highlight acute neurocognitive disruptions during hangover and give emphasis to the concerning cumulative impact of repeated BD episodes long-term.

4.2. Introduction

Alcohol consumption has long been intertwined with youth culture, especially during the transition to adulthood, where university life often serves as a backdrop for heavy drinking (Siqueira, et al., 2015: Weitzman et al., 2003). Social gatherings, including parties, sporting events, and fraternity or sorority traditions, frequently promote a drinking culture that normalizes excessive alcohol consumption (Buettner et al., 2011; Marzell et al., 2015). While such practices are often viewed as a typical aspect of student life, the significant social, cognitive, and health-related consequences -especially for developing brains (Tapert et al., 2022)- are a growing concern in both academic and public health spheres.

Over recent decades, a distinct pattern of alcohol consumption known as binge drinking (BD) has become more widespread among youth (Kuntsche et al., 2017), particularly but not only in Western countries (D'Alessandro et al., 2023). BD is characterized by the rapid consumption of large amounts of alcohol, often leading to intoxication, followed by periods of abstinence, and with at least one binge episode per month (Courtney et al., 2009; National Institute on Alcohol Abuse and Alcoholism, 2024). In the same vein, a binge drinking episode is defined by the consumption of five or more standard drinks – roughly 10g of pure ethanol- (Kalinowski et al., 2016) for men, or four for women, within two hours, resulting in a blood alcohol concentration (BAC) of .08 g/dL or higher. This pattern has been linked to numerous adverse consequences, including traffic accidents, assaults, poor academic performance, and cardiovascular issues (Patrick et al., 2020; White et al., 2018). Furthermore, the high prevalence of BD among young adults is specially concerning, as alcohol's neurotoxic effects can disrupt brain development (Hiller-Sturmhöfel et al., 2018). In this sense, adolescence and youth are vulnerable neurodevelopmental periods, during which heavy alcohol use can lead to long-term cognitive and neural consequences, including structural brain alterations, altered neural activity and poorer cognitive functioning (Lees et al., 2020).

Accordingly, literature shows that BD is linked to reductions in gray matter volume as well neurofunctional alterations, particularly in the prefrontal cortex (Doallo et al., 2014; Sousa et al., 2017), and in reward-related regions (Howel et al., 2013; Infante et al., 2022; McQueeny et al., 2009, Rodrigues et al., 2024; Sousa et al., 2019, 2020). Electroencephalography (EEG) studies have shown that adolescents who engage in BD demonstrate altered neurophysiological activity during cognitive tasks, particularly those related to inhibitory control, attention, and working memory (Almeida-Antunes et al., 2021). Specifically, young binge drinkers (BDs) tend to show abnormal hyperactivation (e.g., increased P3 amplitude -associated with

attentional resource allocation and cognitive processing) during task performance, likely reflecting greater neural effort to compensate for executive functioning deficits (Campanella, et al., 2013; Crego et al., 2009; López-Caneda et al., 2012; Schroder et al., 2019; Smith et al., 2016). However, not all studies report hyperactivation; some have instead identified patterns of hypoactivation with reduced amplitude of ERP components similar to those observed in individuals with alcohol use disorders (AUD) (Crego et al., 2010; Maurage et al., 2012; Petit et al., 2014). For example, Crego et al. (2010) found that young BDs exhibited reduced amplitudes in the Late Positive Component (LPC) -a centro-parietal ERP linked to memory updating and attentional processing- which was associated with decreased activation in the anterior prefrontal cortex during recognition phase of a working memory task. These findings suggest that, in certain cases, the neurocognitive alterations induced by BD may not be fully compensated by adaptive mechanisms. As a result, BD can lead to neurofunctional impairments resembling those typically observed in individuals with alcohol use disorder (AUD), particularly in prefrontal regions involved in executive control, attention and memory processing.

Nevertheless, while extensive research has explored the long-term effects of BD (Almeida-Antunes et al., 2021; Carbia et al., 2018; Lannoy et al., 2019; Pérez-García et al., 2022), the acute neurocognitive consequences of alcohol consumption -particularly on the day after drinking (i.e., during the hangover state)- has received considerably less attention (Stephens et al., 2008). Hangovers are typically characterized by symptoms such as headache, fatigue, nausea, and sensitivity to light and sound, which emerge as BAC approaches zero following alcohol consumption (Verster et al., 2020). These symptoms are attributed to a combination of physiological and biochemical processes, including dehydration, electrolyte imbalances, disrupted sleep, accumulation of byproducts such as acetaldehyde, and neuroinflammatory responses (Crews et al., 2015; Penning et al., 2012; van de Loo et al., 2020).

Emerging evidence suggests that the hangover state is associated with significantly impaired cognitive functions (Gunn et al., 2018). Neuropsychological studies have demonstrated that hangovers are accompanied by slower cognitive processing speeds (Grange et al., 2016), deficits in visuospatial memory (Howse et al., 2018), and impairments in core executive functions that are important for everyday behaviors, such as decision-making, planning, and mental flexibility (Gunn et al., 2020), as well as reduced attentional resources and impaired memory consolidation (Ayre et al., 2022).These disruptions are particularly relevant in academic contexts, as hangover-related cognitive deficits may undermine performance in tasks requiring

sustained attention, complex problem-solving, or the ability to adapt to new information (Stephens et al., 2008). Furthermore, higher quantities of alcohol consumed during binge episodes result in more severe hangover symptoms and pronounced neurocognitive impairments the following day (Prat et al., 2008; Verster et al., 2020), potentially compromising students' academic functioning and daily cognitive performance.

The EEG studies on alcohol intoxication and hangover reveal distinct impacts on various cognitive processes, particularly focusing on cognitive flexibility, response selection, and reward-based learning (Howse et al., 2018; Opitz et al., 2019; Stock et al., 2022; Wolff et al., 2018). Specifically, during high-demand memory tasks, response selection was shown to be impaired, while perception and attention were less impacted during intoxication, but seemingly recovered during hangover (Wolff et al., 2018). On the other hand, a study on reward-based learning found that alcohol hangover led to a reduction in the amplitude of the reward positivity -an ERP component associated with learning (Glazer et al., 2018)- and impaired task performance compared to sober states, suggesting that the neural systems underlying performance monitoring and reward-based learning are compromised during hangover (Howse et al., 2018). Lastly, although both response selection and response inhibition rely on controlled processing, the hangover state does not appear to significantly impair inhibitory control, but it does slightly compromise the controlled process of selecting the correct response, possibly because individuals are likely to adopt a more cautious strategy during selection (Opitz et al., 2019), which is consistent with previous findings showing that hangover selectively disrupts controlled response selection rather than inhibition (Grange et al., 2016).

Overall, these studies collectively indicate that high-dose alcohol intoxication selectively impairs top-down cognitive control mechanisms, particularly those involved in response selection, evaluative response inhibition, and performance monitoring (Chmielewski et al., 2020; Stock et al., 2016; Stock et al., 2022). These impairments are most evident in tasks requiring controlled processing or high cognitive demand, while automatic response tendencies and stimulus–response bindings appear to remain largely intact, even under high intoxication levels (Stock et al., 2021). In contrast, hangover effects are more selective and typically spare basic attention and inhibitory functions, although deficits in reward-based learning and controlled response selection may persist. This differential pattern underscores that acute intoxication and hangover involve distinct neurophysiological mechanisms, reflecting different stages of cognitive disruption.

The present study aimed to investigate both the short-term impact of BD during the hangover state and the long-term consequences of repeated BD episodes on attentional and working memory processes,

cognitive functions essential for learning. We hypothesized that these neurofunctional processes would be disrupted during the hangover state and exhibit long-lasting alterations even in sober states, reflecting both acute and cumulative effects of BD.

4.3. Method

4.3.1. Participants

Participants, aged between 18 and 24 (M = 20.15; SD = 1.52), were recruited through a wide-spread online questionnaire in the University of Minho (Braga, Portugal), leading to a final sample comprised of 52 university students, including 24 Binge Drinkers (BDs) (15 females) and 28 Controls (20 females) (see Table 6 for details). The BD group consisted of individuals who consumed five or more alcoholic standard drinks (four or more for women) -approximately 10g of pure ethanol each as defined by Kalinowski and Humphreys (2016)- on a single occasion within two-hour period, reaching a BAC of .08 g/dL or higher at least once a month over the past year. On the other hand, the Control group consisted of participants who had never experienced a BD episode and scored < 4 on the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001). Additionally, participants who met any of the exclusion criteria listed in Table 7 were not included in the study.

Table 6. Demographic and drinking characteristics of the BD and control groups (mean [SD]).

	Controls Mean ± SD	**Binge Drinkers** Mean ± SD	*t* (34)
Demographic Measures			
N (female)	28 (20)	24 (15)	
Caucasian ethnicity (%)	100	100	
Age	20.44 (1.97)	20.20 (1.32)	.52
Drinking characteristics			
AUDIT (total score)	.92 ± .86	11.52 ± 3.61	-14.29***
Binge Frequency (AUDIT Q3)	0	2.29 ± .46	-25.68***
Standard drinks[1] consumed in a typical week	.15 ± .53	13.17 ± 10.60	-6.39***
Alcohol Craving (PACS total score)	.70 ± 1.94	5.50 ± 4.67	-4.89***

Standard drinks[1] consumed the night before hangover state assessment	-	11.21 ± 2.60	
Alcohol Hangover Severity Scale during the hangover state assessment		49.79 ± 18.95	
Impulsivity (BIS11)			
Total Score	58.00 ± 7.01	59.42 ± 6.96	-0.63
Attentional	15.05 ± 2.61	14.89 ± 2.49	0.19
Non-planning	22.00 ± 4.22	22.58 ± 3.22	-0.48
Motor	20.95 ± 3.00	21.95 ± 3.08	-1.01

*Note: AUDIT, Alcohol Use Disorders Identification Test; BIS11, Barratt Impulsiveness Scale 11; BD, Binge Drinking; PACS, Penn Alcohol Craving Scale; DUDIT, Drug Use Disorder Identification Test; SD, standard deviation. All p-values reported are for two-tailed independent samples t-tests. [1]A standard drink is defined by 10g of pure ethanol. *p ≤ .05. **p ≤ .01. ***p ≤ .001.*

Table 7. Exclusion criteria for both groups.

Exclusion Criteria	**Details**
Sensory Deficits	Non-corrected sensory deficits
Loss of Consciousness	Any episode ≥ 20 minutes
Traumatic Brain Injury (TBI)	Personal history of TBI
Neurological Disorders	Any diagnosed neurological disorder
Psychopathological Disorders	Personal history of DSM-V Axis I & II disorders
Psychopathological Symptoms	SCL-90-R quartile > 90 in ≥ 2 symptom dimensions or overall scale
Alcohol Use Disorder (AUD)	AUDIT score ≥ 20
Cannabis Consumption	Regular use (more than once a week)
Other Drug Use	Regular or occasional use of opiates, hallucinogens, cocaine, amphetamines, or medically prescribed psychoactive substances
Psychopathological Family History	Major depressive disorder, schizophrenia, anxiety disorders, or alcoholism in first-degree relatives

Note: AUDIT, Alcohol Use Disorders Identification Test; SCL-90-R, Symptom Check List 90 Revised.

4.3.2. Procedure

Participants were required to provide informed consent following the ethical guidelines of the Subcomissão de Ética para as Ciências Sociais e Humanas of the University of Minho and the Code of Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki. Then, they underwent a clinical interview that explored specifically, but not exclusively their clinical history as well as their alcohol and substance use patterns (See Table 8).

Table 8. Clinical interview questionnaires and scales.

Questionnaire/Scale	**Reference**
Alcohol Use Disorder Identification Test	Babor et al., 2001
Selected items from the Alcohol Use Questionnaire	Townshend et al., 2002
Penn Alcohol Craving Scale (PACS)	Pombo et al., 2008
Drugs Use Disorder Identification Test - Extended	Berman et al., 2007
Symptom Checklist-90-Revised (SCL-90-R)	Laloni, 2001
Barratt Impulsivity Scale-11 (BIS-11)	Pechorro et al., 2018
Edinburgh Handedness Inventory	Espírito-Santo et al., 2017

After the clinical interview, participants who did not meet any exclusion criteria were divided into two groups: BDs and Controls. BDs underwent EEG assessments during the performance of CPT on two occasions: once on a non-drinking day with no alcohol consumption in the previous day and no BD episode in the last three days, and once during a hangover state following a BD episode -to assess short term effects of BD-. The control group underwent a single EEG assessment where participants were asked to perform the same task.

Participants in the BD group were randomly assigned to counterbalance the order of the assessments: half completed the EEG assessment on a non-drinking day, followed by the assessment during hangover state, while the other half completed the assessment in the reverse order (hangover state first). For the hangover state evaluation, participants were asked to contact the experimenters when they anticipated having a BD episode, scheduling the hangover evaluation for the following day. Furthermore,

participants used the mobile application *AlcoDroid Alcohol Tracker* (Wróblewski et al., 2020) during the BD night to log their alcohol consumption, guaranteeing their BAC reached .08 g/dL, and. Participants were instructed to abstain from substances other than alcohol and to sleep between six and nine hours before data collection. They were also instructed to refrain from smoking and consume tea or coffee for at least one hour before the assessment. Finally, on the day of assessment, breathalyzer tests were conducted to confirm a 0% breath alcohol level, and participants were asked to fulfill the Alcohol Hangover Severity Scale (AHSS) (Penning et al., 2013) before the EEG assessment.

4.3.3. Task

Participants performed a visual CPT (Cornblatt et al., 1988; Crego et al., 2010). Two hundred stimuli measuring 2.6° × 2.6° of visual angle were presented randomly at the center of a computer monitor placed 100 cm in front of the participant's eyes. Each stimulus was displayed for 50 ms with an interstimulus interval (ISI) varying between 2500 and 2800 ms. The stimuli consisted of 60 different abstract figures, which were difficult to verbalize. Participants were instructed to press a button with their preferred hand when the same stimulus appeared in two consecutive trials (matching stimuli, 20% of trials) and did not respond otherwise (non-matching stimuli, 80% of trials) (see figure 5).

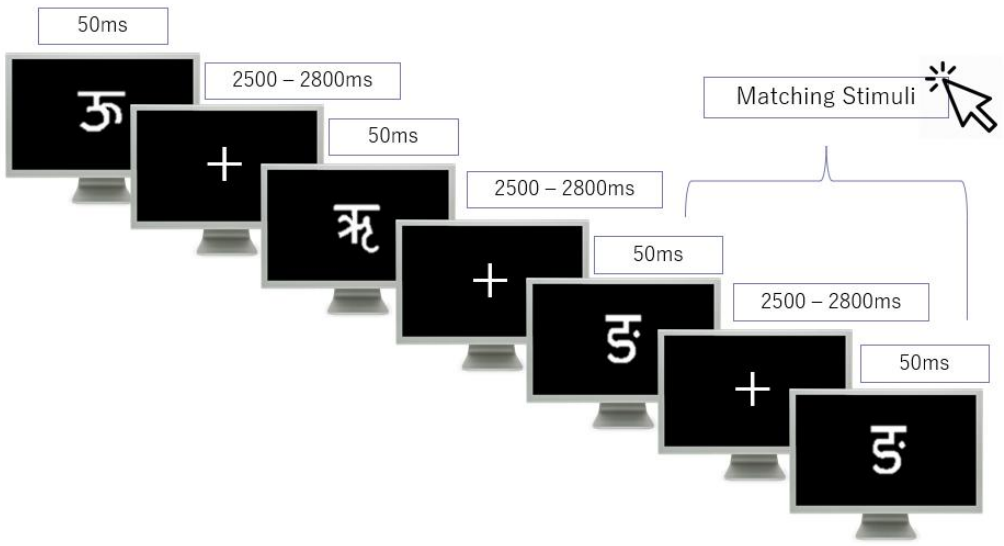


Figure 5. The overall depiction of the one back task. Example of two non-matching stimuli (80% of the stimuli), followed by a matching pair (20% of the stimuli).

4.3.4. EEG Recording and ERP Analysis

EEG was recorded using the Biosemi system, following the 10/10 electrode placement system and a Common Mode Sense (CMS) montage, with a headcap equipped with 64 sintered Ag–AgCl electrodes. Vertical electrooculogram activity was recorded from an electrode placed below the left eye, whilst horizontal eye movements were recorded with bipolar electrodes placed by the outer side of each eye to control for eye movements and blinks. All electrodes were adjusted to maintain their offset lower than 30 mV. The EEG signals were continuously amplified and digitized at a rate of 500 Hz and filtered online with a .01–100 Hz band pass filter.

EEG data was processed and visualized using BrainVision Analyzer 2.2 (Brain Products GmbH, Munchen, Germany). As needed, topographic interpolations were run to maximum 5 electrodes per participant. The signal was re-referenced using the average of all electrodes and then filtered digitally off-line between .1 and 30 Hz via phase shift free Butterworth filter (24 dB/octave roll-off) with an additional notch filter at 50 Hz. Ocular artefacts were corrected using the semi-automatic Independent Component Analysis (ICA) procedure. EEG was segmented into epochs from 100 ms prior to stimulus onset to 900 ms after. Pre-stimulus baseline was adjusted to 0 μV, and epochs with artifacts exceeding ±80 μV at any datapoint were rejected. Subsequently, epochs were averaged by condition (matching and no-matching) separately for each participant, excluding those corresponding to false alarms and omissions.

ERPs were further analyzed by principal component analysis (PCA) with Dien's ERP PCA toolkit (v. 2.68) in MATLAB (Mathworks, v. 9.4.0.885841, R2018a, USA) (Dien, 2010). Data were resampled to 250 points/s and temporal PCA was then computed with a promax rotation. Parallel analysis identified 12 factors, explaining a total variance of .9470. Peak latencies, polarity, and explained variance for each factor are summarized in Table 9. Based on its temporal distribution and polarity, TF2 was identified as the P3, while TF3 corresponded to the LPC (see Figure 6). Using the maximum peak as the center reference, the mean amplitude of TF2 was extracted with a ±50 ms window (total 100 ms), and the mean amplitude of TF3 with a ±100 ms window (total 200 ms), for each subject and condition (matching and non-matching). A total of 10 electrodes were selected for each component for subsequent analysis: for TF2 (P3), five from the Centro-Parietal Region (CP1, CP3, CPz, CP2, CP4) and five from the Parietal Region (P1, P3, Pz, P2, P4); for TF3 (LPC), five from the Central Region (C1, C3, Cz, C2, C4), and five from the Centro-Parietal Region (CP1, CP3, CPz, CP2, CP4).

Table 9. Temporal PCA factors: All the factors identified are ordered by the explained variance, with their latency (ms), maximum negative and positive locations and peak polarity. The factors with the event-related potential (ERP) components of interest for the study (P3 and LPC) are included in the final column.

Factor	Peak Latency (ms)	Peak (-) Channel	Peak (+) Channel	Largest Peak Polarity	Variance	Unique Variance	ERP Wave Identified
TF01	673.4375	P9	CP2	-	.3790	.1686	
TF02	341.4062	P9	Pz	+	.2980	.1064	P3
TF03	558.2031	P10	Pz	-	.0697	.0163	LPC
TF04	148.0469	PO8	Poz	-	.0416	.0280	
TF05	208.5938	P10	Cz	-	.0377	.0209	
TF06	267.1875	Fp2	PO7	+	.0288	.0152	
TF07	108.9844	AF3	PO8	+	.0273	.0133	
TF08	450.7812	Iz	P1	-	.0233	.0094	
TF09	872.6562	P10	F2	-	.0171	.0137	
TF10	175.3906	PO7	Fz	-	.0132	.0069	
TF11	310.1562	PO8	F7	-	.0069	.0057	
TF12	67.9688	Poz	F4	+	.0046	.0046	

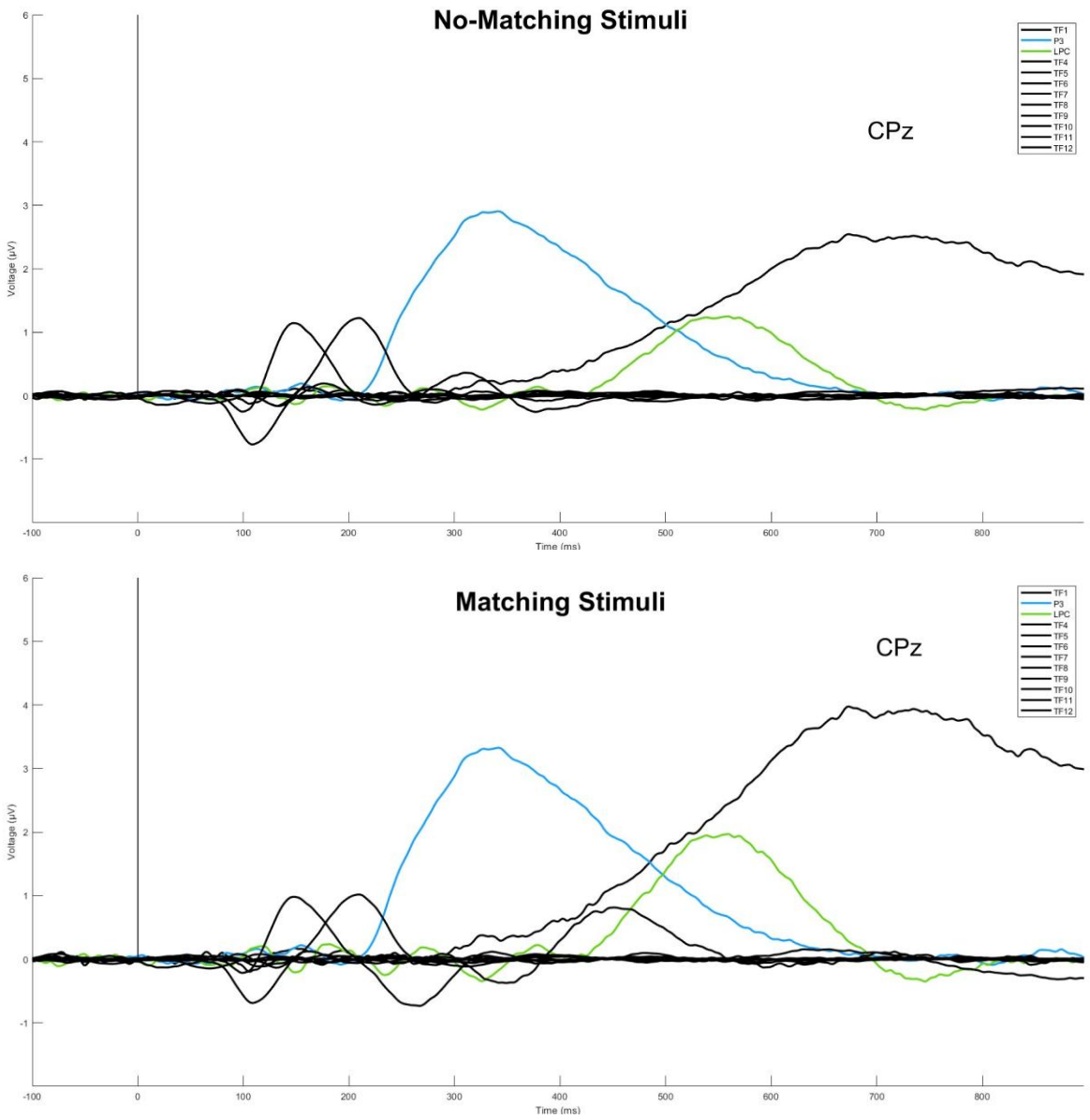


Figure 6. Plots of the grand average waveforms of factor (component) loadings in response to each stimulus at CPz. Temporal factors identified as P3 and LPC are highlighted in blue and green, respectively.

4.3.5. Data Analysis

Behavioral data, including response times, percentage of correct responses, and false alarms, were analyzed using t-tests for dependent samples with assessment (non-drinking day vs. hangover state) as the independent variable. Furthermore, behavioral data was analyzed using t-tests for independent samples, comparing BDs on a non-drinking day with the control group.

For EEG data, two repeated-measures analysis of variance (ANOVAs) were conducted to examine potential differences in P3 and LPC amplitudes. The first ANOVA focused on the BD group and aimed to compare the neural responses across two time points: during a non-drinking day and during a hangover state -short term effects of BD-. This analysis included four within-subject factors: assessment (non-drinking day vs. hangover state), condition (non-matching vs. matching), region (Centro-Parietal vs Central or Parietal, depending on the ERP component) and electrode (five for per region). The second repeated-measures ANOVA was conducted to compare the BD group (in the non-drinking condition) with the Control group -long term effects of BD-. This analysis included one between subjects factor (Group: Controls vs BDs on a non-drinking day) and the same three within-subjects factors: condition, region and electrode. P3 and LPC were analyzed separately, with an alpha level set at ≤ .05. When appropriate, degrees of freedom were corrected using the Greenhouse-Geisser estimate. Post hoc pairwise comparisons were performed with the Bonferroni adjustment for multiple comparisons, also with an alpha level ≤ .05.

Spearman's bilateral correlations were used to examine the relationships between alcohol use variables (AUDIT score, PACS score, quantity of alcohol consumed in a typical week, AHSS score, and quantity of consumed during the BD episode on the day preceding the hangover state assessment) and neurofunctional responses (P3 and LPC amplitudes) during both the non-drinking day and hangover assessments.

4.4. Results

4.4.1. Hangover severity

BDs reported an average score of 49.79 in the AHSS during hangover state – 44 being the cutoff for severe hangover –, with all participants reporting above the 13 points cutoff for mild hangover (Figure 7).

4.4.2. Behavioral results

Behavioral analyses did not reveal significant differences between the BDs assessments non-drinking day and hangover state, neither when comparing Controls with BDs on a non-drinking day. Nonetheless, a tendency was observed, with BDs exhibiting a higher percentage of correct responses during the non-drinking day compared to the hangover state [$t(22) = 1.43$, $p = .08$], as well as lower reaction times [$t(22) = -1.51$, $p = .07$]. Moreover, a tendency for a smaller reaction time from BDs on a non-drinking day when compared to Controls [$t(48) = -1.68$, $p = .10$] (see Table 10).

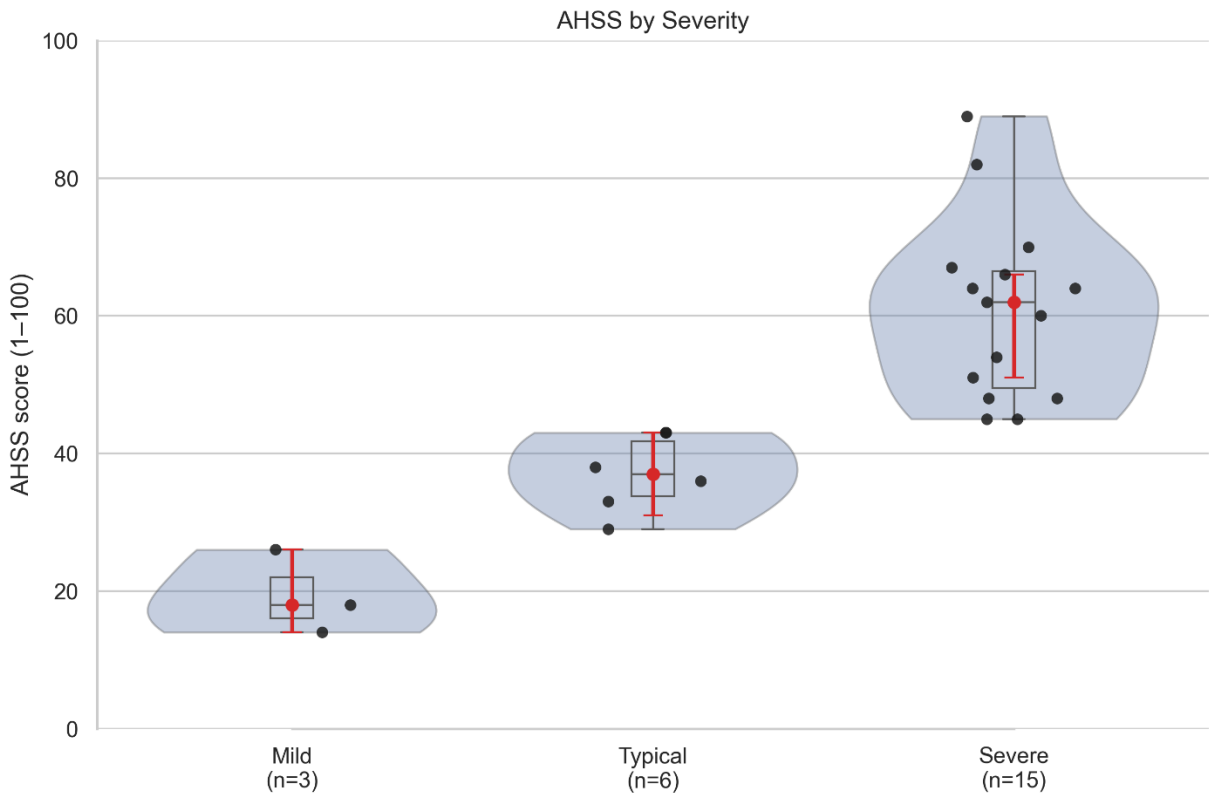


Figure 7. Distribution of AHSS scores by severity group. Violin plots show the kernel-density distribution; boxplots show the interquartile range with median; red markers show group median ± 95% bootstrap CI (2,000 resamples).

Table 10. Behavioral data from the control group and the BD group across both assessment sessions (mean ± SD).

Behavioral performance	**Controls**	**Binge Drinkers**	
		Non-drinking day	*Hangover State*
% Correct responses	84.10 ± 16.93	89.20 ± 8.10	84.65 ± 16.65
% False Alarms	2.58 ± 1.65	2.96 ± 1.77	2.83 ± 2.10
Correct response time (ms)	617.59 ± 103.54	571.90 ± 85.12	593.61 ± 98.30

4.4.3. Electrophysiological results

The analysis of P3 revealed a significant effect of the assessment factor [F(1, 23) = 5.21, p = .032], with P3 amplitude being significantly larger in the non-drinking day (M = 3.03, SD = .31) than in hangover state (M = 2.52, SD = .27). Additionally, there was a significant effect for the Region factor [F(1, 23) = 18.82, p < .001], with P3 amplitude being significantly larger in the parietal region (M = 3.19, SD = .32) than in the centro-parietal region (M = 2.35, SD = .24). No significant differences were found for the condition factor. The parallel analysis, comparing BDs on a non-drinking day with Controls revealed no significant effect of group for the P3 component. (Figure 8).

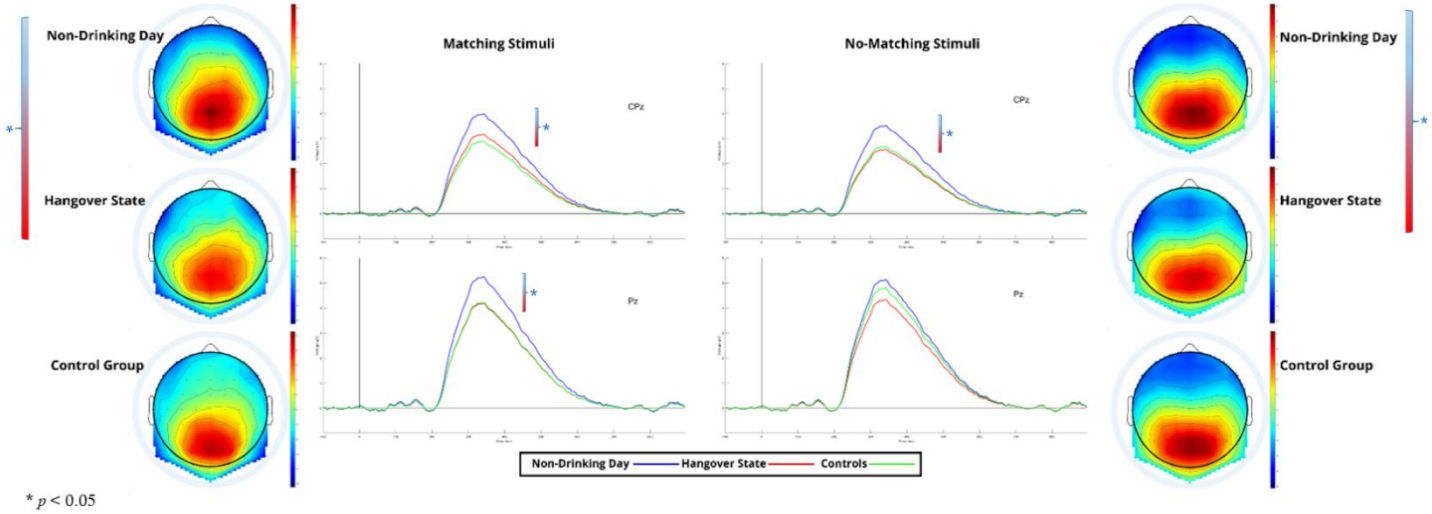


Figure 8. P3 (TF02) waves for matching and non-matching stimuli of the centro-parietal and parietal regions, with the respective voltage topographical distributions at the P3 peak in response to the matching and non-matching stimuli.

The analysis regarding LPC revealed a significant effect of the assessment factor [F(1, 23) = 5.25, p = .031], with larger LPC amplitudes during the non-drinking day (M = .53, SD = .07) compared to hangover state (M = .41, SD = .04). Furthermore, the Region factor also showed a significant effect [F(1, 23) = 16.88, p < .001], with larger LPC amplitudes in the centro-parietal region (M = .54, SD = .05) than in the central region (M = .40, SD = .05). In addition, the Condition factor had a significant effect on the LPC amplitude [F(1, 23) = 13.38, p = .001], which was larger in the matching (M = .56, SD = .06) than in the non-matching condition (M = .38, SD = .05). On the other hand, the parallel analysis comparing BDs on a non-drinking day and Controls revealed a significant effect of group [F(1, 50) = 7.63, p = .008], with larger LPC amplitudes for the BDs on a non-drinking day (M = .53, SD = .07) compared to Controls (M = .33, SD = .05) (Figure 9).

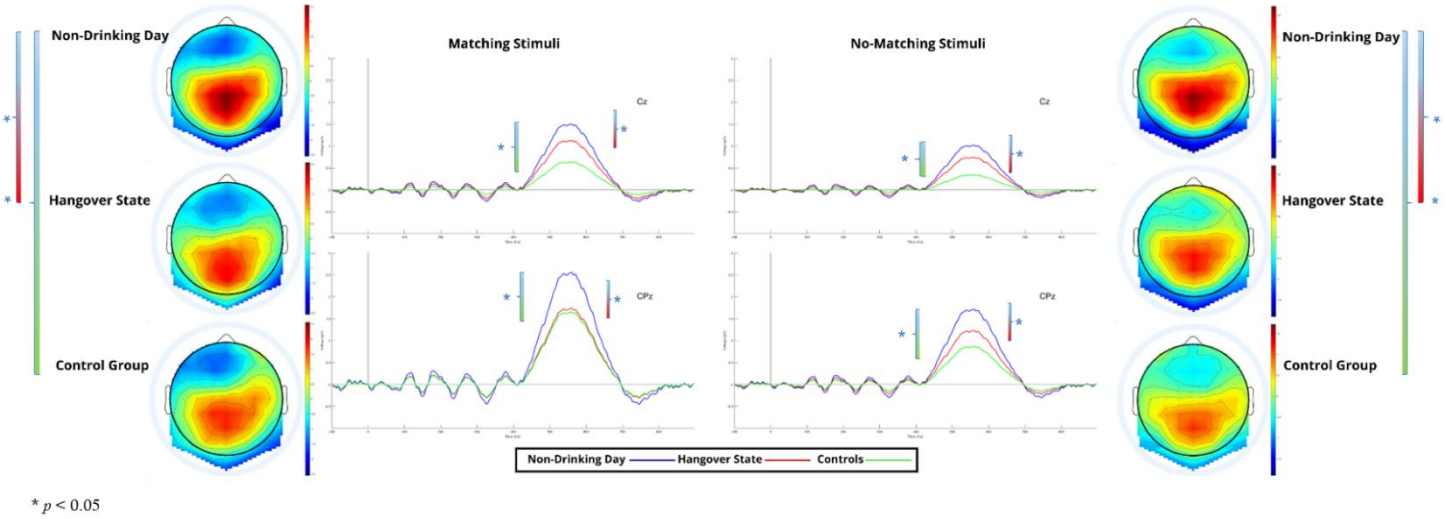


Figure 9. LPC (TF03) waves for matching and non-matching stimuli of the central and centro-parietal regions, with the respective voltage topographical distributions at the LPC peak in response to the matching and non-matching stimuli.

4.4.4. Correlation analysis

Spearman's correlations revealed a significant negative association between PACS score and P3 amplitude in the BD group during the hangover state [$r = -.438$, $p < .05$]. Additionally, a significant negative correlation was observed between LPC amplitude during the hangover state and the quantity of alcohol consumed during the BD episode on the day prior to the assessment [$r = -.548$, $p < .01$]. No correlations were found between either AHSS scores nor hangover severity and neurofunctional alterations.

4.5. Discussion

The present study investigated both the short-term neurocognitive effects of a BD episode -specifically during the hangover state- and the long-term consequences (when compared to controls) of maintaining a BD pattern over several years, in comparison with non- or low-drinkers. In particular, it focused on the impact of BD and alcohol hangover on attention and working memory, using electrophysiological markers (P3 and LPC components) as indicators of cognitive functioning. Although no significant behavioral differences were found between assessments (non-drinking day vs. hangover state) or between groups, as we hypothesized, neurophysiological data revealed significant short-term reductions in P3 and LPC amplitudes in young BDs during the hangover state, which were, in turn, associated with craving levels and the amount of alcohol consumed during the BD episode on the preceding day, respectively. In contrast, when compared to controls,

BDs exhibited increased LPC amplitudes, likely reflecting long-term neural adaptations associated with sustained alcohol use.

The P3 component, particularly in visual working memory tasks, reflects the brain's response to detection and discrimination between relevant and non-relevant stimuli (Polich et al., 2007; Reed et al., 2022). The current study showed that BDs exhibit a reduced P3 amplitude during hangover conditions compared to a non-drinking day. This finding aligns with previous research demonstrating that alcohol hangover causes a short-term impairment on attention and memory-related processing (Devenney et al., 2019; Heffernan et al., 2019; Verster et al., 2003). The diminished P3 amplitude likely reflects reduced neural efficiency in processing task-relevant stimuli, paired with a reduced ability to allocate sufficient attentional resources to the task at hand, potentially due to neuroinflammatory responses and brain's metabolic stress during alcohol hangover (Mackus et al., 2020; Palmer et al., 2019).

Under normal conditions, BDs often rely on increased P3 amplitudes as a compensatory mechanism to maintain cognitive task performance (Almeida-Antunes et al., 2021; Crego et al., 2012; López-Caneda et al., 2013; Park et al., 2018). Consequently, the absence of neurophysiological alterations between BDs on a non-drinking day and controls, coupled with preserved task performance, may reflect the relative simplicity of the working memory paradigm. This task might not have been sufficiently demanding to reveal underlying deficits, consistent with prior findings showing no behavioral differences in a CPT between BDs and controls (Campanella et al., 2013; Crego et al., 2009; Howland et al., 2010; Park et al., 2018). Nevertheless, the reduced P3 amplitude observed during hangover may indicate a diminished capacity for such compensatory mechanisms.

The LPC, an ERP component associated with memory consolidation/updating and evaluative processes (Fields, 2023; Palmer et al., 2013), plays a critical role in information integration, decision-making, and feedback processing (Bland & Schaefer, 2011). These cognitive processes are frequently disrupted in individuals with a history of BD, as evidence suggests that alcohol's neurotoxic effects can impair the neural networks responsible for memory and evaluative functions (Rodríguez et al., 2023; Vetreno et al., 2018). Notably, when comparing BDs on a non-drinking day and in a hangover state, reductions in LPC amplitude were observed. These neurophysiological alterations observed in BDs during hangover, coupled with a tendency for poorer task performance, further support the findings related to the P3 component. Taken

together, these results suggest an impaired ability not only to allocate attentional resources to the task but also to sustain evaluative efforts or adaptive decision-making processes required by the CPT.

Interestingly, BDs demonstrated elevated LPC amplitudes on non-drinking days compared to controls. This finding may suggest a compensatory recruitment of neural resources to offset cognitive processing inefficiencies caused by the long-term effects of BD (Almeida-Antunes et al., 2021; Rodríguez Holguín et al., 2023; Pérez-García et al., 2022), reflecting heightened reliance on prefrontal-hippocampal connectivity to maintain task performance, aligning with previous studies that link increased neural activation to impaired efficiency in BDs (Campanella et al., 2013; Correas et al., 2021; Lannoy et al., 2019; Molnar et al., 2018; Schweinsburg et al., 2010; Squeglia et al., 2011; Suárez-Suárez et al., 2020). Although compensatory mechanisms appear to temporarily buffer against overt performance declines on a non-drinking day, the observed amplitude reductions during hangover raise concerns about the long-term sustainability of these adaptations, particularly with repeated binge episodes. Specifically, continuous compensatory brain activation observed in BDs may, over time, contribute to cognitive fatigue and neural inefficiency, as the brain persistently recruits additional resources to maintain performance (Chanraud & Sullivan, 2014). This heightened effort can tax functional reserves and may ultimately lead to reduced processing capacity, impaired executive control, and an increased vulnerability to long-term cognitive decline (Correas et al., 2021; Campanella et al., 2013; Crego et al., 2009; Wang et al., 2016).

Finally, the correlations observed during the hangover state further reinforce our findings. Specifically, stronger alcohol craving in BDs was linked to a reduced P3 amplitude during hangover. This negative relationship may reflect a diminished allocation of cognitive resources to task-relevant stimuli, as individuals with higher trait-level craving tend to exhibit heightened salience attribution to alcohol-related cues (Robinson & Berridge, 2008; Goldstein & Volkow, 2011), which can persist even in the absence of acute exposure and may interfere with working memory processes (Polich, 2007; Jones et al., 2013). Moreover, lower LPC amplitude during hangover was associated with greater alcohol intake during the BD episode on the preceding day, suggesting that the more intense and hazardous the BD episode, the more pronounced the subsequent neural alterations. Repeated engagement in this pattern of consumption may therefore contribute to a progressive trajectory toward alcohol use disorder and emerging behavioral impairments (Almeida-Antunes et al., 2021; Enoch, 2006; Lannoy et al., 2019).

Collectively, the findings of this study provide critical insights into the short- and long-term effects of BD in young adults. Alcohol hangovers, characterized by neurofunctional disturbances in attentional and memory-related processes, as evidenced by reductions in P3 and LPC amplitudes, may significantly undermine cognitive performance in demanding tasks, such as academic examinations or complex problem-solving activities (Stephens et al., 2008). The normalization of BD in university settings exacerbates these risks, as recurrent hangover experiences could lead to cumulative neural inefficiencies over time, potentially impairing both academic and personal development (Kuntsche et al., 2017).

Several limitations of the present study must be acknowledged. First, although there was a tendency for poor task performance among BDs during the hangover state, the lack of statistically significant behavioral differences may be attributed to the relative simplicity of the working memory task, rather than an absence of cognitive impairments. Tasks with higher ecological validity or those targeting broader cognitive domains may be more sensitive in detecting subtle long-term deficits. Second, individual differences in drinking patterns, hangover severity, and lifestyle factors (e.g., sleep quality, hydration) might have contributed to the observed effects. Future research should integrate these variables to improve the robustness of the findings and to further explore the broader neural consequences of BD and alcohol hangover. Longitudinal studies will also be essential to assess the evolution of compensatory mechanisms over time and determine their implications for cognitive decline. Finally, future research should investigate whether the observed EEG changes during hangover reflect temporary fronto-parietal hypoactivity or neurochemical alterations by using neuroimaging (e.g., fMRI, magnetic resonance spectroscopy and positron emission tomography) comparing non-drinking days and hangover state. Combining task-evoked BOLD with markers of metabolism or inflammation would clarify whether reduced P3/LPC amplitudes are linked to metabolic suppression or neuroinflammatory processes.

In conclusion, this study highlights the significant short-term neurophysiological impacts of BD on attentional resource allocation and memory processing in young individuals, particularly during the hangover state on the day following episodes of excessive alcohol consumption. While some long-term effects may be temporarily masked by compensatory neural mechanisms, repeated BD and hangover episodes could contribute to progressive neurophysiological and behavioral decline, resembling patterns typically associated with alcohol use disorders. These findings underscore the need to develop targeted public health strategies that address not only the long-term risks of BD, but also its immediate cognitive and neurofunctional

consequences, which may affect everyday performance in tasks involving attention and working memory processes, such as academic achievement or decision-making. Thus, raising awareness about these short-term effects could help enhance the effectiveness of prevention strategies among young drinkers.

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Chapter V

Associative memory in alcohol-related contexts: An fMRI study with young binge drinkers

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5.1. Abstract

Background: Alcohol-related cues are known to influence craving levels, a hallmark in alcohol misuse. Binge drinking (BD), a pattern of heavy alcohol use, has been associated with cognitive and neurofunctional alterations, including alcohol attentional bias, memory impairments, as well as disrupted activity in prefrontal and reward-related regions. However, literature is yet to explore how memories associated with alcohol-related cues are processed by binge drinkers (BDs), and how the recall of this information may influence their reward processing.

Aims: The present functional magnetic resonance imaging (fMRI) study aimed to investigate the neurofunctional signatures of BD during an associative memory task.

Method: Thirty-six university students, 20 BDs and 16 alcohol abstainers, were asked to memorize neutral objects paired with either alcohol or non-alcohol related contexts. Subsequently, neutral stimuli were presented, and participants were asked to classify them as being previously paired with alcohol- or non-alcohol-related contexts.

Results: While behavioral performance was similar in both groups, during the recall of alcohol-related-cues, BDs showed increased brain activation in two clusters including the thalamus, globus pallidus and dorsal striatum, and cerebellum and occipital fusiform gyrus, respectively.

Conclusion: These findings suggest that BDs display augmented brain activity in areas responsible for mental imagery and reward processing when trying to recall alcohol-related cues, which might ultimately contribute to alcohol craving, even without being directly exposed to an alcohol-related context. These results highlight the importance of considering how alcohol-related contexts may influence alcohol seeking behavior and, consequently, the maintenance or increase of alcohol use.

5.2. Introduction

Alcohol use is the seventh leading risk factor for premature death, with hazardous consumption patterns contributing to over 5% of all global deaths (Griswold et al., 2018; World Health Organization [WHO], 2019). Particularly, among young people, alcohol use plays a significant social role, being an integral part of academic traditions and parties (Dormal et al., 2019; Kuntsche et al., 2005; Patrick et al., 2016). This social aspect of alcohol consumption is particularly concerning, as alcohol misuse is linked to more than 30% of deaths among individuals aged 15 to 29 years in both America and Europe (WHO, 2011).

Binge drinking (BD) is a recurrent alcohol consumption pattern characterized by alternating episodes of excessive alcohol consumption and periods of abstinence or low consumption. During BD episodes, individuals reach a blood alcohol concentration of 0.08g/dL or higher, typically achieved by consuming five or more drinks for cisgender men and four or more drinks for cisgender women within a 2-hour interval (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2004, 2022). The periods of abstinence or low consumption can last from several days to several weeks, leading to intoxication/abstinence cycles (Maurage et al., 2020). Additionally, it is common to establish as a criterion for this pattern that BD episodes should occur at least once or twice per month during the last 12 months (Courtney & Polich, 2009; Maurage et al., 2020; NIAAA, 2022; Parada et al., 2011). This consumption pattern is a problematic form of alcohol misuse highly prevalent among young people, and notably widespread among European and American college students, with more than one-third engaging in recurrent BD episodes at least once a month (Kraus et al., 2016; NIAAA, 2020). This highlights the concerning prevalence of BD in this population and underscores the significant impact of the college environment on alcohol consumption (Cadigan et al., 2015).

The high prevalence of BD during adolescence and youth is particularly worrying due to the critical neuromaturational processes occurring at these developmental stages (Jones et al., 2018; Sousa et al., 2018). Namely, structural and functional brain changes, such as synaptic pruning and myelination, take place in regions of late neuromaturation like the prefrontal cortex, an area crucial for the development of higher-level cognitive functions, including working memory, inhibitory control, and decision making (Fuhrmann et al., 2015; Gogtay et al., 2004; Luna et al., 2010). These changes render the brain highly vulnerable to the neurotoxic effects of alcohol (Crews et al., 2016). Specifically, alcohol interferes with these processes by disrupting the formation of new neural connections and damaging existing neural pathways, leading to long-term cognitive deficits and impaired brain function (Jacobus et al., 2013). This disruption can

result not only in reduced cognitive abilities, but also poor academic performance, and increased risk of developing psychiatric disorders (Castellanos-Ryan et al., 2020).

BD has often been associated with enhanced impulsivity and reduced inhibitory control (Crews & Boettiger, 2009; Cservenka & Brumback, 2017; Dalley & Robbins, 2017; López-Caneda et al., 2014a). These behavioral alterations have been linked to abnormalities in the frontostriatal system (see Pérez-García et al., 2022, for a review). In particular, studies have found increased volume in the dorsolateral prefrontal cortex, nucleus accumbens, dorsal cingulate, and precuneus among individuals who engage in BD, suggesting that the structural alterations in these areas may underlie the impaired cognitive functions commonly observed in this population (Banca et al., 2016; Doallo et al., 2014; Sousa et al., 2017, 2020). Additionally, binge drinkers (BDs) frequently exhibit brain hyperactivation when compared to their control peers (Cservenka & Brumback, 2017; Schacht et al., 2013; Sousa et al., 2019). Notably, increased prefrontal activity during behavioral or cognitive inhibition tasks has been interpreted as a neurocompensatory mechanism -i.e., the recruitment of additional neural resources- that allows BDs to perform the task at the same level as controls (Almeida-Antunes et al., 2024; Ames et al., 2014; Correas et al., 2021; López-Caneda et al., 2012; Molnar et al., 2018; Suárez-Suárez et al., 2020; Wetherill et al., 2013). Similarly, studies exploring memory processes in BDs have revealed increased fronto–parietal and hippocampal activity during the novel and/or correct encoding of visual or verbal items (Dager et al., 2014; Schweinsburg et al., 2010). This suggests that the less efficient neural processing and compensatory mechanisms observed in inhibitory control are also present during working memory tasks. Moreover, stronger memory for alcohol-related associations -i.e. better recall- for alcohol-related associations was found to be predictive of heavier drinking in patients with alcohol use disorder (AUD) (Goldfarb et al., 2020), underscoring the importance of associative memory in understanding alcohol consumption in real-life scenarios.

Associative memory is defined as the ability to link together two or more memories/items (e.g., images, words, sounds, places) that can later be retrieved through recognition or recall of one of them (Mayes et al., 2007). In the context of alcohol use, this involves stimuli associated with alcohol-related contexts, such as bars, bottles of alcoholic beverages, people drinking and cheering or logos of popular alcohol brands. These stimuli are often encountered in social settings and can trigger memories and associations related to drinking behavior, and alcohol-related cues can elicit craving and influence drinking behavior, a well-documented phenomenon in individuals with AUD (Seo et al., 2014). In contrast, neutral cues are stimuli

that have no direct connection with alcohol consumption. These might include everyday objects, like books, pens, or images of neutral environments, such as a park or a classroom.

Although no study to date has explored brain activity linked to associative memory involving both neutral and alcohol-related cues in young BDs, evidence indicates that the neurofunctional correlates of associative memory are similar to those observed in craving, the formation of consumption habits, and alcohol cue-induced reactivity in heavy alcohol users (Courtney et al., 2016; Kim, 2011; Janak & Chaudhri, 2010; Park et al., 2007; Schacht et al., 2013; Scimeca & Badre, 2012). Specifically, encoding of pairs of images involves activation of a widely spread brain network, including the fusiform gyrus, the precuneus, the hippocampus, and the prefrontal and occipital cortices (Becker et al., 2015; de Chastelaine et al., 2016; Kim, 2011). Memory retrieval, on the other hand, activates regions such as the prefrontal cortex, striatum, and hippocampus (Schott et al., 2019; Scimeca & Badre, 2012). Additionally, the amygdala, the precuneus, and sensory regions including the fusiform gyrus and the occipital cortex, recruited during encoding, are often reactivated during recall, particularly if the memorized information has emotional significance or was encoded through mental imagery (Danker & Anderson, 2010). Likewise, research has shown that heavy alcohol users display higher cue-reactivity to alcohol stimuli, exhibiting increased brain activity in the prefrontal (e.g., ventromedial and dorsolateral prefrontal cortex) and visual (e.g., fusiform gyrus and precuneus) regions as well as in several structures of the limbic system, including the striatum and the thalamus (Courtney et al., 2016; Fukushima et al., 2020; Huang et al., 2018; Park et al., 2007; Schacht et al., 2013). In a related vein, the mechanisms underlying cue-induced craving, commonly observed in addiction (Heinz et al., 2009; Witteman et al., 2015), have been closely related to associative memory (Janak & Chaudhri, 2010). Both processes entail linking of two or more stimuli -whether internal or external- that can later be recalled, either intentionally or spontaneously, upon encountering with one of them (Pershin & Di Ventra, 2010; Wrase et al., 2007).

Notwithstanding, research on the relation between associative memory and the processes underlying alcohol craving (e.g., attentional bias, reward processing, habit formation), and how these interact with alcohol use is still scarce. Aiming to fill this gap, the present study aimed to explore the brain mechanisms involved in the recall of alcohol-related contexts in young BDs. Hence, we conducted a whole-brain functional magnetic resonance imaging (fMRI) analysis and compared cue-induced brain activation between BDs and alcohol abstainers when recalling alcoholic or non-alcoholic contexts in response to associated neutral stimuli.

According to previous research showing augmented brain activity in the reward and the fronto-occipital networks during both the processing of alcohol-related cues and encoding/recovery of visual memories (Almeida-Antunes et al., 2022; Brumback et al., 2015; Courtney et al., 2015; Dager et al., 2014), we hypothesize that BDs will display increased activation of the reward and memory brain regions when recalling alcohol-related contexts.

5.3. Method

5.3.1. Participants

Participants aged between 18-23 years were recruited via an online survey and divided into two groups. Inclusion criteria for the BD group required participants to have consumed four or more drinks for women (five or more for men) in less than two hours at least once per month for the past ten months, ensuring a consistent pattern of BD. The second group served as the control group, consisting of alcohol abstainers without a drinking history; that is, they had never consumed alcohol and, thus, had never experienced a BD episode in their lives. Preselected participants completed a clinical interview including different questionnaires (see Table 11), which assessed their eligibility to participate in the study. Participants were excluded from either group based on the following criteria: a score of 20 or higher on the Alcohol Use Disorders Identification Test (AUDIT), indicating alcohol abuse or dependence; left-handedness, as indicated by a score of -40 or lower on the Edinburgh Handedness Inventory; a Global Severity Index score ≥ 90, or a score ≥ 90on at least two symptomatic dimensions of the SCL-90-R; uncorrected sensory deficits (e.g., participants with poor eyesight who do not use glasses or contact lenses); a personal history of traumatic brain injury or neurological disorder; regular cannabis consumption (i.e., weekly use); a personal history of regular or occasional use of other drugs, including opiates, hallucinogens, cocaine, ecstasy, amphetamines, or medically prescribed psychoactive substances; alcohol abuse or dependence as per DSM-IV-R criteria; a family history of any neurological disorder or DSM-IV axis I disorder in first-degree relatives; a family history of substance abuse, including alcohol; and any contraindications for magnetic resonance imaging (e.g., metal implants, metallic objects, pregnancy, recent surgeries, or any type of medical condition that would prevent them from entering the scanner safely).

Table 11. Scales and Questionnaires used in the clinical interview.

Portuguese version of the Alcohol Use Disorder Identification Test (AUDIT) (Babor et al., 2001; Cunha, J., 2002)
Alcohol Use Questionnaire – items 10, 11 and 12 (Townshend & Duka, 2002)
Semi-Structured Assessment for the Genetics of Alcoholism, the Individual Assessment Module and the Family History Assessment Module (Bucholz, 1994)
Portuguese version of the Symptom Checklist-90 Revised (SCL-90-R) (Derogatis & Unger, 2010; Laloni, 2001)
Portuguese version of Barratt Impulsiveness Scale 11 (BIS11) (Patton et al., 1995)
Edinburg Handedness Inventory (Oldfield, 1971)

Thus, the final sample included 36 college students, 20 BDs (50% female), and 16 alcohol-abstinent individuals (62.5% female). See Table 12 for complete demographic, drinking characteristics and psychological traits.

5.3.2. Procedure

The research protocol followed the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association outlined in the Declaration of Helsinki (World Medical Association, 2013), meeting the requirements for exemption and anonymity, and it was approved by the Ethics Committee for Research in Social and Human Sciences of the University of Minho.

Table 12. Demographic, drinking characteristics and psychological traits of the BD and control groups.

	Controls Mean ± SD	**Binge Drinkers** Mean ± SD	*t (34)*
Demographic Measures			
N (female)	*16 (10)*	20 (10)	
Caucasian ethnicity (%)	*100*	100	
Age	*21.00 (1.71)*	20.45 (1.60)	*-0.99*
Age of BD onset	-	17.45 ± 1.08	
Drinking characteristics			
AUDIT (total score)	*0.62 ± 1.20*	11.20 ± 3.25	*13.43****
BD episodes per month	-	3.58 ± 1.87	*8.54****
Percentage of alcohol intoxication per drinking event	-	43.25 ± 20.41	*9.48****
Number of months with BD pattern	-	35.90 ± 14.03	*11.44****
Quantity of alcohol consumed (g/week)	-	151 ± 44.27	*14.78****
Speed of drinking (g/h during BD episodes)	-	34.50 ± 8.26	*18.69****
Tobacco smokers (female)	-	7 (4)	
Occasional users of cannabis	-	2 (2)	
Psychological Traits			
Impulsivity (BIS11)			
Total Score	*63.56 ± 6.05*	64.80 ± 5.83	*0.62*
Attention	*10.63 ± 2.16*	10.65 ± 2.23	*0.03*
Cognitive Instability	*5.50 ± 1.51*	6.10 ± 1.41	1.23
Motor	*10.00 ± 2.03*	11.80 ± 2.76	2.17*
Perseverance	7.31 ± 2.03	7.05 ± 1.05	-0.64
Self-Control	17.38 ± 2.58	16.50 ± 2.46	-1.04
Cognitive Complexity	12.75 ± 1.88	12.70 ± 1.95	-0.08
Psychopathological symptoms (SCL-90-R)			
Anxiety	0.78 ± 0.61	0.58 ± 0.58	1.01
Depression	1.01 ± 0.64	0.96 ± 0.60	0.22
Global Severity Index	0.62 ± 0.38	0.65 ± 0.41	-0.22

*Note: AUDIT, Alcohol Use Disorders Identification Test; BIS11, Barratt Impulsiveness Scale 11; BD, Binge Drinking; SCL-90-R, Symptom Checklist-90 Revised; SD, standard deviation. All p-values reported are for two-tailed independent samples t-tests. * ≤ 0.05. ***p ≤ 0.001.*

5.3.3. Task

An associative memory task was specially developed to examine memory retrieval mechanisms for alcohol-related contexts (see Figure 10), building upon the task previously developed to assess associative memory with neutral stimuli by Yonelinas and cols. (Yonelinas et al., 2001). One day prior to the scanning, during the encoding phase, participants were asked to memorize 90 pairs of images. Each pair contained an image of an object and a picture of young people in one of two social contexts, i.e., drinking (alcohol context) or studying (no-alcohol context). The social context pictures were created specifically for this task and object images were obtained from the POPORO database (Kovalenko et al., 2012), and classified (1-9) as neutral for emotional valence (M=4.97) and arousal (M=4.63). Participants were instructed to remember which of the two (alcohol/no-alcohol) contexts was associated with each object. Subsequently, participants were randomly presented the neutral stimuli and asked to indicate whether they were previously associated with an alcohol or a no-alcohol context. To guarantee that inside the scanner participants were indeed conducting associative memory processes, as well to ensure homogeneity between individual learning effects, participants' performance was tested the day before the scan, as well as immediately prior to entering the scanner. Participants who did not achieve a minimum of 90% of correct recalls on either occasion were asked to repeat the encoding phase until they reached the required threshold. Participants were then scanned while making recognition memory judgments. Specifically, they were presented with a list of 135 images, consisting of 90 memorized neutral objects and 45 new objects. Each stimulus was presented sequentially followed by a fixation cross. Trials' sequence and presentation time of stimulus and fixation cross were pseudorandomized and determined using optseq2 toolbox (https://surfer.nmr.mgh.harvard.edu/optseq/). Participants were asked to observe each of the images presented and respond by pressing one of two buttons if they thought the item was previously presented -left for pictures associated with alcoholic contexts and right for pictures associated with no-alcohol contexts- and to not respond if they thought the item was new.

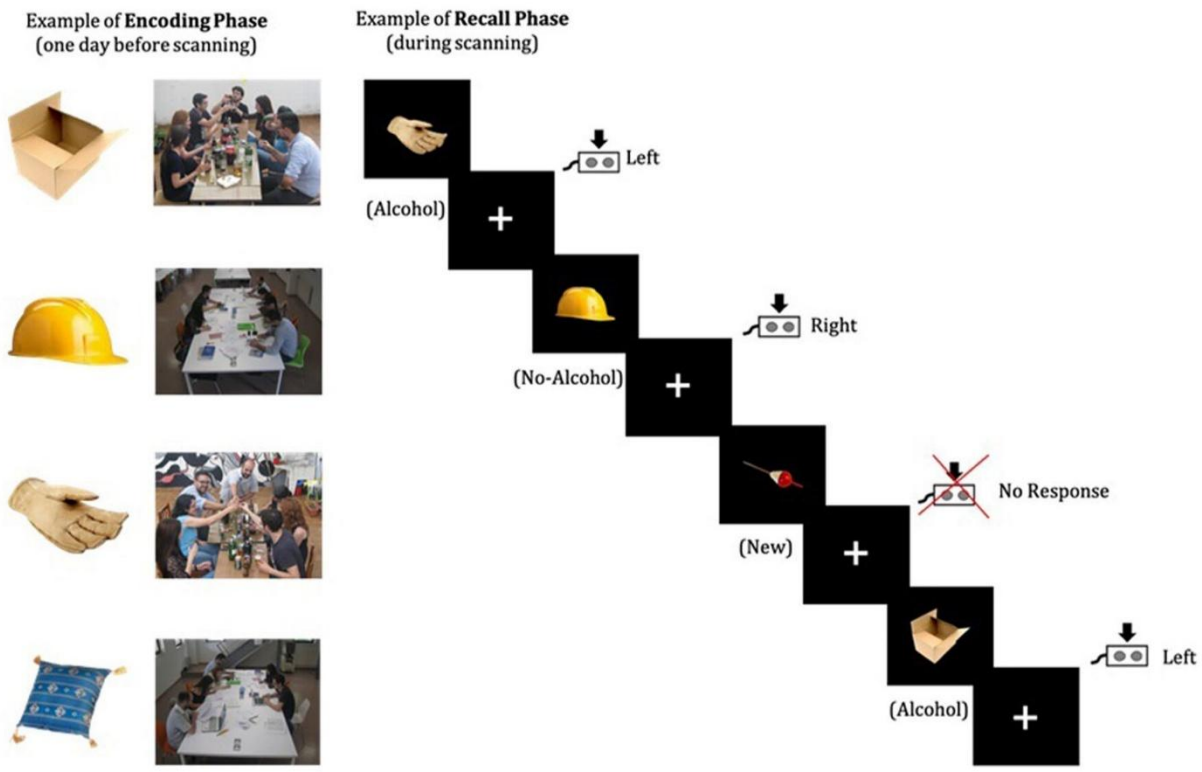


Figure 10. The overall depiction of the associative memory task for alcohol-related contexts. (a) Example of encoding phase: One day before scanning 90 pairs of images are memorized; (b) Example of recall phase: During scanning, participants had to classify each of the 135 neutral stimuli presented as being associated with either an alcohol or no-alcohol context or new stimuli.

5.3.4. Magnetic Resonance Image Acquisition

Functional imaging was acquired with a Siemens Magneton TrioTrim 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany,) equipped with a 32-channel receive-only coil. The blood oxygen level-dependent (BOLD) sensitive echo-planar imaging (EPI) was used with the following acquisition parameters: 39 interleaved axial slices; Repetition Time (TR) = 2000ms; Echo Time (TE) = 29ms; Flip Angle (FA) = 90°; slice thickness = 3mm; voxel size = 3x3x3mm; Field of View (FoV) = 222mm. The acquisition was made in a block with a duration of 10.36 minutes, consisting of 311 volumes.

High-resolution 3D T1-weighted images were also acquired to coregister to the realigned mean functional image. To this end, a magnetization-prepared rapid acquisition gradient echo ascending interleaved sequence was applied using the following parameters: TR/TE = 2700/2.33ms; inversion time = 1000ms; delay time = 1600ms; FA = 7°, 192 slices with 0.8mm thickness; slab thickness = 153.6mm; slice gap = 0mm; in-plane resolution = 1x1mm2; matrix size = 320x310 and 256mm FoV.

5.3.5. Image Pre-Processing and Analysis

The fMRI data preprocessing was performed using Statistical Parametric Mapping (SPM12; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in Matlab (version 2021b, The Mathworks, Inc., Natick, MA).

First, functional and anatomical images were reoriented to the anterior commissure. Subsequently, the intensity inhomogeneity was corrected using the field maps that were acquired during the MRI protocol. Then, functional images were corrected for slice timing and realigned and unwarped to correct for movement artifacts (images with movements that were superior to voxel size were removed). The anatomical T1 images were coregistered to the realigned mean functional image and then images were transformed into standard MNI space using segmentation-based normalization parameters. Finally, the resulting functional images were spatially smoothed using an 8-mm FWHM Gaussian kernel and low-frequency drifts were removed with a high-pass temporal filter (filter width of 128s).

5.3.6. Statistical Analysis

5.3.6.1. Demographic data, drinking variables and psychological traits comparisons

Differences between groups concerning demographic, drinking and psychological traits (impulsivity and psychopathological symptomatology) variables were compared using multiple two-sample t-tests. Additionally, given the uneven number of female participants between the two groups, a chi-square analysis was conducted to assess the potential impact of this distribution.

5.3.6.2. Behavioral Analysis

During the memory test phase, items that had been previously presented in the encoding phase and correctly associated with the alcohol- or non-alcohol-related context were considered correct responses. Thus, the percentage of correct responses was computed according to the following formula: number of correctly recalled items/number of previously recalled items x 100.

Reaction times (RTs) and percentages of correct recalls for alcohol and no-alcohol images were statistically analyzed using two-way mixed-design ANOVA with one within-subjects factor (Condition: Alcohol and No-Alcohol) and one between-subjects factor (Group: BDs and Control) with IBM Statistical Package for

Social Sciences (SPSS, v.28). Lastly, correct inhibitions for the New condition were analyzed using two-sample t-tests.

5.3.6.3. Neuroimaging Analysis

The fMRI analyses were performed using the general linear model approach with SPM12 software. The fMRI paradigm was analyzed by creating a set of regressors at the time of each decision-making, which were convolved with the hemodynamic response function. Three different regressors were created for each participant, one for each of the three conditions: "Alcohol" (trials with correct responses for images of neutral objects associated with alcohol contexts), "No-Alcohol" (trials with correct responses for images of neutral objects associated with study contexts) and "New" (trials with no responses for the new images of neutral objects). The six motion regressors estimated at preprocessing stage and a regressor for the baseline (fixation cross inter-stimulus) were also included in the design matrix. For each subject, three first-level statistical contrast maps were computed: the direct contrasts between the three conditions and the baseline.

Second-level analysis was also performed to analyze the main effects of group in each contrast by two-sample t-tests. Furthermore, one-sample t-tests were conducted to analyze the differences between conditions for each group separately. Whole-brain voxel-wise threshold of $p < 0.001$ was used and FWE (Family-Wise Error) correction for multiple comparisons was applied at the cluster level with a threshold of $p < 0.01$.

5.3.6.4. Correlation Analysis

Pearson's correlations were conducted to examine the associations between brain activation in response to neutral stimuli linked to alcohol-related context in the BD group and various alcohol consumption variables (AUDIT score, age of BD onset, BD episodes per month, percentage of alcohol intoxication per drinking event, number of months with BD pattern, quantity of alcohol consumed -grams of alcohol consumed per week-, and speed of drinking -grams of alcohol consumed per hour during BD episodes-), as well as impulsivity traits measured by the BIS-11. These analyses aimed to assess potential interactions between alcohol use and impulsiveness with the activation levels in brain regions where significant differences were observed.

5.4. Results

5.4.1. Demographic data, drinking variables and psychological traits comparisons

Significant differences between groups for all alcohol consumption variables (AUDIT scores, BD episodes per month, percentage of alcohol intoxication per drinking event, number of months with BD pattern, quantity of alcohol consumed -grams of alcohol consumed per week-, and speed of drinking -grams of alcohol consumed per hour during BD episodes) were observed. These differences were anticipated given the nature and inclusion criteria of each group. Additionally, BDs scored higher than controls for motor impulsivity on the BIS-11 subscale [$t = 2.17$, $p < 0.05$], and no differences were found between groups for BIS-11 main score, its remaining subscales, nor for any of the SCL-90-R subscales (see Table 12 and, for more details, refer to the supplementary material Table A.1). Lastly, a Chi-square test was conducted to assess the difference in sex distribution between the Control and the BD group. The test indicated no significant difference in gender distribution [$\chi^2(1) = 0.562$, $p = 0.453$]. Thus, gender was not included as a covariate in the subsequent behavioral and neurofunctional analyses.

5.4.2. Behavioral results

There were no significant behavioral group differences in RTs and correct recalls neither for both Alcohol and No-alcohol conditions nor between conditions, for both the control and BD groups (see Table 13). Similarly, no differences were found between groups regarding correct inhibitions of the New stimuli.

Table 13. Behavioral Data [Mean (SD)]

	Correct Response (%)			Reaction Times (ms)	
	Alcohol	No-alcohol	New	Alcohol	No-alcohol
Binge Drinkers	91.67 (12.59)	91.33 (13.79)	97.67 (0.07)	1218.19 (281.81)	1235.65 (311.03)
Controls	94.86 (4.98)	93.06 (5.84)	99.17 (0.02)	1214.42 (168.36)	1178.06 (189.44)

5.4.3. Neuroimaging results

5.4.3.1. Group Comparisons

Whole-brain analyses concerning the Alcohol condition revealed increased BOLD activation in BDs during the recall of alcohol-related stimuli when compared with the control group. Specifically, two clusters of regions were identified: the first composed by the bilateral thalamus, globus pallidus, putamen and right caudate nucleus [t(34) > 3.36, p(FWEc) < 0.01, 804 voxel extent threshold]; and the second encompassed the right cerebellum and the fusiform gyrus [t(34) > 3.36, p(FWEc) < 0.01, 754 voxel extent threshold] (see Figure 11 and Table 12). No significative differences between groups were found for the No-Alcohol and the New conditions.

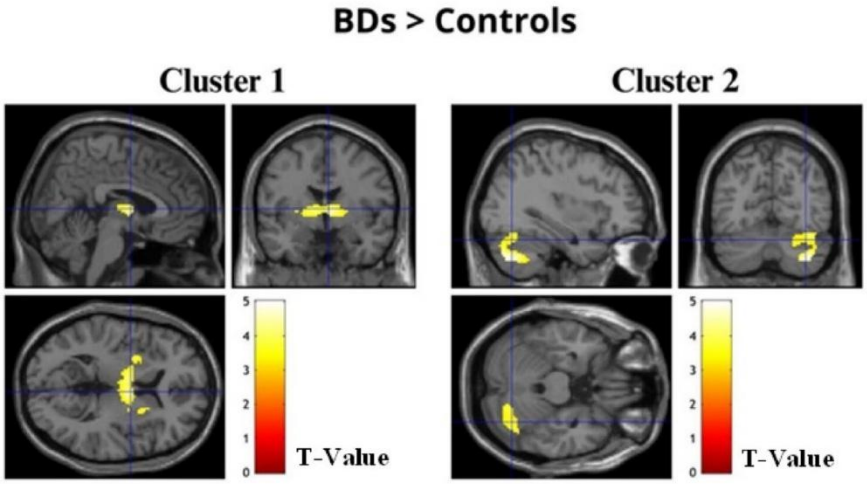


Figure 11. Images of the two clusters of regions display significantly increased activation in BDs when compared to controls for the alcohol condition.

Table 14. Regions significantly activated at whole-brain analysis in the contrast BDs > Control Group for the Alcohol Condition showing significant (p(FWEc) <0.01) BOLD signal changes, with local maxima more than 4.0mm apart.

	t	Coordinates	k
Cluster 1			
Right Thalamus	4.25	10,-6,6	804
Left Thalamus	4.25	-14,-12,2	804
Left Pallidum	4.20	-18,-6,2	804
Right Caudate Nucleus	4.17	22,16,14	804
Left Putamen	3.67	-28,2,4	804
Right Pallidum	3.49	18,-4,0	804
Right Putamen	3.47	24,6,4	804
Cluster 2			
Right Cerebelum Crus2	4.93	34,-66,-42	754
Right Cerebelum Crus1	3.91	38,-72,-32	754
Right Cerebelum_6	3.80	22,-72,-26	754
Right Fusiform Gyrus	3.87	40,-66,-20	754

5.4.3.2. Condition Comparisons within Groups

Whole-brain analyses concerning condition differences revealed that BDs exhibited increased BOLD activation when recalling Alcohol compared to No-Alcohol stimuli. Specifically three clusters of regions were identified: the first composed by the right supramarginal, postcentral and precentral gyrus, rolandic operculum and superior parietal lobule [$t(19) > 3.58$, p(FWEc) <0.01, 3127 voxel extent threshold]; the second encompassed the left fusiform gyrus and cerebellum [$t(19) > 3.58$, p(FWEc) <0.01, 1124 voxel extent threshold]; and the third included right thalamus, and caudate nucleus [$t(19) > 3.58$, p(FWEc) <0.01, 377 voxel extent threshold]. In addition, BDs showed increased BOLD activation when recalling No-Alcohol compared to Alcohol stimuli in the left postcentral and precentral gyrus [$t(19) > 3.58$, p(FWEc) <0.01, 2235 voxel extent threshold] (see Table 15 and Figure 14).

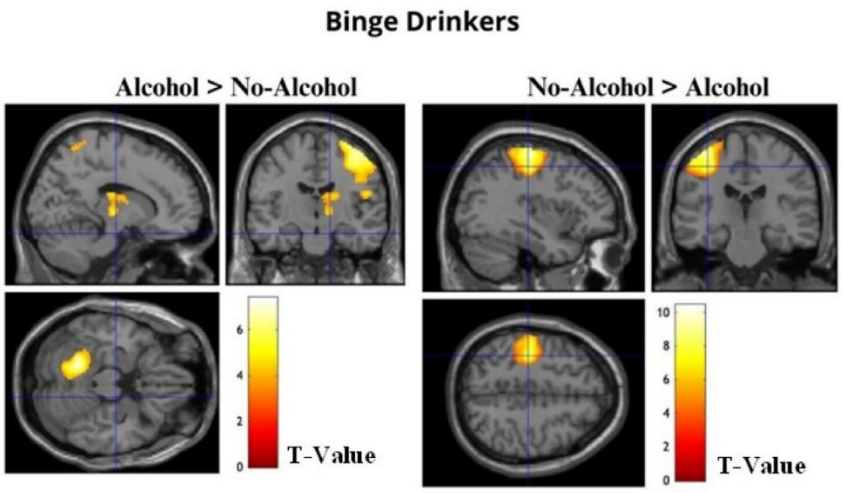


Figure 12. The images show significant activation maps of BDs for the contrasts Alcohol > No-Alcohol and No-Alcohol > Alcohol overlaid on an anatomical MRI image.

Table 15. Regions significantly activated at whole-brain analysis in the contrasts Alcohol > No-Alcohol and No-Alcohol > Alcohol for the BDs showing significant (*p*(FWEc) <0.01) BOLD signal changes, with local maxima more than 4.0mm apart.

	t	Coordinates	k
Alcohol > No-Alcohol			
Cluster 1			
Right Precentral gyrus	6.88	38, -16, 56	3127
Right Postcentral gyrus	6.73	40, -18, 48	3127
Right Superior parietal lobule	5.84	26, -54, 64	3127
Right Rolandic operculum	5.45	50, -18, 20	3127
Right Supramarginal	4.03	58, -18, 20	3127
Cluster 2			
Left Cerebelum_6	7.37	-22, -52, -22	1124
Left Cerebelum_4_5	7.03	-18, -52, -20	1124
Left Fusiform gyrus	4.72	-22, -52, -16	1124
Cluster 3			
Right Thalamus	5.13	16, -18, 18	337
Right Caudate nucleus	4.12	12, -6, 16	337
No-Alcohol > Alcohol			
Left Postcentral gyrus	10.40	-48, -20, 56	2235
Left Precentral gyrus	9.92	-36, -20, 60	2235

For the control group, the whole-brain analysis revealed increased BOLD activation when recalling Alcohol compared to No Alcohol stimuli. Specifically, two clusters of regions were identified: the first composed by the right postcentral and precentral gyrus [*t*(15) > 3.79, *p*(FWEc) <0.01, 1732 voxel extent threshold]; and the second encompassed right supramarginal gyrus and rolandic operculum [*t*(15) > 3.79, *p*(FWEc) <0.01, 400 voxel extent threshold]. In addition, like BDs, the control group showed increased BOLD activation when recalling No-Alcohol compared to Alcohol stimuli in the left postcentral and precentral gyrus[*t*(15) > 3.79, *p*(FWEc) <0.01, 1488 voxel extent threshold] (Table 16, Figure 13).

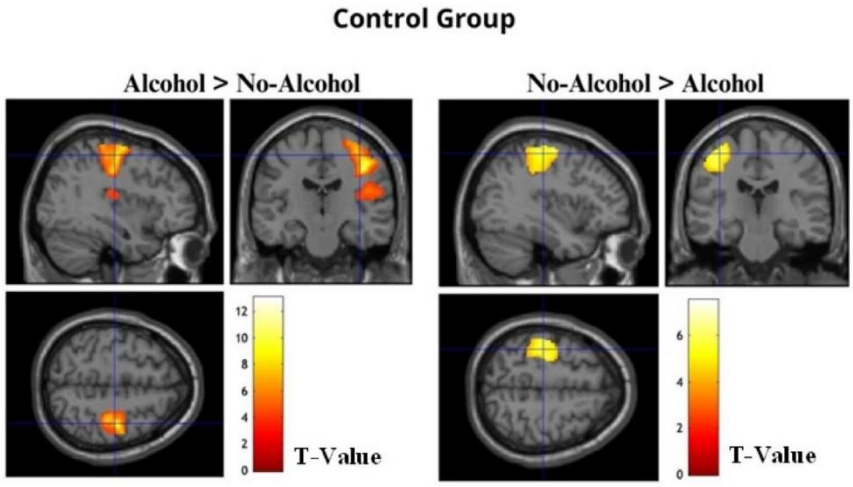


Figure 13. The images show significant activation maps of the Control Group for the contrasts Alcohol > No-Alcohol and No-Alcohol > Alcohol overlaid on an anatomical MRI image.

Table 16. Regions significantly activated at whole-brain analysis in the contrast Alcohol > No-Alcohol and No-Alcohol > Alcohol for the control group showing significant (p(FWEc) <0.01) BOLD signal changes, with local maxima more than 4.0mm apart.

	t	Coordinates	k
Alcohol > No-Alcohol			
Cluster 1			
Right Precentral gyrus	8.52	34, -10, 60	1732
Right Postcentral gyrus	13.01	46, -16, 46	1732
Cluster 2			
Right Rolandic operculum	5.45	46, -18, 20	400
Right Supramarginal	4.51	58, -18, 20	400
No-Alcohol > Alcohol			
Left Precentral gyrus	7.52	-32, -16, 66	1488
Left Postcentral gyrus	6.35	-42, -22, 48	1488

5.4.4. Correlations Analysis

Pearson's correlations between brain activations elicited by neutral stimuli linked to alcohol-related context in the BD group and alcohol consumption variables did not reveal any significant interactions (for more details, see supplementary material Table A.2). Regarding impulsivity, a significant correlation was found between the Self-Control subscale and activation in Cluster 3 (right Thalamus and Caudate Nucleus), when comparing Alcohol with No-Alcohol conditions for BDs [$r = 0.522$, $p < 0.05$]. No further significant correlations were observed between brain activations in response to neutral stimuli associated to alcohol-related context and other impulsivity measures (for more details, see supplementary material Table A.3).

5.5. Discussion

This study aimed to examine the impact of BD on brain mechanisms linked to alcohol-related associative memory in college students. Despite the absence of significant behavioral differences, results showed a brain hyperactivity pattern in young BDs during the recall of alcohol-related stimuli. Notably, BDs exhibited increased activity in two different clusters, including reward processing regions and areas related to memory and mental imagery, when compared with abstainers.

Specifically, BDs displayed greater activation in the bilateral thalamus, globus pallidus, and the dorsal striatum (DS) (putamen, and right caudate nucleus), in comparison to the control group, regions known to be affected by acute alcohol consumption (Patton et al., 2023), and involved in reward processing (Diekhof et al., 2008). Augmented activity in these areas in response to alcohol/drug cues has often been reported in individuals with heavy alcohol/drug use, including BDs (Cservenka & Brumback, 2017; Delgado, 2007; George et al., 2001; Vollstädt-Klein et al., 2010). In this sense, when exposed to alcohol-related cues, heavy drinkers have shown greater activity in visual, memory-related and incentive salience regions, including the fusiform gyrus, thalamus, and striatum nuclei (Everitt, 2014; George et al., 2001; Vollstädt-Klein et al., 2010). Therefore, the increased activation of the thalamus, globus pallidus, and DS observed in BDs might be interpreted as the ability of neutral cues, when paired with alcohol-contexts, to elicit enhanced brain activation in regions associated with craving and reward processing, even in the absence of the context itself.

Importantly, preclinical and clinical research has shown that during cue-reactivity tasks, casual consumers, or those who have recently started consuming alcohol or other drugs, display greater brain activation in the ventral striatum (Courtney et al., 2018; Porrino et al., 2007). Nonetheless, individuals who have transitioned from casual drug use to habitual/compulsive consumption show increased activity –and greater dopamine release- in the DS when exposed to substance-associated cues (Everitt & Robbins, 2013; Heinz et al., 2009; Vollstädt-Klein et al., 2010). In this sense, long-lasting associations between stimulus (drug) and response (craving and substance seeking) have shown to be mediated by the DS (Everitt & Robbins, 2005; Ito et al., 2002), and higher activation in the thalamic and striatal regions has been related to increased impulsivity as well as to reward sensitivity and processing (Fede et al., 2020; Moussawi et al., 2016). Therefore, it is not surprising that neural alterations in the DS are commonly observed in individuals with addictive behaviors (Koob & Volkow, 2016; Volkow et al., 2006). Furthermore, greater cue-induced activation in the DS has been shown to predict relapse in alcohol-dependent individuals (Bach et al., 2015; Grüsser et al., 2004), whilst relapse has been directly associated with higher alcohol craving levels (Sliedrecht et al., 2019; Stohs et al., 2019; Witteman et al., 2015). Accordingly, the results found in the current study, showing that BDs exhibit heightened brain activation primarily in the DS during the recall of alcohol contexts when compared with the control group, are in line with the assumption that BD might potentially be a transitional consumption pattern, bridging the gap between casual consumption and alcohol abuse (Almeida-Antunes et al., 2021; Enoch, 2006; Lannoy et al., 2019; Parsons, 1998).

Moreover, our results revealed that, in comparison with controls, BDs exhibited greater activation in the cerebellum as well as in the fusiform gyrus when recalling alcohol-related contexts. These two regions have been described as relevant in visual processing (Palejwala et al., 2020), and task-driven motor processing in response to a stimulus (Guell & Schmahmann, 2020). Specifically, the fusiform gyrus has been shown to be involved in the processing of visual information and semantic memory (Danker & Anderson, 2010; Mion et al., 2010; Khader et al., 2005), particularly during memory recall and imagery of content-specific or scene-related stimuli (Johnson & Rugg, 2007; Spagna et al., 2021), reinforcing thus the idea that this region is prone to activation during associative memory processing, not only during encoding, but also during the retrieval of previously associated stimuli (Dijkstra et al., 2019; Park et al., 2012). Likewise, the cerebellum, although traditionally described as being purely a motor control region, has also been described as a contributor to cognitive processing and emotional control (Baumann et al., 2015; Schmahmann & Caplan, 2006; Strata, 2015). Regarding drug consumption, it has often been considered as an intermediary between the motor-reward and the motivational-cognitive control systems of the striatal-cortico-limbic circuitry (Moulton et al., 2014). Notably, the cerebellum appears to be a relevant node for drug-related cue association, playing significant roles in conditioning response, goal-directed behavior, and selective attention (Brumback et al., 2015; Gil-Miravet et al., 2019; Miquel et al., 2020; Moulton et al., 2014). These functions are integral to the constructs of craving and addictive behavior, as they influence how individuals respond to drug-related cues and the subsequent behavioral outcomes (Franken, 2003). In the same vein, when exposed to alcohol cues, brain activation in the cerebellum has been positively correlated with AUD through AUDIT scores (Al-Khalil et al., 2021). Therefore, the cerebellum's engagement in these processes underscores its role as a significant hub for drug-related cue association. By integrating motor, cognitive, and emotional responses, the cerebellum mediates the processes that occur between observing environmental cues and the behavioral outcomes associated with addiction.

Consequently, the increased activity observed in these two regions –the fusiform gyrus and the cerebellum- in the BDs relative to the control group, might suggest that, in accordance with what has been described in the literature, BDs exhibit augmented neural reactivity when exposed to alcohol-related stimuli (Almeida-Antunes et al., 2022; Blanco-Ramos et al., 2022; Pérez-García et al., 2022; Petit et al., 2014). In detail, the heightened BDs' BOLD activation in the fusiform gyrus appears to underline the recalling and mental imagery of scene-specific alcohol-related context, while the elevated activation in the cerebellum may be related to the selective attention and increased salience toward alcohol-related stimuli, often seen in BDs

(Gordon, 2007; Johnson & Rugg, 2007). In parallel, this finding might indicate that the mental representation of the drinking context could elicit craving, aligning with previous research suggesting that increased activation in the fusiform gyrus and the cerebellum is directly associated with heightened cue-induced alcohol craving (Moreno-Rius & Miquel, 2017; Olbrich et al., 2006; Park et al., 2007; Schneider et al., 2001).

Comparison of the Alcohol and No-Alcohol conditions revealed increased activation in the primary sensorimotor cortex, contralateral to the hand used by participants to classify the stimuli, in both groups. Accordingly, when participants were presented with alcohol-related stimuli -identified by pressing a button with the left hand- increased activation was observed in the right precentral and postcentral gyri. Conversely, when they were presented with No-Alcohol stimuli -identified by pressing a button with the right hand-, greater activation was seen in the left precentral and postcentral gyri reflecting thus the well-known contralateral motor effect (Allison et al., 2000). Moreover, BDs displayed increased BOLD activation in an additional cluster of regions when presented with alcohol-related stimuli compared to No-Alcohol stimuli. Namely, this heightened activation was observed in the thalamus, caudate nucleus, cerebellum, and fusiform gyrus - regions involved in the visual and reward networks (Guell & Schmahmann, 2020; Palejwala et al., 2020) that show increased cue reactivity to alcohol-related stimuli in heavy drinkers and BDs, as described above (Cservenka & Brumback, 2017; Schacht et al., 2013). This suggests that BD experience intensified alcohol craving in response to neutral stimuli associated with drinking-related contexts, as indicated by increased brain activation in these areas, a response not observed in control participants.

Furthermore, a significant positive correlation was observed between the self-control subscale of the BIS-11 and brain activation in the thalamus and caudate nucleus when BDs were exposed to alcohol-related cues. Specifically, higher scores on this subscale, indicating lower self-control (Patton et al., 1995), were associated with increased activity in these brain regions. Given the thalamus's role in processing sensory information (Shine et al., 2023) and the caudate nucleus's involvement in reward-related processes (Delgado et al., 2004), these findings suggest that BDs with lower self-control may experience intensified cue-induced craving for alcohol, reflected by heightened brain activation in these areas. This relationship aligns with previous research concerning substance use disorders (Li et al., 2010), highlighting the potential link between diminished self-control and increased alcohol craving (Bernard et al., 2021).

At the behavioral level, both groups exhibited comparable performance in both the Alcohol and No-Alcohol conditions, displaying similar accuracy -i.e. number of correct recalls for both conditions. Since the

primary objective of our study was to investigate the brain mechanisms involved in associative memory, we ensured a correct recall rate of at least 90% before conducting the task within the MRI scanner. Therefore, it is possible that a ceiling effect may have influenced the results. In addition, previous studies suggest that through neural compensation, experimental groups (i.e., those with alcohol consumption) can exhibit similar behavioral performance as controls while showing higher brain activation (Almeida-Antunes et al., 2021; Bagga et al., 2014; Hatchard et al., 2017; Suárez-Suárez et al., 2020). Regarding task performance speed, while group comparisons revealed higher motor impulsivity -as measured by the BIS-11- for BDs compared to controls, there were no differences in reaction times between groups for either the Alcohol or No-Alcohol conditions. The tendency to act impulsively with little regard for negative consequences has been widely explored in BDs (Bø et al., 2016; Maurage et al., 2019), highlighting the pronounced reward-seeking and impulsive behaviors characteristic of this population (Lees et al., 2019). Literature has shown that high consumption patterns, such as BD, are associated with higher impulsivity (Balodis et al., 2009). Nevertheless, neuropsychological assessments as well as behavioral results derived from neuroimaging/EEG studies often lack the sensitivity to detect potential brain alterations caused by BD, even in the presence of neurofunctional differences between BDs and controls (Crego et al. 2009, 2012; Carbia et al., 2018).

The present study has some limitations that need to be addressed in future research. First, prior to, or during data collection, no measurement of subjective craving was assessed. Such a measure would have provided important information for understanding how brain activation in the clusters of interest could be related to craving, and how it may influence and/or be influenced by such associative memory processes. Additionally, our sample comprised two polarized groups, including individuals at the two non-clinical polar ends of alcohol consumption, BDs and abstainers. Future investigation, including a group of light or social drinkers (non-harmful, casual consumption), might provide a more comprehensive understanding of the development of BD as a harmful consumption pattern and elucidate how and when craving begins to influence/be influenced by alcohol-related memories. Likewise, longitudinal research on the developmental trajectory of BD and its impact on the brain would be valuable for understanding potential causal effects. This research could further explore how these brain alterations evolve with continued alcohol use and whether they might revert after the cessation of BD episodes (Brumback et al., 2015; López-Caneda et al., 2014b). These insights would enhance our understanding of the *continuum* hypothesis between BD and AUD -the idea that BD and alcohol dependence may constitute successive stages of the same phenomenon (Enoch, 2006; Parsons, 1998). This hypothesis is supported by observed impairments in BDs similar to those seen

in individuals with AUD (e.g., Crego et al., 2010; López-Caneda et al., 2017; Maurage et al., 2009; Petit et al., 2014; Sanhueza et al., 2011), suggesting that BD during adolescence might be a starting point for the development of alcohol dependence in adulthood (Bonomo et al., 2004; McCambridge et al., 2011; McCarty et al., 2004). Lastly, no data was collected regarding the menstrual cycle phase of female participants on the day of the fMRI scan. Recent literature indicates that menstrual cycle phases, particularly fluctuations in progesterone and estradiol levels, can influence brain dynamics (Avila-Varela et al., 2024), so future research should consider these hormonal variations to ensure more robust and reliable results.

In conclusion, despite the absence of significant behavioral differences between groups, neutral cues linked to alcohol-related contexts may trigger heightened brain activity in the BD population. Namely, our findings revealed augmented activation in two clusters comprising the bilateral thalamus and the striatum, as well as by the cerebellum and the fusiform gyrus. These regions have been associated with memory and mental imagery (Spagna et al., 2021; Mion et al., 2010), the processing of visual cues (Tsapkini, et al. 2011), and reward and craving modulation (Braus et al., 2001; Moulton et al., 2014; Paulus, 2007). Results are in line with existing literature indicating that prior consumption contexts significatively influence craving and relapse in alcohol-dependent individuals (Janak & Chaudhri, 2010). Moreover, our findings suggest that real-life contexts involving alcohol consumption (Kuerbis et al., 2020; Nees et al., 2012) may become linked or associated with otherwise neutral stimuli. Consequently, these newly associated stimuli could elicit brain responses similar to those triggered by direct exposure to alcohol-related contexts. This association might lead to an increase in craving and, subsequently, substance-seeking and taking behaviors (Papachristou et al., 2012; Weiss, 2005). Overall, while evidence remains limited, this study sheds light on the importance of alcohol-associated memories and their potential impact on craving and alcohol use in BDs. Future research on alcohol abuse and BD should consider the context of consumption and explore how those environmental cues might influence alcohol-seeking behavior and the maintenance or escalation of alcohol consumption.

5.6. References

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Chapter VI

Memory suppression in individuals with alcohol use disorder: Evidence for altered brain functional coupling

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6.1. Abstract

Alcohol use disorder (AUD) has been associated with impairments in inhibitory control, episodic memory, and heightened salience of alcohol-related cues, yet the neural mechanisms underlying voluntary suppression of alcohol memories remain poorly understood. The present study aimed to investigate behavioral and neurofunctional correlates of memory inhibition in abstinent AUD individuals using an adapted Think/No-Think Alcohol paradigm combined with task-based functional connectivity analyses. Forty-one participants (26 abstinent individuals with alcohol use disorder; 15 controls) completed encoding, Think/No-Think (during functional magnetic resonance imaging) and retrieval phases. Individuals with AUD showed reduced encoding and overall recall performance, while suppression-induced forgetting was comparable between groups. At the neural level, during attempts to suppress alcohol-related memories, AUD participants exhibited increased connectivity between reward-related subcortical regions and prefrontal, perceptual, and interoceptive cortices, suggesting increased engagement of salience and reward systems during suppression demands, whereas controls preferentially recruited classic top-down memory control circuitry. In contrast, during suppression of non-alcohol memories, AUD participants showed stronger fronto-posterior coupling than controls, indicating that suppression-related control mechanisms remained recruitable but were engaged in a stimulus-dependent manner, alongside evidence of generalized salience-related modulation of perceptual processing. Additionally, during the recall of alcohol-related stimuli, the AUD group showed stronger coupling within salience and valuation circuitry, while controls engaged goal-directed and perceptual imagery systems. Within the AUD group, craving, particularly compulsivity, was associated with greater recall of suppressed alcohol-related memories and with altered functional connectivity in regulatory and salience networks. Together, the findings suggest that memory control in AUD is characterized not by overt behavioral suppression failure but by salience-biased redistribution of neural recruitment. These results highlight neural-level vulnerability in memory regulation that may contribute to craving persistence and relapse risk, providing potential targets for neurocognitive interventions aimed at strengthening memory control in individuals with AUD.

6.2. Introduction

Alcohol Use Disorder (AUD) is a prevalent and chronic condition characterized by the problematic consumption of alcohol, leading to negative consequences such as impaired control over drinking, persistent desire to drink despite negative outcomes, tolerance, and withdrawal symptoms[1,2]. Despite extensive evidence of its harmful effects on public health and well-being, alcohol consumption remains a significant global concern[3,4]. Recent estimates indicate that, in 2019 alone, alcohol use contributed to approximately 2.6 million deaths worldwide, accounting for nearly 5% of all deaths globally[5]. The burden is particularly high in Europe, where alcohol use is responsible for around 800,000 deaths annually -almost a third of global estimates-, and where the prevalence of AUD among adults reaches 9%, making the European region one of the most affected worldwide[6]. In Portugal, although alcohol consumption among individuals aged 15-74 is around 54%, approximately 3.5% of the adult population meets screening criteria for AUD[7,8]. Importantly, these figures are likely to underestimate the true burden of alcohol-related problems, as a substantial proportion of affected individuals do not seek treatment or receive a formal diagnosis[9,10].

Beyond its well-documented deleterious impact on multiple organs -including the liver, cardiovascular system, pancreas, and immune function[11-13]- excessive alcohol consumption also exerts profound alterations on the structure and function of the brain[14,15]. In particular, alcohol-related neurotoxicity primarily affects frontal brain regions that are crucial for executive functions such as working memory and inhibitory control (IC)[16-19]. These functions are essential for regulating behavior and decision-making and are highly vulnerable to alcohol-induced damage[20,21]. Given the crucial role of IC in regulating impulsive behaviors, impairments in this domain are linked to multiple psychiatric conditions, with especially strong associations observed in addictive disorders, including AUD[22-24]. Concurrently, individuals with AUD commonly display a reduced ability to refrain from alcohol consumption, underscoring the significance of IC in alcohol abuse[25-27].

Chronic alcohol misuse may also result in widespread memory impairments, including deficits in episodic memory[28,29]. Notably, heavy drinking induces neurotoxic effects in the hippocampus and associated limbic circuitry[30-], regions that are critical in the encoding and retrieval of personal experiences. Such alcohol-related alterations have been associated with reduced hippocampal volumes and poorer performance on both verbal and visual memory tests[29,33,34]. Consequently, alcohol-dependent individuals may experience difficulties in learning new information and recalling contextual details of past events[33]. Importantly, these memory deficits reflect dysfunction not only within the limbic networks but also across frontal control systems[35,36]. In

this sense, frontal regions, such as the orbitofrontal cortex and the dorsolateral prefrontal cortex (DLPFC), play a key role in organizing, monitoring, and retrieving memories[37,38], with alcohol-related atrophy in these areas further undermining strategic encoding and retrieval in AUD[28,39].

In addition, the DLPFC, exerts top-down control over medial temporal structures (particularly the hippocampus), and can modulate emotion-related regions (including the amygdala), thereby shaping retrieval of emotionally salient memories and responses to drug-related cues[40-42]. Alterations in DLPFC functioning are therefore involved in the reduced cognitive control characteristic of drug dependence[43,44], the heightened vulnerability to cue-induced relapse[45,46], and the subjective experience of craving[47,48].

Together, this body of evidence suggests that chronic AUD disrupts the neural circuits underlying episodic memory, leading to impairments in learning and recall[49]. Within this integrative framework linking frontal control and memory processes, interventions aimed at strengthening the DLPFC functioning, either through cognitive training or non-invasive electric/magnetic stimulation, have shown promise in reducing craving among heavy drinkers[50,51].

Memory inhibition, defined as the ability to suppress unwanted or contextually irrelevant thoughts, recruits neural mechanisms that overlap with those supporting IC, involving increased engagement of prefrontal regions, together with top-down modulatory control over hippocampal activity during memory suppression[52-55]. Building on the central roles of IC and memory inhibition, retrieval suppression mechanisms have been extensively investigated using the Think/No-Think (TNT) paradigm. In this task, participants are instructed either to actively retrieve and maintain (Think) or to suppress (No-Think) the recall of target items previously learned in association with specific cues[52,56]. A robust body of evidence demonstrates that repeated suppression of retrieval leads to reduced later memory for No-Think items, often below the levels observed for both Think and Baseline items, a phenomenon known as suppression-induced forgetting (SIF)[57]. This effect has been consistently observed across a wide range of stimuli, including neutral word lists, emotionally valanced and motivationally salient images, and real-life emotional or autobiographical events[58-63].

Notwithstanding, converging evidence indicates that memory suppression mechanisms can be disrupted across several clinical populations characterized by intrusive thoughts and maladaptive memory representations[64]. For instance, individuals with post-traumatic stress disorder exhibit reduced ability to suppress unwanted and negatively valenced memories[65-67]. Nevertheless, despite addictive behaviors have

been closely linked to maladaptive and persistent substance-related memories that often drive compulsive use[68-71], the extent to which memory suppression mechanisms are disrupted in substance use disorders has received limited empirical attention[72]. Specifically, to the best of our knowledge, only three studies have directly examined memory inhibition in individuals with alcohol-related problems, focusing on detoxified patients with alcohol dependence[73] and young hazardous or binge drinkers[63,74]. Collectively, these studies indicate that alcohol-related problems are associated with alterations in memory suppression abilities, with impaired suppression observed particularly in more severe or clinically relevant patterns of use, and atypical behavioral and neural responses emerging already at earlier stages of alcohol misuse, especially when suppressing alcohol-related memories. Notably, however, despite the potential implications for craving regulation and relapse vulnerability, no study has yet systematically examined the behavioral and neural mechanisms of memory suppression in individuals with AUD when confronted with alcohol-related memories.

To address this gap, the present study employed the Think/No-Think Alcohol task[61] to assess memory inhibition, with a particular focus on alcohol-related memories, in abstinent individuals with AUD. We hypothesized that participants with alcohol abuse would exhibit impaired memory suppression, with greater difficulty suppressing alcohol-related compared with non-alcohol-related memories, alongside abnormal brain functional connectivity within IC and memory-related networks relative to healthy controls. Additionally, we expected that higher levels of alcohol craving would be associated with poorer suppression of alcohol-related memories. By characterizing the neurofunctional networks engaged during attempts to suppress alcohol-related memories in individuals with AUD, and their relationship with alcohol craving, the present findings may contribute to a better understanding of the cognitive and neurobiological mechanisms underlying AUD and inform the development of targeted cognitive or neuromodulatory interventions aimed at enhancing memory inhibition and reducing relapse vulnerability.

6.3. Method

6.3.1. Participants

The final sample comprised 41 participants aged between 26 and 65 years (M = 47.63, SD = 9.26), including 26 individuals with AUD (nine females) and 15 healthy controls (seven females). Participants in the AUD group were required to have a previous clinical diagnosis, were currently enrolled in a rehabilitation program, reported no past or current dependence on other substances, and had maintained abstinence for

at least four weeks prior to assessment. Control participants reported no lifetime history of alcohol abuse or illicit drug use and no psychiatric or neurological disorders. The two groups were matched for sex and age.

Participants were recruited through a widespread online screening questionnaire, physical advertisements placed on the University of Minho campus, and collaboration with drug and alcohol rehabilitation facilities located in the districts of Braga, Viana do Castelo, and Porto (Portugal). Eligibility was verified through a clinical interview (see Supplementary Table B.1) to ensure that all inclusion criteria were met and that no exclusion criteria were present. Detailed sociodemographic characteristics of the sample are provided in Table 17.

6.3.2. Procedure

Selected participants were fully informed about the whole procedure and required to provide informed consent following the ethical guidelines of the Ethics Committee for Research in Social and Human Sciences (CEICSH) of the University of Minho, and the Code of Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki World[75]. Additionally, the full procedure was analyzed and approved by the ethics committee of the Hospital de Braga, where the data collection took place and the CEICSH of the University of Minho (CEICSH 060/2019).

Table 17. Sociodemographic, consumption characteristics and psychological profile of the participants.

	Controls Mean ± SD (*n*)	AUD Mean ± SD (*n*)	*t* (39)
Demographic measures			
N (females)	15 (7)	26 (9)	
Age	48.00 ± 10.53 (15)	47.42 ± 8.72 (26)	0.189
Years of education	12.07 ±4.30 (15)	7.92 ±4.08 (26)	3.07**
Consumption Characteristics			
AUDIT (total score)	1.67 ±1.05 (15)	18.23 ± 13.93 (26)	-6.03***
Years since AUD diagnosis		18.17 ±12.59 (24)	
Weeks since abstinence		42.44 ± 43.52 (25)	
			t (27)
Alcohol Craving (ACQ-SF-R)	1.63 ± 0.83 (9)	2.04 ± 1.00 (20)	-1.08
Emotionality	1.38 ± 0.87 (9)	2.24 ± 1.68 (20)	-1.81*
Purposefulness	2.07 ± 1.68 (9)	2.25 ± 1.18 (20)	-0.32
Compulsivity	1.25 ± 0.50 (9)	1.63 ± 0.89 (20)	-1.49

DUDIT (tobacco use frequency)	0.87 ± 1.77 (15)	2.73 ± 2.51 (26)	-2.78**
Psychological Profile			
Impulsivity (BIS11)	52.11 ± 7.20 (9)	65.35 ± 9.93 (20)	-3.58***
Attentional	13.00 ± 2.12 (9)	17.30 ± 3.66 (20)	-3.27**
Non-planning	19.33 ± 4.27 (9)	27.60 ± 4.95 (20)	-4.33***
Motor	19.77 ± 2.94 (9)	20.45 ± 4.94 (20)	-0.37
Depression (BDI-II)	4.67 ± 3.46 (9)	14.63 ± 11.65 (20)	-3.42**
Anxiety (BAI)	20.55 ± 12.02 (9)	16.95 ± 16.18 (20)	0.60

Note: SD - standard deviation; AUD - Alcohol Use Disorder; AUDIT - Alcohol Use Disorder Identification Test; ACQ-SF-R - Alcohol Craving Questionnaire - Shortform - Revised; DUDIT - Drug Use Disorder Identification Test; BIS11 - Barrat Impulsivity Scale-11; BDI - Beck Depression Inventory; BAI - Beck Anxiety Inventory; +p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001

Participants completed an adapted version of the Think/No-Think Alcohol task[61] throughout its three phases: encoding (performed prior to scanning), the TNT phase (performed during functional magnetic resonance imaging [fMRI] acquisition), and a final recall test. During encoding, participants learned 24 image pairs. Each pair consisted of a neutral cue image[76] paired with an image depicting a beverage[77] (12 alcoholic, 12 non-alcoholic). To ensure feasibility for the clinical sample while maintaining procedural equivalence across groups, the encoding phase was simplified by reducing the number of cue-target pairs and implementing a block-wise, criterion-based learning procedure, which was applied identically to both AUD and control participants. Hence, the 24 pairs were divided into six blocks of four pairs each. Each block was presented and inquired about between three and five times; after every presentation cycle the four items in the block were assessed with two memory questions: (a) "How many people were there in the image?" (response options: 0, 1) and (b) "Which drink was present?" (response options: Water, Juice, Milk, Beer, Wine, Liquor). An item was considered correctly encoded only if the participant answered both questions correctly. After the third presentation of a block, participants progressed to the next block only if at least three of the four (75%) pairs in that block were correctly encoded. If this criterion was not met the block was presented and probed again. If after this additional presentation fewer than two pairs were correctly encoded, a single final repetition of the block was administered.

Following successful encoding of all six blocks, participants entered the scanner to perform the TNT phase. The 12 cue images within each beverage category were assigned to one of three conditions (Baseline, Think, No-Think) such that each beverage type contributed four pairs to each condition. This resulted in eight Baseline pairs (not presented during the TNT phase), eight Think pairs and eight No-Think pairs. During the

TNT phase, only the neutral cue images were presented. Think cues were indicated by a green border, and participants were instructed to actively recall, via mental imagery, the paired target image and its associated features (drink type and number of people). In contrast, the No-Think cues were identified by a red border, and participants were instructed to prevent the associated target image from entering consciousness (i.e., to actively suppress retrieval). Lastly, in the final recall test, all 24 neutral cue images were presented, and participants answered the same two memory questions used during encoding. Performance in this test served as the behavioral index of retrieval and suppression success.

6.3.3. fMRI data acquisition and processing

Functional imaging was acquired with a Siemens Magneton TrioTrim 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a 32-channel receive-only coil. The blood oxygen level-dependent (BOLD) sensitive echo-planar imaging (EPI) was used with the following acquisition parameters: 42 interleaved transversal slices; repetition time (TR) = 1460 ms; echo time (TE) = 12 ms; flip angle (FA) = 90°; slice thickness = 3 mm; voxel size = 3 mm × 3 mm × 3 mm; and field of view (FoV) = 200 mm. The acquisition was made in two blocks, with a duration of 681.82 seconds, consisting of 467 volumes, and 674.52 seconds, consisting of 462 volumes. High-resolution 3D T1-weighted (T1w) images were also acquired for coregistration with the realigned mean functional image. To this end, a magnetization-prepared rapid acquisition gradient echo ascending interleaved sequence was applied using the following parameters: TR/TE = 2450/4.13 ms; inversion time = 1100 ms; FA = 9°, 176 slices with 1 mm thickness; slab thickness = 176 mm; slice gap = 0 mm; in-plane resolution = 1 × 1 mm2; matrix size = 320 × 310; and 256 mm FoV.

Preprocessing was conducted using fMRIPrep[78] (See supplementary material B.1 for detailed pipeline). One T1w image per subject was processed. The T1w image was skull-stripped, and brain tissue was segmentated into cerebrospinal fluid, white matter, and gray matter. Cortical surface reconstruction was carried out with FreeSurfer. Spatial normalization to MNI space was performed using nonlinear registration, aligning the T1w image to the MNI152NLin2009cAsym template.

For each subject, two BOLD runs were preprocessed. A reference volume was generated for motion correction, and head motion parameters were estimated using MCFLIRT (FSL[79]). BOLD images were co-registered to the T1w reference using boundary-based registration with six degrees of freedom[80], and several confound regressors were computed for each run. Physiological noise components were estimated using

component-based noise correction method (CompCor). Temporal (tCompCor) and anatomical (aCompCor) components were calculated after high-pass filtering (128s cutoff). Components explaining up to 50% of variance within their respective nuisance masks were retained. Motion parameters, their temporal derivatives, and quadratic terms were included as nuisance regressors[81] Volumes with FD > 0.5 mm or standardized DVARS > 1.5 were identified as motion outliers. All spatial transformations (motion correction, co-registration, and normalization) were combined and applied in a single interpolation step using cubic B-spline interpolation.

6.3.4. Behavioral Data Analysis

Behavioral analyses were conducted to characterize encoding, recall, and SIF in the Think/No-Think Alcohol task using SPSS (version 29; IBM Corp). Encoding performance was defined as the percentage of correctly learned cue-target pairs during encoding and analyzed using a mixed repeated-measures ANOVA with Stimulus (Alcohol, NoAlcohol) as a within-subject factor and Group (AUD, Control) as a between-subject factor.

Final recall performance was conditionalized on successful encoding, such that only items correctly learned during the encoding phase were included in recall analyses. For each participant and experimental condition, conditionalized recall accuracy was expressed as the percentage of encoded items correctly recalled (recalled/encoded × 100). Primary analysis of recall performance was conducted using mixed repeated-measures ANOVA with Condition (Think, Baseline, NoThink) and Stimulus (Alcohol, NoAlcohol) as within-subject factors and Group (AUD, Control) as a between-subject factor. Suppression-related analysis was conducted separately for each Stimulus type using mixed repeated-measures ANOVA with Condition (Baseline, NoThink) as within-subject factor and group (AUD, Control) as a between-subject factor. Lastly, SIF was computed separately for Alcohol and NoAlcohol stimuli as the difference between conditionalized recall in the Baseline and NoThink conditions (SIF = Baseline - NoThink). Group differences in SIF were assessed using mixed repeated-measures ANOVA with Stimulus (Alcohol, NoAlcohol) as within-subject factor and Group (AUD, Control) as a between-subject factor. Given observed group differences in encoding performance, complementary analyses were conducted to examine whether individual differences in encoding contributed to recall outcomes. Specifically, overall encoding accuracy (centered at the sample mean) was included as a covariate in secondary mixed ANOVA models of conditionalized recall. These analyses were conducted to assess whether group differences in recall were explained by encoding performance. All significant results observed were two-tailed for a $p < 0.05$.

6.3.5. fMRI Data Analysis

Analyses of fMRI data were performed using CONN[82] (RRID:SCR_009550) release 22.v2407[83] and SPM[84] (RRID:SCR_007037) release 25.25.01.02 (see supplementary material B.2 for detail analysis procedure). Functional data was denoised using a standard denoising pipeline[83] including the regression of potential confounding effects characterized by white matter timeseries, cerebrospinal fluid timeseries, session and task effects and their first order derivatives, as well as linear trends within each functional run. Denoising was followed by bandpass frequency filtering of the BOLD timeseries[85] between 0.008 Hz and 0.09 Hz.

Psychophysiological interaction analyses were used to study the changes in functional connectivity across groups and stimulus conditions[86]. Thirty-five seed regions were defined using the Harvard-Oxford cortical and subcortical atlases as implemented in the CONN toolbox[82]. The full list of seed regions and their cognitive grouping is provided in Supplementary Material Table B.2. For each seed-target pair, a generalized psychophysiological interaction model[88,89] (gPPI) was defined, with seed BOLD signals as physiological regressor, condition-specific boxcar signals convolved with the SPM canonical hemodynamic response function as psychological regressors, and the product of the two as psychophysiological interaction terms. Functional connectivity differences across conditions were characterized by the Fisher-transformed semi partial correlation coefficient of the psychophysiological interaction terms in each model.

Second level analysis was performed using a General Linear Model[85] (GLM). For each individual voxel, a separate GLM was estimated, with first-level connectivity measures at that voxel as the dependent variable (one independent sample per subject and one measurement per condition), and groups as independent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory[85,90]. Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold, uncorrected and a familywise corrected p-FDR < 0.05 cluster-size threshold[91].

6.3.6. Correlations

Within the AUD group, exploratory Pearson correlations were conducted between behavioral indices (conditionalized recall and SIF), craving measures from the ACQ-SF-R, and functional connectivity beta values extracted from clusters showing significant group effects.

6.4. Results

6.4.1. Behavioral results

Encoding performance analysis revealed a significant main effect of Group, $F(1,39) = 6.70$, $p = .013$, $\eta p^2 = .15$, indicating lower overall encoding performance in the AUD group. No main effect of Stimulus nor a Stimulus × Group interaction was observed. Between-group comparisons indicated that the control group encoded significantly more alcohol-related stimuli ($p = .048$) and non-alcohol stimuli ($p = .020$) than the AUD group, indicating that group differences in encoding were not stimulus-specific.

Conditionalized recall performance analysis revealed a significant main effect of Group, $F(1, 39) = 5.41$, $p = .025$, $\eta p^2 = .12$, indicating higher overall recall accuracy in controls relative to individuals with AUD. A significant Stimulus × Condition quadratic interaction was also observed, $F(1, 39) = 19.60$, $p < .001$, $\eta p^2 = .33$. Post-hoc differences showed that alcohol stimuli had a higher recall than no-alcohol stimuli in the Baseline condition ($p < .001$), and no-alcohol stimuli had a higher recall than alcohol stimuli in the NoThink condition ($p = .002$). Parallelly, alcohol stimuli had higher recall in the Baseline condition than in the NoThink condition ($p = .010$), whereas no-alcohol stimuli had higher recall in the NoThink condition than in the Baseline condition ($p = .008$). No interactions involving Group were found. Additionally, suppression-related effects were observed for the Alcohol Stimuli $F(1, 39) = 9.74$, $p < .01$, $\eta p^2 = .20$, with Alcohol NoThink < Alcohol Baseline pairs recalled. Conversely, a recall facilitation for the NoAlcohol NoThink stimuli was observed $F(1, 39) = 10.35$, $p < .01$, $\eta p^2 = .21$, with better recall of No Alcohol NoThink than NoAlcohol Baseline stimuli. Accordingly, SIF analysis revealed a significant difference between Stimuli $F(1, 39) = 28.82$, $p < .001$, $\eta p^2 = .43$, with alcohol stimuli having higher SIF than no-alcohol stimuli. No Group differences or interactions involving were observed in any of these effects.

In light of group differences in encoding performance, a complementary analysis was conducted, including overall encoding accuracy (centered) as a covariate in the recall model. Encoding performance significantly predicted conditionalized recall, $F(1,38) = 7.85$, $p = .008$, $\eta p^2 = .17$. After accounting for

encoding performance, the main effect of Group on recall was no longer significant, $F(1,38) = 1.58$, $p = .216$, $\eta p^2 = .04$. Importantly, inclusion of encoding performance did not alter the Stimulus × Condition interaction, indicating that stimulus-dependent suppression patterns were not driven by encoding differences.

Following previous research recommending the exclusion of participants with encoding below 75%[92] all analyses were initially conducted excluding four participants, who did not meet this criterion. As the behavioral results remained unchanged, the full sample was subsequently retained for the final analysis.

6.4.2. Seed-based functional connectivity results

6.4.2.1. Alcohol related trials

Seed-based functional connectivity analysis revealed significantly altered task-based patterns when comparing those with AUD and controls. Particularly, during the Alcohol-NoThink trials, when compared to controls, participants with AUD exhibited increased connectivity between the right thalamus (seed point) and a cluster of voxels in the right occipital fusiform gyrus (k = 138; +18, -94, -14); between the right putamen (seed point) and a cluster of voxels in left middle frontal gyrus (k = 119; -46, +52, -02); between the right caudate (seed point) and a cluster of voxels in the left central opercular cortex and the postcentral gyrus (k = 81; -62, -20, +16); and, between the posterior cingulate (seed point) and a cluster of voxels in the right occipital fusiform gyrus and the right cerebellum (k = 71; +32, -78, -18). During the Alcohol-Think trials, participants with AUD exhibited increased connectivity between the right accumbens (seed point) and two clusters of voxels, one in the anterior cingulate gyrus (k =80; +02, -08, +38), and the other in the orbitofrontal cortex (k = 133; -44, +26, -16) (see Table 18; Figure 14; Figure 15).

Table 18. Increased functional connectivity for AUD participants when compared with controls during Alcohol-Think and -NoThink trials.

Seed	Cluster	Cluster size (#voxels)	Peak MNI coordinates			*p*-FDR
			x	y	z	
Functional connectivity during Alcohol-NoThink Trial						
Right Thalamus	Occipital Fusiform Gyrus; Lingual Gyrus	138	18	-94	-14	0.001799**
Right Putamen	Left Middle Frontal Gyrus; Left Lateral Orbital Gyrus	119	-46	52	-02	0.005412**
Right Caudate	Left Central Opercular Cortex; Postcentral Gyrus	81	-62	-20	16	0.029804*
Posterior Cingulate	Right Cerebellum; Right Occipital Fusiform Gyrus	71	+32	-78	-18	0.041474*
Functional connectivity during Alcohol-Think trials						
Right Accumbens	Anterior Cingulate Gyrus	80	02	-08	38	0.020601*
	Left Orbitofrontal Cortex	133	-44	26	-16	0.002451**

Note: MNI: Montreal neurological institute; *$p < 0.05$; **$p < 0.01$

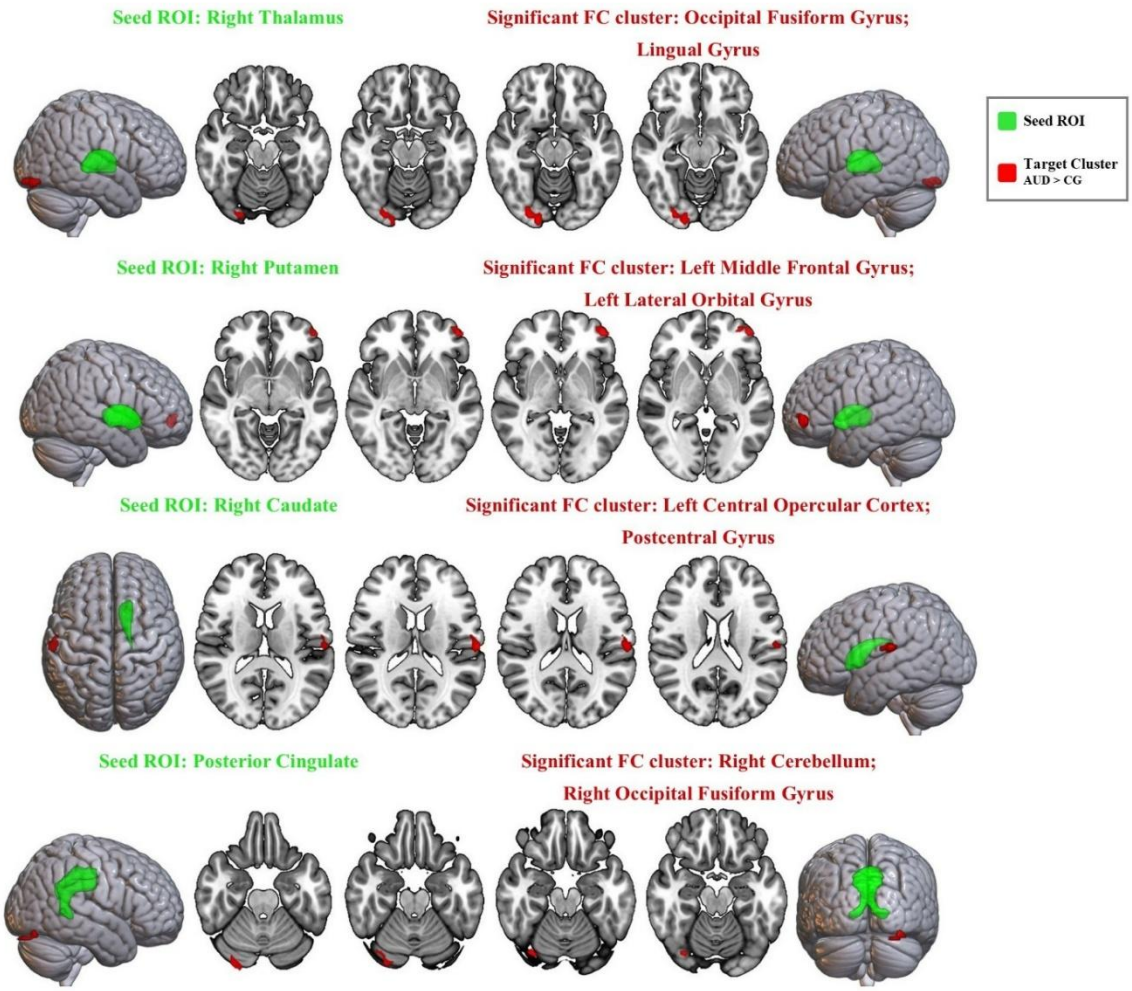


Figure 14. NoThink Alcohol seed-to-voxel functional connectivity depiction. Each line represents functional connectivity differences between regions in which AUD showed stronger coupling than Controls. Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold, and a familywise corrected p-FDR < 0.05 cluster-size threshold.

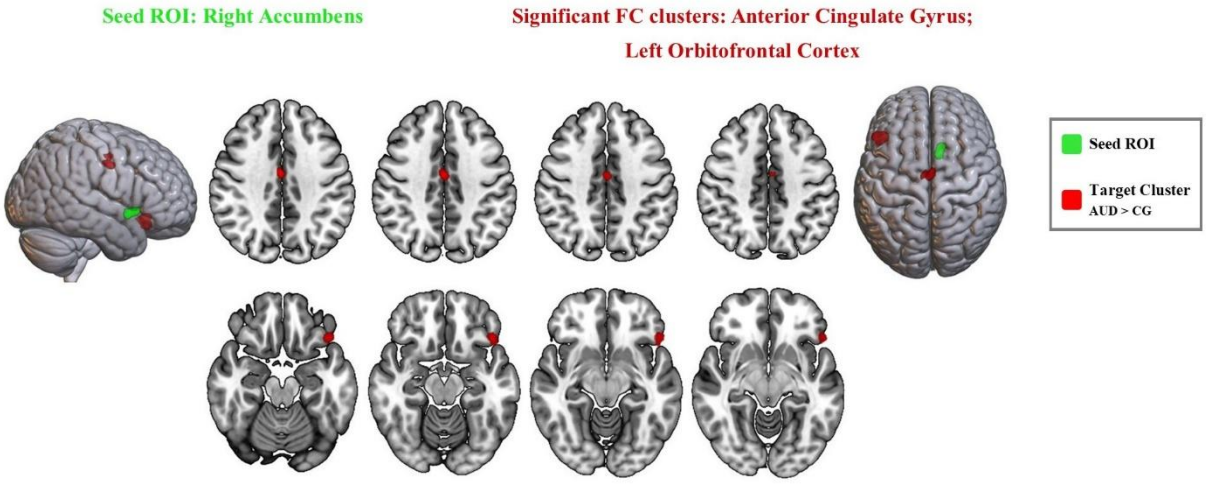


Figure 15. Think Alcohol seed-to-voxel functional connectivity depiction. Each line represents functional connectivity differences between regions in which AUD showed stronger coupling than Controls. Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold, and a familywise corrected p-FDR < 0.05 cluster-size threshold.

Conversely, during the Alcohol-NoThink trials, when compared to AUD participants, the control group exhibited increased functional connectivity between the right middle frontal gyrus (seed point) and a cluster of voxels in left post/precentral gyrus (k = 117; -32, -32, +60); between the right inferior frontal gyrus (seed point) and a cluster of voxels in the posterior cingulate and precuneus (k = 92; -10, -50, +32); and, between the anterior cingulate (seed point) and a cluster of voxels in the bilateral lingual gyrus (k =126; +06, -96, -14). During Alcohol-Think trials participants of the control group exhibited greater functional connectivity than those with AUD between the right caudate (seed point) and two clusters of voxels, one in the bilateral cerebellum (k = 218; -04, -84, -26), and another in the right occipital cortex (k = 75; +30, -100, +02); between the Left Posterior Temporal Fusiform Gyrus (seed point) and a cluster of voxels in the Right Middle Frontal Cortex (k = 210; +26, +42, +14) (see Table 19; Figure 16; Figure 17).

Table 19. Increased functional connectivity for the control group when compared with AUD participants during Alcohol-Think and -NoThink trials.

Seed	Cluster	Cluster size (#voxels)	Peak MNI coordinates			*p*-FDR
			x	y	z	
Functional connectivity during Alcohol-NoThink Trial						
Right Middle Frontal Gyrus	Left Postcentral Gyrus; Left Precentral Gyrus	117	-32	-32	60	0.003858**
Right Inferior Frontal Gyrus	Posterior Cingulate Gyrus; Precuneus	92	-10	-52	32	0.012291*
Anterior Cingulate	Bilateral Lingual Gyrus	126	06	-96	-14	0.002121**
Functional connectivity during Alcohol-Think trials						
Right Caudate	Bilateral Cerebellum	218	-04	-84	-26	0.000070***
	Right Occipital Cortex	75	30	-100	02	0.037275*
Left Posterior Temporal Fusiform Gyrus	Right Middle Frontal Cortex	210	26	42	14	0.000076***

Note: MNI: Montreal neurological institute; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

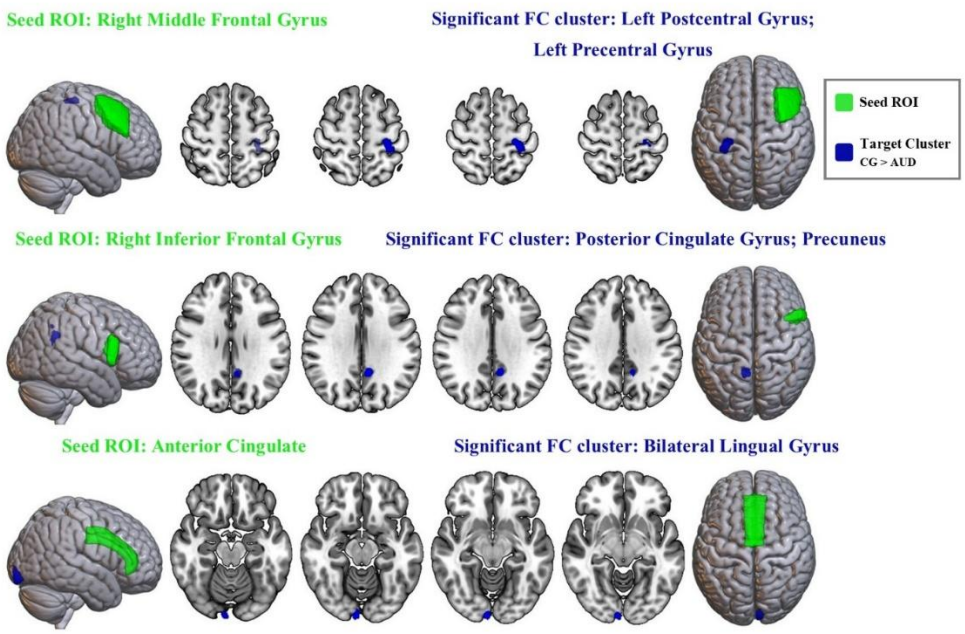


Figure 16. NoThink Alcohol seed-to-voxel functional connectivity depiction. Each line represents functional connectivity differences between regions in which Controls showed stronger coupling than AUD. Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold, and a familywise corrected p-FDR < 0.05 cluster-size threshold.

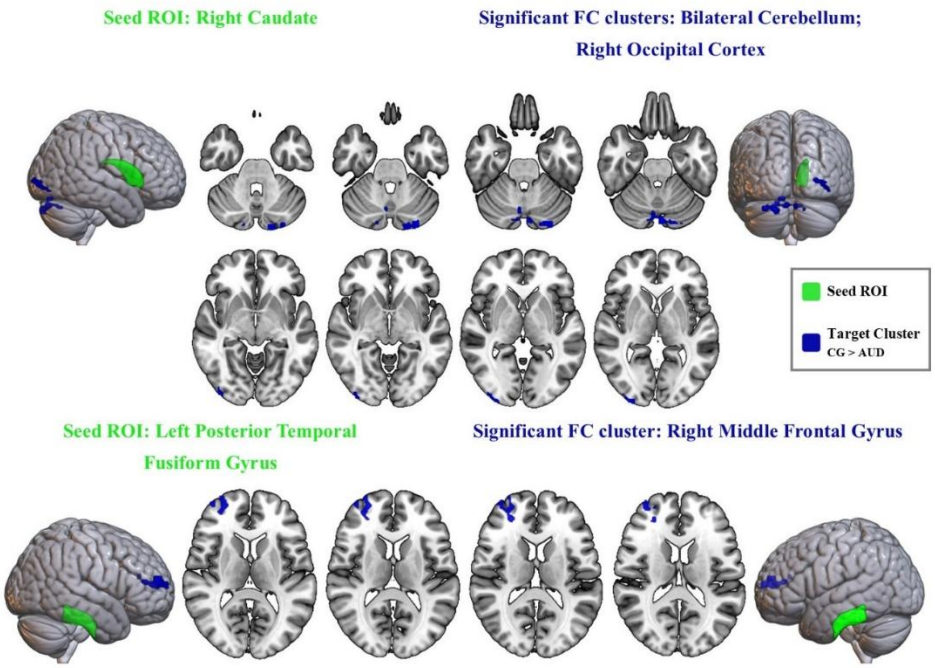


Figure 17. Think Alcohol seed-to-voxel functional connectivity depiction. Each line represents functional connectivity differences between regions in which Controls showed stronger coupling than AUD. Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold, and a familywise corrected p-FDR < 0.05 cluster-size threshold.

6.4.2.2. Non-Alcohol related trials

Regarding the NoAlcohol-NoThink pairs, when compared to controls, participants with AUD exhibited increased coupling between the right accumbens (seed point) and a cluster of voxels in occipital cortex (k =95; -28, -88, -02); the right middle frontal gyrus (seed point) and a cluster of voxels in the right middle and inferior occipital gyrus (k =77; +50, -76, +12); and the left anterior parahippocampal gyrus (seed point) and a cluster of voxels in the inferior temporal gyrus (k =100; +58, -62, -18). In parallel, during the NoAlcohol-Think trials, when compared to controls, participants with AUD exhibited increased connectivity between the right caudate (seed point) and a cluster of voxels in the bilateral paracingulate gyrus (k =267; -02, +50, +04); and the right thalamus (seed point) and a cluster of voxels in the right cerebellum (k =92; +44, -66, -24) (see Table 20). No other significant differences in functional connectivity were observed.

Table 20. Increased functional connectivity for AUD participants when compared with controls during NoAlcohol-Think and -NoThink trials.

Seed	Cluster	Cluster size (#voxels)	Peak MNI coordinates			*p*-FDR
			x	y	z	
Functional connectivity during NoAlcohol-NoThink Trial						
Right Accumbens	Occipital Cortex	95	-28	-88	-02	0.014052*
Right Middle Frontal Gyrus	Right Middle Occipital Gyrus Right Inferior Occipital Gyrus	77	50	-76	12	0.040907*
Left Anterior Parahippocampal Gyrus	Left Central Opercular Cortex; Inferior Temporal Gyrus	100	+58	-62	-18	0.009354**
Functional connectivity during NoAlcohol-Think trials						
Right Caudate	Bilateral Paracingulate Gyrus	267	-02	50	04	0.000011***
Right Thalamus	Right Cerebellum	92	44	-66	-24	0.009502**

Note: MNI: Montreal neurological institute; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

6.4.2.3. Between-Conditions comparisons

Within the AUD group, the Alcohol-Think > NoAlcohol-Think contrast revealed significantly increased functional connectivity between the left inferior frontal gyrus (seed point) and two clusters of voxels in the bilateral occipital cortex, one in the right occipital cortex (k = 115; +32, −100, +02; *p*-FDR = 0.003264), and another in the left occipital cortex (k = 60; −12, −96, +12; *p*-FDR = 0.047072). Additionally, the Alcohol-NoThink > NoAlcohol-NoThink contrast revealed significantly increased functional connectivity between the right inferior frontal gyrus (seed point) and a cluster of voxels in the left angular gyrus, left supramarginal gyrus, and left lateral occipital cortex (k = 190; −48, −56, +54; *p*-FDR = 0.000049). Conversely, the NoAlcohol-NoThink > Alcohol-NoThink contrast revealed significantly increased functional connectivity between the right inferior frontal gyrus (seed point) and a cluster of voxels in the right superior temporal gyrus and middle temporal gyrus (k = 189; +66, −18, −02; *p*-FDR = 0.000049). No other between-conditions significant results were found.

6.4.3. Correlations

Within the AUD group, higher overall craving was positively correlated with recall of alcohol-related stimuli during No-Think trials ($r = .47$, $p = .042$), with the Compulsivity subscale showing a stronger positive correlation with the same type of stimuli recall ($r = .62$, $p = .005$). Higher AUDIT scores were also associated

with greater recall of Baseline alcohol trials (r = .42, p = .030). At the neural level, Emotionality subscale was positively correlated with functional connectivity between the right inferior frontal gyrus and posterior cingulate gyrus/precuneus during alcohol No-Think trials (r = .54, p = .018). No other significant correlations were observed across other regions or conditions.

6.5. Discussion

The present study examined neurofunctional correlates of memory inhibition in AUD using an adapted Think/No-Think Alcohol paradigm. Specifically, this study aimed to determine whether abstinent individuals with AUD exhibit impaired suppression of alcohol-related memories and whether such impairments are reflected in altered neural recruitment during attempts to regulate memory retrieval. Although no group differences were observed at the behavioral level in SIF, marked differences emerged in the functional connectivity patterns engaged during Think and No-Think conditions. This dissociation suggests that alterations in memory control in AUD may be more evident at the level of neural reorganization and network recruitment than at the behavioral performance, a pattern that has been frequently reported in neuroimaging studies of individuals with AUD and related populations [93-95].

At the behavioral level, individuals with AUD showed significantly reduced encoding performance for both alcohol-related and non-alcohol stimuli, consistent with extensive evidence of learning and episodic memory impairments associated with chronic alcohol use. Neuropsychological and neuroimaging studies have repeatedly documented deficits in the acquisition and consolidation of new information in AUD, linked to structural and functional alterations in medial temporal lobe and prefrontal regions critical for episodic memory formation[28,33,34,96]. Within this framework, encoding strength emerged as a major determinant of subsequent recall performance, underscoring that learning-stage limitations constitute a critical constraint on recall-based measures in memory control paradigms and must be taken into account when interpreting TNT performance in clinical populations.

Consequently, despite theoretical expectations that alcohol-related memories, due to their intrinsic salience and motivational relevance, would be less susceptible to suppression in AUD, SIF did not differ between groups for either stimulus type. Importantly, however, suppression effects were stimulus-dependent across both groups. Alcohol cues exhibited SIF, whereas non-alcoholic drink cues showed the opposite pattern, with higher recall in the No-Think than Baseline condition. This reversal pattern is consistent with

models proposing that No-Think trials reflect a dynamic balance between weakening via active inhibitory control and strengthening driven by repeated cue exposure and automatic retrieval processes[56,97]. When suppression engagement is sufficiently strong, as appears to be the case for alcohol cues, inhibitory mechanisms supported by prefrontal regions can override hippocampal retrieval processes and yield SIF[98]. However, the absence of below-Baseline forgetting has been repeatedly documented in the TNT literature[92,99,100], indicating that forgetting depends on task conditions and the degree of control engagement. Because this stimulus-dependent reversal was observed in both groups and remained after controlling for encoding performance, it likely reflects task-inherent dynamics rather than AUD-specific impairment.

This pattern diverges from some clinical applications of the TNT paradigm, where patient populations characterized by intrusive cognition show reduced memory suppression relative to controls, such as individuals with post-traumatic stress disorder[65]. However, other studies have reported preserved behavioral suppression effects despite clear neural differences, as observed in major depressive disorder[64,101]. A critical consideration in interpreting these findings is that SIF depends on the availability of sufficiently robust memory traces[56,92]. In clinical samples characterized by impaired learning and reduced encoding strength, such as AUD, limitations in mnemonic capacity may constrain the extent to which behavioral suppression effects can be expressed, even when memories remain highly salient at a neural level. In a related line of research, recent work in young binge drinkers using the same Think/No-Think Alcohol paradigm reported preserved behavioral suppression of alcohol-related memories alongside pronounced alterations in functional connectivity, which were interpreted as compensatory neural recruitment in response to heightened alcohol-cue salience[74]. In contrast, the present findings in a clinical AUD sample suggest a qualitatively different pattern, in which altered functional connectivity may no longer reflect effective compensation, but rather the emergence of less selective and more inefficient neural engagement under memory control demands. From this perspective, preserved behavioral suppression in AUD may mask an underlying neural vulnerability, reflecting an early or latent stage of network dysfunction driven by impaired encoding capacity and exaggerated salience attribution, rather than a failure of suppression mechanisms per se.

From a neurofunctional perspective, when attempting to suppress alcohol-related memories (Alcohol-NoThink trials), functional connectivity analyses revealed multiple group differences in the neural systems recruited. Relative to controls, individuals with AUD showed increased coupling between subcortical regions central to reward learning and habit formation and cortical regions implicated in cognitive control and sensory

processing[18,102]. Specifically, enhanced connectivity between the putamen and the left middle frontal gyrus (included in the DLPFC) and between the putamen and the lateral orbitofrontal cortex suggests altered integration between striatal motivational signals and prefrontal control and valuation processes[103]. The putamen is critically involved in stimulus-response learning and habit formation, particularly in the context of addiction, where alcohol-associated cues gain privileged access to action selection and control systems[102,104,105]. Accordingly, increased coupling with prefrontal regions during suppression attempts may reflect memory intrusions and inefficient engagement of control mechanisms in response to strong alcohol-cue-driven signals, rather than effective top-down inhibition, despite preserved behavioral suppression.

In parallel, individuals with AUD also exhibited increased connectivity between subcortical structures and posterior perceptual and sensorimotor regions. Particularly, enhanced coupling between the right thalamus and the occipital fusiform/lingual gyrus suggests sustained engagement of visual and imagery-based representations during suppression attempts, consistent with the role of these regions in visual imagery and the retrieval of content-specific and scene-related information[106,107]. In line with this interpretation, similar thalamo-striatal and fusiform hyperconnectivity has been reported in young binge drinkers during the suppression and recall of alcohol-related memories, where it was interpreted as reflecting heightened mental imagery and associative reactivation of alcohol contexts despite preserved behavioral performance[74,108], suggesting that alcohol-related memories may continue to recruit perceptual imagery systems during suppression attempts.

Lastly, the increased functional connectivity between the right caudate and the left central opercular/postcentral cortex in the AUD group suggests involvement of somatosensory and interoceptive processing during attempts to suppress alcohol-related memories. Specifically, beyond their role in oral and gustatory sensation, the central opercular and adjacent postcentral regions have been increasingly implicated in bodily awareness and interoceptive components of craving, linking internal bodily states with motivational and action systems in addiction[109-111]. Accordingly, enhanced striatal-opercular coupling during Alcohol-NoThink trials may reflect increased monitoring of bodily or visceral responses elicited by alcohol-related cues, consistent with models proposing that craving emerges from the integration of interoceptive signals with reward and habit circuitry[112,113].

By comparison, control participants preferentially recruited connectivity profiles consistent with classic top-down control mechanisms during Alcohol-NoThink trials. Relative to individuals with AUD, controls

showed increased functional connectivity between prefrontal control regions and posterior cortical areas, including coupling of the right middle frontal gyrus (DLPFC) with precentral/postcentral cortex, the right inferior frontal gyrus with posterior cingulate cortex/precuneus, and the anterior cingulate cortex with bilateral lingual gyrus. These regions are central to voluntary memory suppression, supporting goal maintenance, inhibitory control, and conflict monitoring during No-Think trials[53,54,56,114]. In particular, inferior frontal gyrus-posterior midline coupling is consistent with effective regulation of internally oriented memory processes, given the role of the posterior cingulate cortex and precuneus in autobiographical memory retrieval and mental imagery[115,116]. In this sense, the augmented prefrontal-posterior connectivity observed in healthy subjects during Alcohol-NoThink trials may reflect more selective downregulation of alcohol-related imagery, in line with prior evidence linking successful suppression to reduced reactivation of hippocampal and posterior cortical regions[95,117]. Similarly, anterior cingulate cortex coupling with the lingual gyrus may index top-down modulation of early visual and imagery-related processing, limiting the perceptual elaboration of alcohol cues when retrieval is intentionally constrained[117,118].

During Alcohol-Think trials, group differences pointed to distinct mechanisms of alcohol-memory retrieval. In individuals with AUD, alcohol recall was characterized by stronger coupling of the nucleus accumbens with cingulate and orbitofrontal regions, signaling incentive salience attribution that prioritizes motivational engagement during alcohol-memory recall, consistent with addiction models in which alcohol memories are accessed through sensitized reward-related and habit-based mechanisms rather than neutral episodic recall[18,107,119]. In contrast, the control group exhibited stronger coupling between the caudate nucleus and cerebellar and occipital regions, consistent with coordinated, goal-directed retrieval supported by dorsal striatal selection/monitoring processes and cerebellar contributions to cognitive coordination and prediction[120,121]. Complementing this pattern, healthy participants also showed increased connectivity between the posterior fusiform gyrus and the right middle frontal cortex, indicating stronger integration between mental imagery and frontal monitoring during recall[107,108,122,123]. Taken together, these control-dominant couplings suggest that alcohol-memory retrieval in healthy individuals relies on coordinated perceptual reactivation under top-down regulation. Although the caudate is part of the striatum and is implicated in addiction-relevant functions, it is often linked to strategic action-outcome selection and controlled processing rather than ventral striatal incentive salience per se[124,125]. Within this framework, reduced caudate-cerebellum/occipital coupling in AUD may reflect diminished recruitment of goal-directed coordination and perceptual reconstruction during

alcohol recall, consistent with a shift toward more cue-triggered access, dominated by motivational valuation circuitry.

Notably, during NoAlcohol-Think trials, individuals with AUD showed increased connectivity relative to controls between the right caudate nucleus and the bilateral paracingulate gyrus, as well as between the right thalamus and the right cerebellum. Although these connections do not anatomically match those observed in controls during Alcohol-Think trials, they engage similar control- and coordination-related systems involving dorsal striatal and cerebellar nodes, which are commonly associated with goal-directed retrieval and cognitive coordination rather than automatic motivational access[126-128]. This convergence at the systems level suggests that, in AUD, retrieval of non-alcohol-related memories requires enhanced engagement of control-oriented circuitry, consistent with increased recruitment of neuronal resources when mnemonic content lacks intrinsic salience, without evidence that such recruitment confers behavioral or motivational benefit[129-131]. By contrast, retrieval of alcohol-related memories in AUD participants appear to bypass these control-oriented pathways and instead preferentially engages reward- and valuation-related circuitry, underscoring a dissociation between effortful retrieval mechanisms for neutral material and automatic, salience-driven access for alcohol-related content.

Furthermore, during attempts to suppress non-alcohol-related memories (NoAlcohol-NoThink trials), individuals with AUD exhibited stronger coupling than controls between prefrontal control regions and posterior perceptual and medial temporal areas, including connectivity linking the right middle frontal gyrus with occipital cortex and the anterior parahippocampal gyrus with inferior temporal regions. Because fronto-occipital coordination of this type is classically implicated in voluntary memory suppression[53,54,56], this pattern may indicate that core suppression-related circuitry remains functionally recruitable in AUD. Critically, however, these same control-related configurations were not preferentially engaged during suppression of alcohol-related memories, where controls showed greater fronto-posterior coupling and AUD instead recruited striatal, interoceptive, and perceptual systems[18,107,110]. Therefore, our results may suggest not a generalized inefficiency of suppression mechanisms in AUD, but a stimulus-dependent redistribution of control recruitment, whereby alcohol-related motivational salience constrains engagement of typical suppression circuitry. In the absence of alcohol salience, suppression-related coordination becomes more strongly expressed but appears broader and less selectively tuned than in controls, indicating altered allocation, rather than absence or inefficiency, of cognitive control.

Lastly, increased connectivity was also observed between the right nucleus accumbens and occipital cortex during NoAlcohol-NoThink trials in individuals with AUD. Although the nucleus accumbens has been classically associated with reward processing[132,133], converging evidence indicates that it also plays a broader role in incentive salience attribution and the modulation of attentional and perceptual processes beyond reward-specific contexts[108,134]. Crucially, because this effect emerged during suppression of non-alcohol related material, it cannot be attributed to alcohol-specific reward processing. Instead, accumbens-occipital coupling is consistent with a generalized salience-driven modulation, whereby sensitized striatal systems intrude into the processing of neutral mnemonic content under cognitive control demands. Such aberrant salience attribution aligns with addiction models proposing that striatal sensitization biases attentional and mnemonic processing even in the absence of explicit drug cues, contributing to non-selective engagement of perceptual systems during tasks requiring suppression or regulation of memory retrieval[18,110].

Within-group stimulus contrasts further demonstrated that, in AUD, prefrontal connectivity patterns were systematically modulated by mnemonic content across both retrieval and suppression phases. During suppression, alcohol (vs non-alcohol) memories preferentially increased right inferior frontal coupling with left parietal and lateral occipital regions, whereas non-alcohol suppression preferentially engaged right inferior frontal connectivity with right superior and middle temporal cortices. During retrieval, alcohol (vs non-alcohol) recall was associated with increased left inferior frontal coupling to bilateral occipital cortex. Given the established role of inferior frontal regions in inhibitory and retrieval control[52,53,54], these findings indicate that the cortical targets of prefrontal regulatory coupling shift as a function of stimulus type. Alcohol-related content consistently biased connectivity toward posterior representational systems, consistent with stimulus-dependent reconfiguration of control networks rather than a generalized suppression deficit.

Importantly, correlation analysis within the AUD group further supported salience-driven alcohol-memory processing. Higher overall craving, particularly greater scores on the Compulsivity subscale of the ACQ-SF-R, were associated with increased recall of NoThink alcohol-related stimuli, indicating reduced ability to disengage from alcohol memories under suppression demands. The compulsivity dimension of the ACQ-SF-R indexes intrusive urges and diminished goal-directed control[135], suggesting that suppression failure in AUD is closely linked to altered incentive-driven processes. In addition, greater alcohol-use severity (AUDIT scores) was associated with enhanced recall of Baseline alcohol items, signaling increased mnemonic accessibility for alcohol-related material.

At the neural level, greater scores on the Emotionality factor -which reflects craving driven by negative affect[135]- were associated with stronger functional connectivity between the inferior frontal gyrus and posterior cingulate/precuneus during alcohol-memory suppression, suggesting increased recruitment of regulatory control networks under affective load. Together, these associations are consistent with a model in which craving-related affective and compulsive processes may influence both behavioral suppression and neural recruitment.

Collectively, the present findings support a model in which memory control in AUD is characterized not by successful compensatory recruitment, but by altered engagement of control- and salience-related networks. Although suppression-related performance did not differ between groups, impaired encoding constrained overall recall performance, and increased functional connectivity did not translate into behavioral benefit. Unlike non-clinical hazardous-use populations, where heightened neural recruitment has been interpreted as compensatory, that is, it maintains performance in comparison to controls, the present findings suggest that, in AUD, increased connectivity reflects reduced selectivity and salience-biased allocation of cognitive resources under memory control demands. This pattern is consistent with models proposing a transition from adaptive recruitment at earlier stages of alcohol use to maladaptive or dysregulated neural engagement in chronic AUD, driven by impaired learning capacity and exaggerated salience attribution rather than failure of suppression mechanisms per se[134,136].

Several limitations should be considered. First, marked encoding impairments in AUD constrained downstream recall and reduced the sensitivity of behavioral suppression indices. Although recall was evaluated conditionally on successful encoding and learning variability was accounted for, encoding deficits remain an inherent feature of the clinical population. Second, the TNT paradigm did not include trial-level behavioral indices during suppression, such as intrusion reports or used strategies, which may be more sensitive to salience-driven reactivation than final recall accuracy. Third, medication use was not systematically tracked; however, depressive, anxiety, and general psychopathology symptoms were assessed, reducing the likelihood that the observed effects are explained solely by affective symptom severity. Finally, the smaller control group may have limited power to detect subtle behavioral effects, although the functional connectivity findings and within-group correlations mitigate this concern partially.

Future research should extend these findings by combining the Think/No-Think Alcohol paradigm with trial-level behavioral measures, such as intrusion frequency, subjective suppression difficulty, or imagery

vividness ratings, to more directly capture salience-driven memory reactivation processes. Longitudinal designs tracking individuals across different stages of abstinence and recovery would help clarify whether inefficient enhanced coupling of control mechanisms persist, reorganize, or normalize over time. Finally, comparing alcohol-related stimuli with other motivationally salient but non-drug cues would help determine the specificity of the observed imbalance to alcohol-related content.

In sum, the present study shows that memory control in abstinent individuals with AUD is characterized by altered neural dynamics of salience and regulation that are not readily captured by recall-based suppression measures alone, highlighting the importance of neural-level approaches for advancing our understanding of memory vulnerability and cognitive control in addiction.

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6.7. References

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Chapter VII

General Discussion

7. General Discussion

Alcohol misuse is associated with a diversity of neurocognitive alterations affecting executive control, memory processes, and motivational systems (Almeida-Antunes et al., 2021; Pérez-García et al., 2022; Roberge et al., 2025; Wilcox et al., 2014). In particular, growing evidence suggests that alcohol-related cues and craving play a central role in the maintenance and escalation of alcohol consumption (Barak & Goltseker, 2021; Goldfarb et al., 2020; Vafaie & Kober, 2022). Despite this, the neurocognitive mechanisms through which alcohol-related memories interact with craving and cognitive control across different stages of alcohol use remain insufficiently understood. The present thesis sought to address this gap by examining how alcohol consumption, ranging from binge drinking to alcohol use disorder, affects memory processes, cognitive control, and their neural correlates using behavioral, electrophysiological, and neuroimaging approaches.

To address this objective, four empirical studies were conducted. First, a Portuguese validation of the Alcohol Craving Questionnaire – Short Form – Revised provided a psychometrically robust measure of acute alcohol craving, supporting the assessment of the subjective motivational states associated with alcohol use. Second, an electrophysiological study examined the short- and long-term effects of binge drinking on attention and working memory, showing that although behavioral performance remained largely preserved, binge drinkers exhibited alterations in electrophysiological markers of cognitive processing, suggesting subtle neural disruption and possible compensatory recruitment. Third, a functional magnetic resonance imaging study investigated the neural mechanisms underlying associative memory retrieval for alcohol-related information in binge drinkers, revealing increased engagement of reward and perceptual brain regions when retrieving alcohol-related associations. Finally, a functional connectivity study using an adapted Think/No-Think Alcohol paradigm examined the behavioral and neural mechanisms of intentional memory suppression in individuals with alcohol use disorder, showing that although suppression-induced forgetting was behaviorally comparable between groups, alcohol use disorder was associated with altered connectivity patterns during attempts to suppress alcohol-related memories.

Taken together, the findings of this thesis support three main conclusions. First, alcohol misuse is associated with neural alterations that may emerge even when overt performance remains relatively preserved, particularly at earlier stages of hazardous drinking. Second, alcohol-related memories appear to acquire increased motivational relevance, such that retrieval of alcohol-related information engages reward- and salience-related systems beyond the effects of immediate cue exposure alone. Third, as alcohol misuse

becomes more severe, the regulation of alcohol-related memories may increasingly depend on neural dynamics shaped by motivational circuitry, suggesting that alcohol-related memory processes may represent a key mechanism linking craving, cognitive control, and relapse vulnerability. Although some findings were more nuanced than originally hypothesized, particularly in showing preserved behavioral suppression despite altered functional connectivity in alcohol use disorder, the overall pattern of results consistently supported the central aim of the thesis, that is, to determine how alcohol-related memory processes interact with motivational salience and cognitive control across the spectrum of alcohol misuse. The following sections discuss these findings in the context of current neurocognitive models of addiction.

7.1. Early Neurocognitive Alterations and Progression Across Alcohol Misuse

Evidence from behavioral and neurofunctional research indicates that hazardous alcohol use is associated with alterations in neural systems supporting executive control, attention, and memory, even in the absence of overt cognitive impairment (La Berre et al., 2017; Parada et al., 2012; Mota et al., 2013). Within contemporary neurobiological models of addiction, these changes are often interpreted as reflecting an increasing imbalance between motivational systems that assign value to drug-related cues and prefrontal systems involved in cognitive regulation (Koob & Volkow, 2016; Lüscher et al., 2020). The findings of the present thesis are consistent with this general framework, but they further suggest that alcohol-related neurocognitive alterations may be detectable already at the stage of hazardous drinking and may involve not only reward-related responding, but also attention- and memory-related processing.

The clearest evidence for early alteration emerged from the electrophysiological study on binge drinking, in which attentional and working memory processes were assessed during a visual task under hangover and non-hangover conditions. In the hangover state, binge drinkers showed reduced P3 and LPC amplitudes relative to controls, despite no significant group differences in behavioral performance. Given the established association of the P3 with attentional allocation (Olofsson et al., 2008; Polich, 2007) and of the LPC with later evaluative and memory-related processing (Rugg & Curran, 2007), this pattern suggests that a recent binge episode may transiently disrupt the neural implementation of these cognitive operations even when task accuracy remains preserved. This dissociation between altered neural activity and preserved performance is important, because it indicates that early alcohol-related effects may be detectable at the neural level before they become evident in overt performance.

By contrast, when the same group was assessed on a non-drinking day, binge drinkers exhibited increased LPC amplitudes relative to controls, again in the absence of clear behavioral impairment. In the context of preserved task performance, this enhanced late positive activity may reflect greater neural recruitment to maintain adequate functioning. Although compensatory interpretations should be made cautiously, this pattern is broadly in line with previous reports suggesting that hazardous alcohol use can be associated with altered or less efficient neural processing despite apparently intact behavior (Crego et al., 2009; Campanella et al., 2013; Molnar et al., 2018). Considered together, these findings suggest that binge drinking is not simply associated with acute transient dysfunction during hangover, but also with more persistent differences in cognitive processing.

These observations are relevant because they suggest that early alcohol-related neurocognitive changes may not initially manifest as generalized behavioral failure. Rather, these findings suggest that hazardous drinking may involve a dissociation in which functionally meaningful alterations in attention and memory systems are already present before clinically evident deficits emerge. In this sense, the present findings support the view that binge drinking may represent an early stage of neurofunctional alteration, consistent with continuum accounts proposing that hazardous alcohol use and alcohol use disorder differ more in degree and system-level organization than in entirely distinct mechanisms (Gowin et al., 2021; Lannoy et al., 2017; Parsons, 1998; Rossetti et al., 2023).

The thesis further refines this continuum perspective by showing that progression across alcohol misuse may not simply involve stronger versions of the same deficits, but a qualitative shift in where neurocognitive changes become most evident. In the ERP study with young binge drinkers, the findings indicated altered neural implementation of attentional and memory-related processing, particularly during the hangover state, as reflected in reduced P3 and LPC amplitudes despite limited behavioral disruption. Even on a non-drinking day, increased LPC amplitudes suggested that apparently preserved performance may rely on greater neural recruitment. In the fMRI associative memory study, binge drinkers likewise performed similarly at the behavioral level but exhibited increased activation in reward- and imagery-related regions during the recall of alcohol-associated contexts, indicating that alcohol-related information may acquire enhanced salience even when retrieved indirectly through neutral cues. This interpretation is also consistent with related findings from our research group showing enhanced electrophysiological functional connectivity during the processing of alcohol-related images in young binge drinkers, particularly across fronto-parieto-

occipital networks (Almeida-Antunes et al., 2022), as well as altered connectivity between inhibitory-control and memory networks during the suppression of alcohol-related memories (Almeida-Antunes et al., 2024). In contrast, in the AUD study, the most prominent feature was not a clear behavioural deficit in memory suppression, but altered functional coupling during attempts to regulate alcohol-related memories, suggesting that, as alcohol misuse becomes more severe, the critical change may lie less in overt performance deficits and more in the progressive reorganization of the neural systems through which alcohol-related information is processed, retrieved, and brought under cognitive control.

7.2. Alcohol-Related Memory as a Mechanism Linking Craving and Cognitive Control

A central contribution of the present thesis is the proposal that alcohol-related memory processes may represent a key mechanism through which motivational significance influences both craving and cognitive regulation. Addiction models have long emphasized the role of cue reactivity and reward-related dysregulation in alcohol use (Fukushima et al., 2020; Koob & Vendruscolo, 2025; Martins et al., 2021; Robinson & Berridge, 1993), however, the present findings suggest that associative memory processes may help explain how alcohol-related information retains motivational force even in the absence of direct alcohol cues (Cofresí et al., 2019; Das et al., 2015). In this sense, alcohol-related memories may function as a *bridge* between prior drinking experiences, current craving states, and the ability to regulate alcohol-related thoughts once they are activated.

This interpretation is consistent with cognitive accounts of craving that conceptualize craving not merely as an affective response, but as a process grounded in the retrieval and elaboration of substance-related representations (Andrade et al., 2012; Kavanagh et al., 2005; May et al., 2004). Through repeated pairings between alcohol use and contextual, sensory, and emotional states, environmental stimuli can become linked to the rewarding effects of drinking. Once established, these associations may allow alcohol-related representations to be reactivated not only by explicit alcohol cues, but also by internal or contextual triggers that reconstruct prior drinking experiences in memory (López-Caneda & Almeida-Antunes, 2025; May et al., 2015). From this perspective, alcohol-related memory processes are well-positioned to contribute to the subjective experience of craving by linking prior reward experience to present cognitive and affective states.

The functional neuroimaging findings provide direct support for this interpretation. In the associative memory study, binge drinkers showed increased activation in subcortical regions implicated in reward and salience processing, including the thalamus, globus pallidus, and dorsal striatum, as well as in perceptual and imagery-related regions such as the cerebellum and fusiform gyrus, during the retrieval of alcohol-related contextual associations. Importantly, these effects emerged during retrieval of previously learned associations, indicating that motivationally relevant neural systems were engaged not only by direct alcohol cue exposure, but also by memory-based reconstruction of alcohol-related information. That is, neutral stimuli previously paired with alcohol-related scenes were sufficient to elicit stronger recruitment of regions implicated in reward and perceptual processing. Consequently, this finding extends traditional cue-reactivity accounts by suggesting that the motivational pull of alcohol-related information may be sustained through associative retrieval processes themselves. Moreover, alcohol-related memories may therefore remain influential even in ostensibly neutral environments, because what is being reactivated is not merely the perceptual category of alcohol, but a richer representation of prior alcohol-related experience.

This account also helps interpret the findings from the Think/No-Think Alcohol study. Individuals with alcohol use disorder exhibited behavioral suppression of alcohol-related memories comparable to that of control participants, but showed altered connectivity patterns during suppression attempts, particularly involving regions implicated in salience attribution, reward valuation, and reward-guided action, such as the putamen, caudate and thalamus. This suggests that the regulation of alcohol-related memories may occur under different motivational conditions in alcohol use disorder. Rather than indicating a simple inability to inhibit retrieval, the results point to a situation in which control processes are deployed in the presence of representations that already carry heightened incentive value. Under such circumstances, successful performance at the behavioral level may still be achieved, but through altered neural dynamics reflecting stronger interaction between regulatory and motivational systems.

Considered together, these findings support the view that alcohol misuse may involve not only stronger alcohol-related representations, but also a closer interaction between those representations and the systems involved in their regulation. Importantly, however, the binge-drinking and AUD studies did not assess the same cognitive process: the former examined the retrieval of alcohol-related associative memories, whereas the latter focused on the intentional suppression of such memories. For this reason, the comparison should be interpreted cautiously. Nevertheless, the findings converge in suggesting that alcohol-related

memory processes become increasingly embedded within motivationally relevant neural systems. In binge drinkers, retrieval of alcohol-related associations was accompanied by a stronger motivational and perceptual neural signature, whereas in individuals with AUD, attempts to suppress alcohol-related memories engaged altered connectivity patterns involving salience- and value-related circuitry. Rather than reflecting the same process at different levels of severity, these results suggest that different stages of alcohol-related memory processing may each be shaped by motivational significance in ways that are relevant for craving and cognitive control. In this sense, alcohol-related memory processes may help explain both the persistence of alcohol-related thoughts and their close relationship with relapse vulnerability.

7.3. Alcohol-Related Memory Processes in Addiction: Integrated Theoretical and Translational Implications

The findings of the present thesis have broader implications for neurocognitive models of addiction. Dominant frameworks have emphasized a progressive shift from prefrontal regulatory control toward subcortical motivational systems, such that drug-related cues acquire increasing value and exert greater influence over behavior (Koob & Volkow, 2016; Everitt & Robbins, 2016). Accordingly, the present findings are broadly consistent with these models but also suggest that episodic and associative memory processes may be an important mechanism through which this shift is instantiated. Alcohol-related cues may not influence behavior solely because they directly activate reward systems, but also because they trigger memory representations that carry contextual, sensory, and motivational information about prior drinking. Consequently, this memory-based account helps explain why alcohol-related cognition can remain influential even in the absence of explicit cues and why alcohol-related thoughts can be both intrusive and difficult to regulate.

A second theoretical implication concerns the interpretation of preserved behavior in the presence of altered neural dynamics. Across the thesis, neural differences were observed without corresponding behavioral deficits. In binge drinking, this pattern was evident in the electrophysiological findings, where altered P3/LPC responses coexisted with largely preserved performance. In alcohol use disorder, it was evident in the Think/No-Think Alcohol study, where comparable suppression-induced forgetting was accompanied by altered functional connectivity during suppression. Together, these findings caution against relying solely on overt performance when evaluating alcohol-related neurocognitive dysfunction. They suggest that important changes may lie in the efficiency, distribution, or coordination of neural systems rather than

in obvious behavioral impairment. This is particularly relevant for models of addiction progression (Lüscher & Janak, 2021; Mollick & Kober, 2020; Uhl et al., 2019) as it implies that early or intermediate stages of alcohol misuse may already involve meaningful reorganization of neural processing that is not immediately apparent at the behavioral level.

These observations also have translational relevance. Current interventions for alcohol misuse often focus on reducing craving, altering drinking behavior, risk reduction, or strengthening inhibitory control (Kozak et al., 2019; Landy et al., 2016; Ray et al., 2019). The present findings suggest that alcohol-related associative memories may themselves represent a useful therapeutic target. If alcohol-related thoughts and urges are partly sustained by the retrieval of motivationally significant memory representations, then interventions aimed at weakening, updating, or better regulating those representations may have clinical value. Approaches such as memory reconsolidation procedures, cognitive bias modification, and training paradigms based on memory suppression or inhibitory control may therefore be relevant, not because they target reward processes in isolation, but because they may reduce the accessibility or motivational impact of alcohol-related memories.

More specifically, the pattern of findings observed in the present thesis raises a broader question for future research regarding whether interventions focused exclusively on strengthening prefrontal control (Lapenta et al., 2018; Luigjes et al., 2019; Zhang et al., 2024) are sufficient when the regulation of alcohol-related thoughts appears to occur within a neural context increasingly shaped by salience- and valuation-related systems. Although the present work was not designed to test interventions directly, it suggests that future translational studies may benefit from considering not only control enhancement, but also the interaction between regulatory and motivational networks. In this context, previous work from our research group has proposed memory inhibition training combined with transcranial direct current stimulation as a potential approach to modulation alcohol-related memory processes, cue reactivity, craving, and alcohol use (Almeida-Antunes et al., 2022), consistent with recent evidence showing associations between suppression training and reductions in clinical symptomatology, including anxiety and depressive symptoms (Mamat & Anderson, 2023). From this perspective, one promising avenue for future work would be to examine whether stimulation protocols designed to influence the balance between regulatory and salience systems could enhance the effects of memory-based interventions. For example, in addition to strengthening prefrontal control, stimulation targeting fronto-insular nodes of the salience network could be tested alongside memory

inhibition training to evaluate whether reducing cue-driven salience signals diminishes the intrusiveness or motivational pull of alcohol-related thoughts. At present, however, this should be understood as a theoretically informed proposal rather than a conclusion directly supported by the present data. Even so, it represents a meaningful direction for future research emerging from the overall pattern of findings reported in this thesis.

Overall, the present thesis supports a model in which alcohol misuse involves more than altered reward sensitivity or weakened control. Instead, the findings suggest that alcohol-related memories may become increasingly important in shaping both craving and regulation across the spectrum of alcohol misuse. By integrating evidence from psychometric, electrophysiological, and neuroimaging approaches, this work highlights the possibility that memory processes help bind together environmental cues, motivational states -including craving-, and control demands in addiction. Understanding this interaction may therefore be essential for clarifying why alcohol-related thoughts persist and for identifying new pathways for intervention.

7.4. Limitations

Although the findings presented in this thesis provide novel insights into the interaction between alcohol-related memory processes, motivational salience, and cognitive control, several limitations should be considered when interpreting the results. These limitations arise both from the methodological characteristics of individual studies and from broader considerations related to overall research design.

First, the validation study of the Alcohol Craving Questionnaire – Short Form – Revised provides an important tool for assessing acute alcohol craving in Portuguese populations; however, several limitations should be acknowledged. As with many psychometric validation studies, the results were based on self-report measures, which may be influenced by response biases or inaccuracies in introspective reporting. In addition, although the sample included individuals with varying levels of alcohol consumption, the study relied primarily on non-clinical participants, which may limit the generalizability of the findings to clinical populations with more severe alcohol use disorder. Future research would benefit from further examining the psychometric properties of the instrument across diverse clinical samples and longitudinal contexts.

Second, the electrophysiological study examining the effects of binge drinking on attention and working memory should be interpreted in light of certain methodological constraints. The cross-sectional design prevents causal conclusions about whether the observed neural differences reflect pre-existing vulnerabilities or the consequences of repeated binge drinking episodes. Furthermore, electrophysiological

measures such as event-related potentials provide excellent temporal resolution but limited spatial precision, which constrains the ability to draw definitive conclusions about the neural generators underlying the observed effects. Finally, although the study examined both hangover and non-drinking states, individual variability in drinking patterns, sleep quality, and physiological recovery following alcohol consumption may have introduced additional variability into the results.

Third, the functional neuroimaging study investigating associative memory retrieval for alcohol-related information in binge drinkers also presents several limitations. The associative memory paradigm relied on experimentally learned associations, which may not fully capture the complexity, personal relevance, or emotional richness of real-world alcohol-related memories that develop over years of drinking experiences. The sample size, while consistent with many neuroimaging studies, may also have limited power to detect more subtle group differences. Replication in larger samples and with more ecologically valid paradigms would therefore strengthen confidence in these findings. Additionally, no measurement of alcohol craving was collected, which could have shed light on the possible interactions between alcohol-memories salience and acute craving.

Fourth, the study examining intentional memory suppression in individuals with alcohol use disorder using the adapted Think/No-Think paradigm also presents several considerations. Although the paradigm provides a well-established framework for investigating memory control processes, laboratory-based suppression tasks do not fully reproduce the affective intensity, autobiographical relevance, or contextual complexity of intrusive alcohol-related thoughts in everyday life. Moreover, the task does not provide an objective trial-by-trial measure of whether suppression was successfully achieved on each No-Think trial, nor does it allow direct tracking of whether alcohol-related memories intruded into awareness during suppression attempts. Instead, inhibition is inferred indirectly from later memory performance, which limits the extent to which the success of online suppression can be directly evaluated. Future studies would benefit from incorporating paradigms that allow a more direct assessment of inhibition, for example through priming-based measures of residual memory activation. In this regard, further methodological developments within this line of research may help provide more sensitive and direct indices of suppression-related effects. Furthermore, the functional connectivity analyses used to examine neural interactions during memory suppression are inherently correlational, limiting inferences regarding directionality or causality between brain regions. While the results suggest altered interaction between salience- and control-related networks, further work using

complementary approaches, such as longitudinal designs or causal modeling techniques, will be necessary to clarify these mechanisms.

Beyond the limitations specific to each study, several broader considerations apply to the thesis as a whole. First, the studies relied primarily on cross-sectional designs, which limits the ability to determine the temporal direction of the observed relationships between alcohol use and memory-related neural alterations. Accordingly, although the findings are consistent with a continuum account of alcohol misuse, they cannot directly demonstrate developmental progression from binge drinking to alcohol use disorder. Longitudinal research will be necessary to determine whether the strengthening of alcohol-related memory processes represents a predisposing vulnerability, a consequence of repeated alcohol exposure, or a dynamic interaction between both. Second, although the thesis discusses binge drinking and alcohol use disorder within a common conceptual framework, it does not include a study assessing different stages of alcohol misuse with the same methodology, task, and outcome measures. As a result, comparisons between binge drinkers and individuals with alcohol use disorder necessarily rely on evidence drawn from distinct paradigms and neurocognitive measures, which limits the possibility of making direct inferences about progression across the spectrum of alcohol misuse. Future research would benefit from adopting comparable experimental designs across different drinking profiles in order to more directly examine similarities and differences in alcohol-related memory processes across stages of severity. Third, although the thesis integrates multiple methodological approaches, the samples were drawn from relatively specific populations, particularly young binge drinkers and individuals with alcohol use disorder, which may limit generalizability to other age groups, cultural contexts, or clinical profiles. Relatedly, alcohol use disorder is a heterogeneous condition, and the present studies were not designed to examine whether the observed memory-control dynamics vary as a function of severity, abstinence status, comorbidity, or craving profile. Finally, the experimental paradigms necessarily simplify real-world alcohol-related cognition. Alcohol-related memories in everyday life are often autobiographical, affectively charged, and embedded in complex social and contextual environments. Thus, future work should incorporate more naturalistic designs to better capture how memory, craving, and regulation interact outside the laboratory.

Despite these limitations, the present thesis provides converging evidence from behavioral, electrophysiological, and neuroimaging approaches supporting the view that alcohol-related memory processes play a central role in the interaction between motivational salience and cognitive control in alcohol

misuse. By examining these processes across different stages of alcohol consumption, from binge drinking to alcohol use disorder, the work contributes to a more integrated understanding of how memory, motivation, and regulation interact in the development and maintenance of alcohol-related behaviors.

7.5. Conclusions

Alcohol misuse represents a major public health concern and clarifying the cognitive and neural mechanisms underlying its development and persistence remains a central challenge for addiction research. The present thesis sought to contribute to this effort by examining how alcohol consumption, ranging from binge drinking to alcohol use disorder, affects memory processes, cognitive control, and their neural correlates. Specifically:

1. The Study 1 (Chapter 3) supports the relevance of alcohol craving as a meaningful dimension in the study of alcohol misuse, while also providing a validated instrument for its assessment in Portuguese-speaking populations. This contribution is particularly important because it provides a culturally adapted measure through which subjective craving can be examined in relation to alcohol use severity and neurocognitive markers.
2. The findings from Study 2 (Chapter 4) indicate that even at earlier and non-clinical stages of alcohol misuse, subtle neurocognitive alterations may already be detected. Binge drinking and the hangover state were associated with changes in P3 and LPC amplitudes, suggesting alterations in attentional allocation and later memory-related processing despite relatively preserved behavioral performance. The reduction of these components during hangover points to acute post-intoxication disruption, whereas increased LPC amplitudes in binge drinkers on a non-drinking day suggest longer-term compensatory or inefficient recruitment of neural resources.
3. The results from Study 3 (Chapter 5) suggest that, in a non-clinical sample of young binge drinkers, alcohol-related information is processed with enhanced motivational salience rather than as neutral contextual content. Binge drinkers showed increased activation during retrieval of alcohol-related associations in perceptual and subcortical regions linked to reward, salience, and imagery-related processing. These findings suggest that alcohol-related contextual memories may acquire enhanced motivational relevance even before clinically evident alcohol-related impairments emerge.
4. The findings of Study 4 (Chapter 6) indicate that, at more severe stages of alcohol misuse, the regulation of alcohol-related memories may not necessarily be characterized by overt behavioral

suppression deficits, but rather by altered interactions between cognitive control, memory, salience, and reward-related systems. In individuals with alcohol use disorder, memory suppression was associated with altered functional connectivity patterns, suggesting that attempts to regulate alcohol-related memories are influenced and increasingly biased by motivational salience, engaging a reorganized neural architecture involving prefrontal control regions, medial temporal memory systems, and salience/reward-related networks.

Taken together, these findings support the view that alcohol misuse may involve a progressive reorganization of the relationship between memory systems, motivational processes, and cognitive control. Across the studies, alcohol-related memory processes emerged as a potential mechanism linking environmental cues, craving, and regulatory difficulty across the spectrum of alcohol misuse. Overall, this thesis contributes to the growing literature emphasizing the role of memory in addiction. By integrating electrophysiological and neuroimaging evidence, it highlights alcohol-related memory processes as a potentially important mechanism in the persistence of alcohol-related thoughts and behaviors. A better understanding of how these memory-based processes interact with motivational and regulatory systems may help clarify vulnerability to problematic alcohol use and relapse, while also supporting the development of more targeted and mechanistically informed interventions.

7.6. References

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APPENDIXES

Appendix A. Supplementary Material Chapter 5

Table A.1. Group Comparisons between Controls and Binge Drinkers for each SCL-90 Index for both sexes.

Measure	Group	Whole Sample Mean (SD)	*p*-value	Females Mean (SD)	*p*-value	Males Mean (SD)	*p*-value
Somatization	Control	0.518 (0.463)	0.338	0.675 (0.528)	0.268	0.258 (0.162)	0.265
	BD	0.673 (0.480)		0.920 (0.434)		0.425 (0.402)	
Obsessive Compulsive	Control	1.106 (0.491)	0.183	1.168 (0.440)	0.122	1.002 (0.596)	0.577
	BD	1.327 (0.482)		1.485 (0.433)		1.170 (0.498)	
Interpersonal Sensitivity	Control	0.959 (0.564)	0.793	1.212 (0.450)	0.326	0.528 (0.499)	0.259
	BD	0.917 (0.402)		1.012 (0.437)		0.822 (0.360)	
Depression	Control	1.006 (0.640)	0.825	1.164 (0.659)	0.611	0.743 (0.562)	0.634
	BD	0.960 (0.597)		1.025 (0.540)		0.896 (0.672)	
Anxiety	Control	0.781 (0.611)	0.716	0.893 (0.701)	0.420	0.595 (0.411)	0.764
	BD	0.580 (0.577)		0.631 (0.720)		0.530 (0.422)	
Hostility	Control	0.588 (0.551)	0.318	0.841 (0.554)	0.418	0.167 (0.134)	0.162
	BD	0.480 (0.340)		0.669 (0.352)		0.291 (0.202)	
Phobic anxiety	Control	0.323 (0.304)	0.953	0.386 (0.297)	0.918	0.219 (0.312)	0.336
	BD	0.329 (0.233)		0.373 (0.230)		0.284 (0.241)	
Paranoid Ideation	Control	0.879 (0.524)	0.437	0.864 (0.452)	0.774	0.904 (0.674)	0.194
	BD	0.773 (0.369)		0.916 (0.343)		0.630 (0.353)	
Psychoticism	Control	0.498 (0.268)	0.482	0.574 (0.226)	0.332	0.373 (0.306)	0.105
	BD	0.516 (0.321)		0.448 (0.331)		0.585 (0.313)	
Global Severity Index	Control	0.618 (0.380)	0.834	0.679 (0.414)	0.368	0.517 (0.323)	0.397
	BD	0.647 (0.415)		0.853 (0.426)		0.442 (0.298)	
Positive Symptom Total	Control	38.492 (17.073)	0.825	41.204 (15.742)	0.246	33.972 (19.729)	0.173
	BD	38.293 (15.410)		33.199 (14.070)		43.387 (15.675)	
Positive Symptom Distress Index	Control	1.570 (0.393)	0.474	1.613 (0.403)	0.523	1.499 (0.402)	0.449
	BD	1.485 (0.333)		1.497 (0.389)		1.474 (0.287)	

Note: SD – Standard Deviation; BD – Binge Drinkers.

Table A.2. Correlations between alcohol use measures and significative brain activation for each cluster.

		AUDIT Score	BD events per month	Percentage of alcohol intoxication per drinking event	Quantity of alcohol consumed (gr/week)	Speed of drinking gr/h	Months with a BD pattern	Age onset of BD pattern
Group Comparisons: BDs > Control Group for the Alcohol Condition								
Cluster 1 TH & DS	Pearson's correlation	0.104	-0.225	-0.310	0.055	-0.310	-0.055	-0.075
	p-value	0.671	0.340	0.184	0.819	0.184	0.818	0.669
Cluster 2 CB & FG	Pearson's correlation	-0.205	-0.084	-0.074	0.183	-0.157	0.002	0.037
	p-value	0.400	0.726	0.757	0.441	0.509	0.993	0.835
Condition Comparisons: Alcohol > No-Alcohol for the BDs								
Cluster 3 TH & CN	Pearson's correlation	0.154	0.149	0.184	-0.110	-0.307	-0.262	-0.019
	p-value	0.530	0.531	0.437	0.644	0.188	0.265	0.937

Note: TH – Thalamus; DS – Dorsal Striatum; CB – Cerebellum; FG – Fusiform Gyrus; CN – Caudate Nucleus

Table A.3. Correlations between significative brain activation for each cluster with BIS11 score and each subscale.

		Total Score	Attention	Cognitive Instability	Motor	Perseverance	Self-Control	Cognitive Complexity
Group Comparisons: BDs > Control Group for the Alcohol Condition								
Cluster 1 TH & DS	Pearson's correlation	-0.101	-0.275	-0.017	-0.083	-0.074	0.124	0.026
	p-value	0.671	0.241	0.944	0.727	0.755	0.604	0.914
Cluster 2 CB & FG	Pearson's correlation	-0.167	-0.132	-0.017	-0.212	-0.015	0.059	-0.101
	p-value	0.482	0.578	0.944	0.370	0.951	0.806	0.672
Condition Comparisons: Alcohol > No-Alcohol the BDs								
Cluster 3 TH & CN	Pearson's correlation	-0.141	-0.250	-0.213	-0.394	0.181	0.522*	-0.179
	p-value	0.553	0.289	0.367	0.086	0.446	0.018	0.449

Note: TH – Thalamus; DS – Dorsal Striatum; CB – Cerebellum; FG – Fusiform Gyrus; CN – Caudate Nucleus; * $p < 0.05$.

Appendix B. Supplementary Material Chapter 6

Table B.1. Scales and Questionnaires used in the clinical interview.

Portuguese version of the Alcohol Use Disorder Identification Test (AUDIT) (Babor et al., 2001; Cunha, 2002)
Alcohol Use Questionnaire – items 10, 11 and 12 (Townshend & Duka, 2002)
Portuguese version of the Alcohol Craving Questionnaire – Short Form – Revised (Rodrigues et al., 2021; Singleton, 1995)
Drugs Use Disorder Identification Test – Extended (Berman et al., 2007)
Portuguese version of Barratt Impulsiveness Scale 11 (BIS11) (Patton et al., 1995)
Beck Depression Inventory–II (BDI-II) (Beck, 1996; Campos et al., 2011)
Beck Anxiety Inventory (BAI) (Beck et a., 1988; Cunha, 2001)
Edinburg Handedness Inventory (Espírito-Santo et al., 2017; Oldfield, 1971)

Table B.2. Seed regions grouped by cognitive component used in gPPI analyses

Cognitive Component	Regions
Inhibitory Control	Superior Frontal Gyrus (2 ROIs; L/R)
	Middle Frontal Gyrus (2 ROIs; L/R)
	Inferior Frontal Gyrus (4 ROIs; L/R x triangularis/opercularis)
	Anterior Cingulate Cortex
Memory	Parahippocampal Gyrus (4 ROIs; L/R x Posterior/Anterior)
	Hippocampus (2 ROIs; L/R)
	Posterior Cingulate Cortex
	Temporal Fusiform Gyrus (4 ROIs; L/R x Posterior/Anterior)
	Temporal Occipital Fusiform Gyrus (2 ROIs; L/R)
	Occipital Fusiform Gyrus (2 ROIs; L/R)
	Precuneus
Reward Processing	Amygdala (2 ROIs; L/R)
	Accumbens (2 ROIs; L/R)
	Caudate Nucleus (2 ROIS; L/R)
	Putamen (2 ROIs; L/R)
	Thalamus (2 ROIs; L/R)

Note: ROIs - regions of interest; L - Left; R - Right.

B.1. Full preprocessing pipeline using *fMRIPrep*

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 24.1.1 (Esteban et al. (2019); Esteban et al. (2018); RRID:SCR_016216), which is based on *Nipype* 1.8.6 (K. Gorgolewski et al. (2011); K. J. Gorgolewski et al. (2018); RRID:SCR_002502).

B.1.1. Anatomical data preprocessing

A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset. The T1w image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.5.3 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL (version unknown), RRID:SCR_002823, Zhang, Brady, and Smith 2001). Brain surfaces were reconstructed using recon-all (FreeSurfer 7.3.2, RRID:SCR_001847, Dale, Fischl, and Sereno 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al. 2017). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with antsRegistration (ANTs 2.5.3), using brain-extracted versions of both T1w reference and the T1w template. The following template was were selected for spatial normalization and accessed with *TemplateFlow* (24.2.0, Ciric et al. 2022): *ICBM 152 Nonlinear Asymmetrical template version 2009c* [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym].

B.1.2. Functional data preprocessing

For each of the 2 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume was generated, using a custom methodology of *fMRIPrep*, for use in head motion correction. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL , Jenkinson et al. 2002). The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve and Fischl 2009). Co-registration was configured with six degrees of freedom. Several confounding time-series were

calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, Power et al. (2014)) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. (2002)). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, Behzadi et al. 2007).

Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, a mask of pixels that likely contain a volume fraction of GM is subtracted from the aCompCor masks. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. Additional nuisance timeseries are calculated by means of principal components analysis of the signal found within a thin band (crown) of voxels around the edge of the brain, as proposed by (Patriat, Reynolds, and Birn 2017). All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using nitransforms, configured with cubic B-spline interpolation.

Many internal operations of *fMRIPrep* use *Nilearn* 0.10.4 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation.

B.1.3. Copyright Waiver

The above boilerplate text was automatically generated by fMRIPrep with the express intention that users should copy and paste this text into their manuscripts unchanged. It is released under the CC0 license.

B.1.4. References

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B.2. Full functional connectivity analysis pipeline using *CONN*

Analyses of fMRI data were performed using CONN[1] (RRID:SCR_009550) release 22.v2407[2] and SPM[3] (RRID:SCR_007037) release 25.01.02.

B.2.1. Preprocessing: Potential outlier scans were identified using ART[4] as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations[5,6], and a reference BOLD image was computed for each subject by averaging all scans excluding outliers.

B.2.2. Denoising: In addition, functional data were denoised using a confound regression pipeline incorporating established nuisance regressors[7]. This included the removal of potential confounding effects derived from white matter (5 regressors), CSF (5 regressors), session and task effects and their first order derivatives (8 regressors), and linear trends (2 regressors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries[8] between 0.008 Hz and 0.09 Hz. CompCor regressors[9,10] were estimated within each subject's eroded white matter and CSF masks by extracting the mean signal and the largest principal components orthogonal to the mean signal. Based on the number of nuisance regressors included, the effective temporal degrees of freedom of the denoised BOLD signal ranged from 212.4 to 261.2 (mean 221.8) across subjects[6].

B.2.3. Quality Control (QC): Quality Control procedures included the computation of Data Validity, Quality, and Sensitivity scores, providing quantitative assessments of global distributional biases, motion-related confounds, and group-level sensitivity to small FC effects after preprocessing and denoising. First, global biases in FC estimates were characterized by the Data Validity score, measuring the displacement of the empirical FC distribution peak from zero, its expected value in the absence of systematic biases[11]. Second, motion and outlier-related confounds were evaluated using QC-FC correlations[12] between FC values and subject motion and outlier-prevalence measures. These effects were summarized by the Data Quality score, defined as the Overlap Coefficient between the observed QC-FC correlation distribution and its permutation-derived null distribution[13,6]. Last, Sensitivity was quantified as the statistical power to detect a small target FC effect (r=0.1) in a fixed-effects analysis, using a Welch-Satterthwaite approximation for effective degrees of freedom[14], and excluding participants whose QC metrics were extreme outliers (values more than three interquartile ranges beyond the first or third quartile). Data Validity, Quality, and Sensitivity scores are expressed in percent units and interpreted using three broad categories: low (<80%), intermediate (80–95%),

and high (>95%) values. After preprocessing and denoising, the dataset yielded high Data Validity (99.5%), intermediate Data Quality (87.4%), and high Sensitivity scores (100%). Detailed QC statistics and plots are provided in the Appendix.

B.2.4. First-level analysis: Psychophysiological interaction analyses were used to study the changes in functional connectivity across no task or experimental conditions. Seed regions included 35 Harvard-Oxford atlas ROIs[15]. Separately for each pair of seed and target areas, a generalized psychophysiological interaction model (gPPI[16,17]) was defined with seed BOLD signals as physiological factors, boxcar signals characterizing each individual task condition convolved with an SPM canonical hemodynamic response function as psychological factors, and the product of the two as psychophysiological interaction terms. Functional connectivity changes across conditions were characterized by the Fisher-transformed semipartial correlation coefficient of the psychophysiological interaction terms in each model.

B.2.5. Group-level analyses were performed using a General Linear Model (GLM[18]). For each individual voxel a separate GLM was estimated, with first-level connectivity measures at this voxel as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable), and groups or other subject-level identifiers as independent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory[19,20]. Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold, and a familywise corrected p-FDR < 0.05 cluster-size threshold[21].

B.2.6. References

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