Universidade do Minho
Escola de Psicologia

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Exploring the Electrophysiological Underpinnings of Binge Drinking: Brain Functional Connectivity Insights into Alcohol Attentional Bias and Memory Suppression of Young Adults

outubro de 2023

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Natália Almeida Antunes

UMinho | 2023





Cofinanciado por:







UNIÃO EUROPEIA
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Universidade do Minho
Escola de Psicologia

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Tese de Doutoramento
Doutoramento em Psicologia
Neurociência Psicológica

Trabalho efetuado sob a orientação do
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do
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outubro de 2023

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Agradecimentos

Aos meus orientadores, Doutor Eduardo López-Caneda, Doutor Alberto Crego e Doutora Adriana Sampaio, por todas as contribuições feitas à presente dissertação e pela disponibilidade e suporte que me providenciaram ao longo destes anos. Ao Doutor Eduardo, serei eternamente grata, por ter acreditado em mim desde o primeiro momento, por me ter orientado, inspirado e desafiado a ser melhor. Obrigada por todas as oportunidades, por ter feito desta experiência uma experiência mais rica, especial e positiva, simplesmente obrigada por ter desempenhado o papel de orientador na perfeição.

Aos meus amigos e colegas de trabalho, com quem tive a sorte de partilhar este percurso na Epsi. À Dani por todas as pausas para café com longas conversas e por ser uma amiga de mão cheia. À Rita Pereira, pela serenidade que sempre me transmitiu mesmo nos momentos de maior pressão. Ao Rui, por ser o meu companheiro de trabalho desde o mestrado e por ter tornado este caminho mais animado. À Marta Sousa, por rir comigo das desgraças que iam acontecendo, por todos os desabafos e conselhos que me levantavam em dias de lamúria, mas acima de tudo por estar presente sempre que eu mais precisei. À Cat, à amiga e companheira da vida, desde o PhD às viagens pelo mundo, pelo apoio incondicional, pelas palavras certas nos momentos certos e por estar sempre presente. Um enorme obrigada por fazeres deste caminho, um caminho mais leve, mais fácil, mais inesquecível e com mais significado. Sou uma sortuda por ter partilhado este percurso com uma pessoa tão especial como tu. Ao Duarte pelo apoio nos primeiros anos desta minha viagem académica. Aos amigos que a universidade me deu, Big, Ju e Ribas pela amizade sem igual. Às amigas de sempre, Rita, Bia, Letícia e Nês por nunca me falharem nos momentos mais difíceis.

Ao Centro de Investigação de Psicologia (CIPsi) por ter acolhido a minha aprendizagem e trabalho e à Fundação para a Ciência e Tecnologia (FCT) pelo apoio financeiro que permitiu a prossecução e conclusão deste projeto (referência: SFRH/BD/146194/2019). Ao Professor Fernando Maestú e ao *Center for Cognitive and Computational Neuroscience (C3N)* por me terem acolhido tão bem em Madrid durante o meu período fora. Um especial agradecimento ao Doutor Luís Antón Toro, o meu supervisor no C3N, por toda a paciência e disponibilidade e por todos os conhecimentos transmitidos.

Aos meus pais por todo o apoio, suporte e segurança que me deram ao longo destes anos, sem eles nada disto seria possível. Obrigada pelo amor incondicional e por se manterem presentes apesar de todas as adversidades que foram surgindo. Ao meu irmão pela relação de amor-ódio que sempre nos caracterizou, por me fazer levar os problemas menos a sério e me inspirar a ser melhor. À Maf, por ser aquela que ajuda direta e indiretamente e pela calada, fazeres-me feliz. Obrigada aos quatro por nunca me terem falhado e por me terem aturado nos momentos mais difíceis e tempestuosos.

Statement of Integrity

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Explorando os Fundamentos Eletrofisiológicos do *Binge Drinking*: *Insights* da Conectividade Funcional Cerebral sobre o Viés Atencional ao Álcool e a Supressão de Memória em Jovens Adultos

Resumo

O Binge Drinking (BD) é um padrão altamente prevalente entre jovens adultos, caracterizado por episódios de consumo excessivo de álcool alternados por períodos de baixo consumo ou abstinência que tem sido associado a alterações cerebrais. Tentando compreender como o BD pode afetar o cérebro jovem adulto, a presente dissertação teve como objetivo compreender as consequências eletrofisiológicas (EEG) associadas ao BD em jovens. Primeiramente, através de uma revisão sistemática com 34 estudos demonstrámos que os *binge drinkers* (BDs) apresentam anormalidades no EEG durante tarefas cognitivas e em estado de repouso, sendo a elevada P3 elicitada durante tarefas de atenção, memória de trabalho e controlo inibitório (CI) o resultado eletrofisiológico mais sólido. Este estudo destacou que a combinação de CI alterado e reatividade aumentada ao álcool pode constituir um fator de risco para desenvolver dependência do álcool. Considerando estes resultados, o primeiro estudo teve como objetivo explorar a conectividade funcional (CF) cerebral subjacente ao viés atencional ao álcool em jovens BDs. Os BDs exibiram um padrão de hiperconectividade nas redes atencionais quando expostos a estímulos alcoólicos, o que leva a um aumento no processamento de tais estímulos. Pelo contrário, exibiram um padrão de hipoconectividade para imagens não alcoólicas, refletindo a diminuição do processamento de informação não alcoólica. Com o objetivo de explorar a interação entre a reatividade a estímulos alcoólicos e CI alterado, o segundo estudo foi pioneiro ao avaliar os padrões comportamentais e de CF subjacentes à supressão da memória, especialmente aqueles relacionados à supressão de memórias alcoólicas em BDs. Os BDs apresentaram maior dificuldade em suprimir memórias não alcoólicas, o que foi acompanhado por uma redução da CF entre as redes de CI e memória -sugerindo uma fraca capacidade de CI e um pobre processamento desses estímulos. Por outro lado, os BDs exibiram um padrão de hiperconectividade entre essas redes ao tentarem suprimir memórias relacionadas com o álcool, indicando um mecanismo neurocompensatório com o objetivo de suprimir memórias alcoólicas altamente salientes e potencialmente intrusivas. Estes resultados alinham-se com os modelos neurobiológicos da adição, indicando que o BD pode levar a uma maior saliência de estímulos alcoólicos, um processamento diminuído de recompensas não alcoólicas e um controle de cima para baixo enfraquecido, potencialmente marcando a mudança do uso recreativo para o uso compulsivo de álcool e ressaltando o risco de desenvolvimento de dependência de álcool entre jovens BD.

Keywords: *Binge Drinking;* Electroencefalografia; Viés atencional ao álcool; Supressão de memórias, Conectividade Funcional

Exploring the Electrophysiological Underpinnings of Binge Drinking: Brain Functional Connectivity Insights into Alcohol Attentional Bias and Memory Suppression of Young Adults

Abstract

Binge Drinking (BD) is a pattern highly prevalent among young adults characterized by episodes of excessive drinking alternated by periods of low consumption or abstinence that has been associated with brain alterations. Trying to understand how BD may affect the young adult brain, the present dissertation firstly aimed to comprehend the electrophysiological (EEG) consequences associated with BD in adolescents and young adults. Firstly, through a systematic review with 34 studies we showed that Binge Drinkers (BDs) display EEG abnormalities during cognitive tasks and resting state, being the augmented P3 elicited during attention, working memory, and inhibitory control (IC) tasks the most solid electrophysiological finding. Importantly, this study highlighted that the combination of altered IC and augmented alcohol reactivity may constitute a risk factor for developing alcohol dependence. Considering these findings, the first empirical study aimed to explore the brain functional connectivity (FC) underlying alcohol attentional bias in young BDs. BDs exhibited a hyperconnectivity pattern in the attentional networks when exposed to alcoholic cues, which lead to an increased processing of such stimuli. Contrarily, they displayed a hypoconnectivity pattern for non-alcoholic images, reflecting diminished processing of non-alcoholic information. Aiming to explore the interplay between the reactivity to alcohol-related stimuli and altered IC, the second study was pioneering in exploring the behavioral and FC patterns underlying memory suppression, especially those related to the suppression of alcohol-related memories in young BDs. BDs presented greater difficulty suppressing non-alcoholic memories, which was accompanied by reduced FC between IC and memory networks – suggesting weak IC ability and poor processing of these low-rewarding stimuli. Conversely, BDs displayed a hyperconnectivity pattern between these networks when tried to suppress alcohol-related memories, indicating a neurocompensatory mechanism aiming to suppress highly salient - and potentially intrusive- alcoholic memories. Concluding, the findings of the present dissertation align with neurobiological addiction models, indicating that BD may lead to heightened salience for alcoholic stimuli, diminished processing of non-alcohol rewards, and weakened top-down control, potentially marking the shift from recreational to compulsive alcohol use and underscoring the risk of developing alcohol dependence among young BDs.

Keywords: Binge Drinking; Electroencephalography; Alcohol attentional bias, Memory suppression; Functional Connectivity.

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Abbreviations

AAL	Automatic Anatomical Atlas
ACC	Anterior Cingulate Cortex
ACQ-SF-R	Alcohol Craving Questionnaire – Short Form – Revised
ACR	Alcohol Cue Reactivity task
AMY	Amygdala
APPE	Associação Portuguesa de Psicologia Experimental
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorders Identification
AUDIT-K	Alcohol Use Disorders Identification - Korean
BAC	Blood Alcohol Concentration
BD	Binge Drinking
BDs	Binge Drinkers
BEM	Boundary Elements Model
BFc	Beamformer Filter correction
BIS-11	Barratt Impulsivity Scale-11
CBPT	Cluster-Based Permutation Test
CNS	Central Nervous System
Cs	Controls
CT	Cognitive Training
DDs	Daily Drinkers
DLPFC	Dorsolateral Prefrontal Cortex
Dm	Difference due to memory
DUDIT-E	Drug Use Disorders Identification Test-Extended
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
EC	Entorhinal Cortex
EEG	Electroencephalogram/Electroencephalographic/Electroencephalography
EHI	Edinburg Handedness Inventory
eLORETA	Exact Low-Resolution Brain Electromagnetic Tomography Analysis
ERN	Error-Related Negativity
EROs	Event-Related Oscillastions

ERP	Event-Related Potential
ERPs	Event-Related Potentials
ESPAD	European School Survey Project on Alcohol and other Drugs
FC	Functional Connectivity
FDR	False Discovery Rate
Fri	Friday
fMRI	functional Magnetic Resonance Imaging (fMRI)
FRN	Feedback-Related Negativity
FSW	Frontal Slow Wave
GBPS	Galician Beverage Picture
GP	Globus Palidus
GSI	Global Severity Index
HBDs	High Binge Drinkers
IC	Inhibitory Control
ICA	Independent Component Analysis
IFC	Inferior Frontal Cortex
IFG	Inferior Frontal Gyrus
IGT	Iowa Gambling Task
JCR	Journal Citation Reports
LBDs	Light Binge Drinkers
LCMV	Linear Constrain Minimum Variance
lFOC	Left Frontal Orbital Cortex
lFusiG	Left Fusi Gyrus
lHip-lParahip	Left Hippocampus – Left Parahipocampus
lIFG	Left Inferior Frontal Gyrus
lMFG	Left Middle Frontal Gyrus
LoC	Loss of Consciousness
LPC	Late Positive Component
LPP	Late Parietal Positivity
lSFG	Left Superior Frontal Gyrus
M	Mean
MDs	Moderate Drinkers

MEG	Magnetoencephalography
MI	Memory Inhibition
Mon	Monday
MNI	Montreal Neurological Institute
mPFC	Medial Prefrontal Cortex
NA	Not applicable
NC	Nucleus Caudatus
NDs	Non-Drinkers
NHLBI	National Heart, Lung, and Blood Institute
NIAAA	National Institute on Alcohol Abuse and Alcoholism
N/LDs	Non/Light-Drinkers or Non-Low-Drinkers
PACS	Penn Alcohol Craving Scale
Pe	Error positivity
PFC	Prefrontal Cortex
PHC	Parahippocampal Cortex
PLV	Phase-Locking Value
PMC	Pre-Motor Cortex
Precu	Precuneus
Pre-SMA	Pre-Supplementary Motor Area
Prh	Perirhinal Cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUT	Putamen
RAVLT	Rey Auditory Verbal Learning Task
RCT	Randomized Controlled Trial
rFusiG	Right Fusiform Gyrus
rHip-rParahip	Right Hipocampus – Right Parahipcocampus
rIFG	Right Inferior Frontal Gyrus
rMFG	Right Middle Frontal Gyrus
ROI	Region of Interest
ROIs	Regions of Interest
rSFG	Right Inferior Frontal Gyrus
SADs	Standard Alcoholic Drinks

SAMHSA	Substance Abuse and Mental Health Services Administration
SCL-90-R	Symptom Checklist-90-Revised
SD	Standard Deviation
SMA	Supplementary Motor Area
SubTHA	Subthalamic nucleus
SUDs	Substance Use Disorders
TADD	Typical and Atypical Drinking Diary
tDCS	Transcranial Direct-Current Stimulation
THA	Thalamus
Thu	Thursday
TLFB	Alcohol Timeline Followback
TNT	Think/No-Think
TNTA	Think/No-Think Alcohol
Tue	Tuesday
UM	University of Minho
UPPS-P	Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency
VPP	Vertex Positive Potential
Wed	Wednesday
WHO	World Health Organization
WM	Working Memory

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Thesis Overview

The present dissertation aims to take a step further in the investigation of the impact of Binge Drinking (BD) in young adults. Firstly, it strives to understand the consequences of this pattern on the brain function- as measured by the electroencephalographic (EEG) activity - of adolescents and young adults binge drinkers (BDs). Following an in-depth knowledge through immersion in this field, it becomes highly pertinent to explore the brain mechanisms that have been shown to be most frequently affected by this pattern of consumption, namely attentional reactivity towards alcohol cues and inhibitory control (IC) in young BDs. Aiming to address these points, the current thesis is organized into four parts: Introduction, Method, Empirical Studies, and Discussion, which are subdivided into chapters.

Chapter 1 is the General Introduction and presents the overall theoretical concepts and the rational underlying this work, summarizing all the parts that constitute it. In the following chapter, a revision of the empirical evidence about the effects of BD on the EEG activity of adolescents and young adults is provided (Chapter 2). Finally, this first part culminates with a critical viewpoint offering a discerning and thought-provoking perspective on the potential role of memory suppression - a crucial component of IC - as a viable approach for addressing addiction and substance-related problems, such as BD (Chapter 3). The second part (Chapter 4) describes a double-blind, randomized controlled trial (RCT), where the methodology adopted in this thesis is detailed. This pre-registered protocol (ClinicalTrials.gov identifier: NCT05237414) represents the major project where the current thesis is inserted. Subsequently, the third part, comprises the empirical studies accomplished during the doctoral project, and addresses the primary goal of this protocol. Specifically, the first study (Chapter 5) sought to explore the functional connectivity (FC) signatures underlying alcohol attentional bias in college students BDs while the second study (Chapter 6) aimed to evaluate the potential behavioral and neurofunctional responses associated with memory inhibition, particularly those linked to the suppression of alcohol-related memories. To conclude, in the fourth and last part, the findings of the two empirical studies are discussed in accordance with the insights provided by the systematic review and the most recent literature (Chapter 7). In addition, limitations and future directions are considered, and an overall conclusion of the present work is presented.

In general, the work presented in this thesis represents a first step trying to deepen the knowledge about the interplay between altered IC and heightened alcohol-cue reactivity, characteristic of young BDs, throughout the study of (alcohol-related) memory suppression, an ability that has hardly received attention in this population as well as in individuals with substance use disorders. Therefore, these findings can provide relevant insights for alcohol research and clinical practice.

PART I: INTRODUCTION

CHAPTER 1: General Introduction

Substance abuse continues to be a critical global issue, with alcohol taking the lead as the most widely consumed substance in the world, transcending cultural, geographical, and socioeconomic boundaries (World Health Organization [WHO], 2018). Over the decades, alcohol became deeply connected to our social sphere, appearing as a symbol of celebration, camaraderie, and relaxation, and, consequently, being an integral part of most social gatherings and festivities (Babor et al., 2022; Rehm et al., 2009; WHO, 2018). In addition, alcohol, like many other psychoactive substances, frequently serves as a coping mechanism to deal with life adversities and personal problems, with the notable difference that alcohol sales are permissible in most countries worldwide and readily accessible at an affordable price. This normalization of alcohol use, coupled with its easy availability, creates an environment where its consumption is not only tolerated but often encouraged, fostering a society where excessive use and abuse can be easily ignored or marginalized (Babor et al., 2022; Rehm et al., 2009).

Although many users perceive alcohol as pleasurable, its excessive use is associated with a broad range of mental and behavioral disorders as well as other conditions (e.g., liver disease, cardiovascular and respiratory diseases, and cancer) and injuries (e.g., sexually transmitted infections, suicide and homicide) (Brady, 2006; Cortez-Pinto et al., 2010; Day & Rudd, 2019; George, 2019; Mehta, 2016; Telles-Correia & Mega, 2015; Trangenstein et al., 2021), being responsible for 5.1% of the global burden of disease and injury (WHO, 2022). Besides the deleterious impact on physical and mental health, alcohol abuse causes considerable social (e.g., risky sexual behaviors, poor quality of life) and economic costs to individuals, communities, and societies around the globe (George, 2019; Dormal et al., 2018; Palfai & Luehring-Jones, 2021; Rehm et al., 2009). Disturbingly, each year three million lives are lost due to alcohol abuse, accounting for 5.3% of total deaths globally (WHO, 2018). Moreover, harmful alcohol use also represents a primary contributor to premature mortality and disability, particularly affecting individuals aged between 20 and 39 years, where approximately 13.5% of all fatalities can be attributed to alcohol (WHO, 2022).

The issue of alcohol consumption among young people has been a matter of worry, with Binge Drinking (BD) - a pattern of excessive alcohol consumption highly prevalent among adolescents and young adults- raising particular concern within both the scientific community and society (Maurage et al., 2020). This pattern has become a major public health and social problem worldwide due to its detrimental effects, including important psychosocial problems, such as poor academic performance, violence, and

unprotected sexual activities, which may compromise in several ways the safety and the future of young people (Carbia et al., 2017; Crews et al., 2016; Hingson et al., 2017; Hjarnaa et al., 2023).

1.1. Binge Drinking and The Young Brain

BD, also known as heavy episodic drinking, is a pattern of alcohol consumption characterized by the intake of large amounts of alcohol -namely 5 or more standard drinks for males (4 or more for females)- over the course of 2h, which results in a blood alcohol concentration (BAC) of 0.08 g/dL or above (National Institute of Alcohol Abuse and Alcoholism [NIAAA], 2004). In addition, these episodes of excessive drinking are often followed by periods of low consumption or abstinence, resulting in an intermittent and harmful alcohol drinking pattern (Maurage et al., 2020).

This pattern is especially prevalent, in American, European, and Western Pacific countries, particularly among young adults, peaking between ages 18 and 25, with a prevalence in this population around 30% (Kraus et al., 2016; Substance Abuse and Mental Health Services Administration [SAMSHA], 2022). This alcohol consumption pattern is even more prevalent in college students, reaching around 40% of the students having recurrent BD episodes (Herrero-Montes et al., 2022; NIAAA, 2018), when alcohol use is perceived as a recreational behavior with low risk and positive expectancies, often serving as a mean of social acceptance within peer groups (Bosari et al., 2007; Patrick & Schulenberg, 2010). In addition, the age of onset of this type of consumption has decreased - from 18 to 15 - during the last decades, and adolescents are also increasingly affected (WHO, 2018), with 34% of European students aged 15-16 reporting to have engaged in BD during the previous month (European School Survey Project on Alcohol and other Drugs [ESPAD], 2020). The significantly high rates of BD in adolescents and young adults are causing substantial concern due to the critical phase of brain development occurring at this stage, which may render this organ particularly susceptible to the harmful impact of alcohol's toxic effects (Crews et al., 2007; Jacobus & Tapert, 2013).

During adolescence, brain undergoes major morphological, functional, and chemical changes (Morris et al., 2018; Zhao et al., 2021). Specifically, this period is characterized by the occurrence of two main cellular processes particularly in the frontal lobes, namely synaptic pruning (i.e., elimination of unnecessary or weak connections, or synapses between neurons) and myelination (i.e., formation of the protective sheath, called myelin, around nerve fibers or axons allowing for faster transmission of nerve impulses), which lead to an overall reduction in grey matter and an increased in white matter volumes, respectively (Gogtay et al., 2004; Jones et al., 2018; Raznahan et al., 2011; Tamnes et al., 2010; Wierenga et al., 2014). Regarding the functional level, essential changes on the brain connectivity occurs

at this stage, leading to more efficient interactions between brain regions (Grayson & Fair, 2017; Vogel et al., 2010). Altogether these changes contribute to the refinement of higher order cognitive functions including cognitive flexibility, working memory and inhibitory control (IC), which are mainly linked to the maturation of frontal areas (Boelema et al., 2014; Casey et al., 2008; Crone & Ridderinkhof, 2011; Crone & Steinbeis, 2017; Luna et al., 2015). As a result, the prefrontal cortex (PFC) – one of the main regions recruited during executive functioning - is still maturing during adolescence. However, the brain regions linked to motivational and reward processes (i.e., amygdala and striatum) are fully developed at this period (Casey & Jones, 2010; Kolk & Rakic, 2022; Van Duijvenvoorde et al., 2016). This imbalance between the upregulated reward system and the still-maturing PFC translates into reduced control over impulses and desires and increased reward sensitivity and sensation seeking, which make adolescents more prone to be involved in risky behaviors, such as getting into conflicts and fights, unsafe sexual practices, and drug or alcohol abuse, including BD (Bjork & Pardini, 2015; Casey & Jones, 2010; Galvan et al., 2006; Steinberg, 2005). In addition, the fact that the brain continues to develop into early adulthood renders this population both more prone to engage in BD and simultaneously more vulnerable to the neurotoxic effects of alcohol comparatively to adults (Pfefferbaum et al., 2018), which may compromise the healthy maturation of the brain (Jones et al., 2018; Lees et al., 2020).

In this regard, the BD effects on the still developing brain during adolescence and young adulthood have aroused heightened interest among researchers and several studies concerned with this topic were conducted during the last decades (López-Caneda, Cavadeira, et al., 2019). Evidence from these studies revealed a wide range of neuropsychological, structural, and functional anomalies associated with this pattern during this life-change period (Carbia et al., 2018; Cservenka & Brumback, 2017; Lees et al., 2019; Pérez-García, Suárez-Suárez, et al., 2022). Neuropsychological studies showed that BD impairs executive function, particularly IC processes, and verbal memory ability, which are cognitive functions supported by brain regions experiencing a protracted maturation process (e.g., PFC) (Carbia et al., 2017; Goudrian et al., 2007; Parada et al., 2011; Scaife & Duka, 2009). Albeit directionality of the findings remains unclear until now, neuroimaging studies also revealed structural alterations in the gray matter volume and/or thickness of prefrontal and subcortical limbic areas, with abnormal volumes being observed in dorsolateral PFC (DLPFC) (Doallo et al., 2014; Morris et al., 2018; Sousa et al., 2017), nucleus accumbens (Howel et al. 2013; Sousa et al., 2020) and insula (Pérez-Garcia, Cavadeira, et al., 2022). These are highly relevant regions which serve as a key pathway for the interoceptive effects in addiction and, thus, influence motivated behavior (Naqvi & Bechara, 2010). Regarding brain functioning, studies have shown abnormal cerebral activity during attentional, working memory and response

inhibition tasks as well as during resting-state conditions (Lees et al., 2019; Lannoy et al., 2019). Furthermore, BD has been linked to increase attention towards alcohol-related cues, which can influence excessive alcohol consumption, maintenance of use, and levels of craving (Fahardi & Cox, 2009; Field et al., 2008; Langbridge et al., 2019; Pennington et al., 2020; Simon et al., 2022; Townshend & Duka, 2001). Importantly, reducing this alcohol attentional bias has been related to decreased alcohol use, with sustained effects observed even three months later (Fadardi & Cox, 2009).

The long-term effects of BD are not yet fully understood due to the scarcity of longitudinal research in this area; however, some studies revealed altered brain developmental trajectories, characterized by accelerated gray matter shrinkage in frontal and temporal regions in young heavy drinkers when compared to aged-matched controls (Pfefferbaum et al., 2016; Spear et al., 2018; Sullivan et al., 2020; Squeglia et al., 2014). A similar pattern of results –including gray matter loss in subcortical regions (i.e., hippocampus, parahippocampus, nucleus accumbens)- has been observed in young adults after a continued history of heavy alcohol consumption (Heikkinen et al., 2017; Meda et al., 2017, 2018; Pérez-Garcia, Cavadeira, et al., 2022). Therefore, the engagement in BD during adolescence and the maintenance of this pattern for long periods seem to have adverse consequences in healthy brain development. Concerningly, BD during youth has been considered one of the leading risk factors for alcohol use disorder (AUD) (Addolorato et al., 2018; Olsson et al., 2016; Silins et al., 2018). In view of this, deepening the knowledge about the consequential effects of this consumption pattern, as well as finding ways to decrease or interrupt the binge alcohol consumption, become the main goals and concerns of BD research to improve health and well-being of young individuals.

1.2. Inhibitory Control

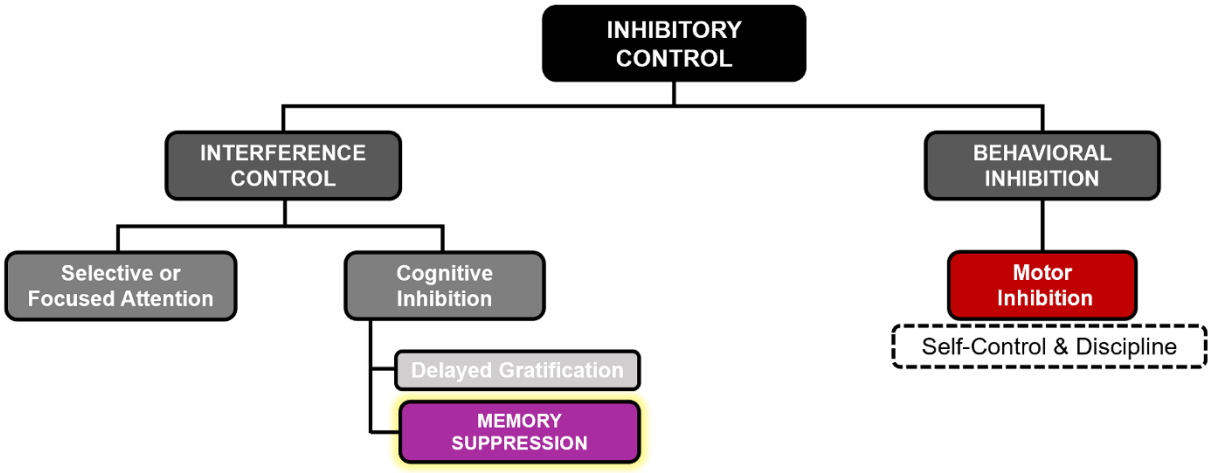
Among the various cognitive processes affected by the consumption of psychoactive substances, IC has received special attention, since it has been closely involved in the ability to regulate or control drug consumption. Accordingly, several addiction models have pointed the crucial role of this ability in substance use/abuse, including in AUD (Crews & Boettiger, 2009; Bava & Tapert, 2010; Bari & Robbins, 2013).

IC is a crucial executive function that allows individuals to suppress or restrain automatic and impulsive responses, thoughts, or actions (Diamond, 2013; Ridderinkhof et al., 2004). It is a heterogeneous and complex construct that can be divided into several subtypes or components based on different theoretical frameworks. However, it is commonly divided into two main dimensions, behavioral inhibition, and interference control (see Figure 1; Diamond et al., 2013). Behavioral inhibition or response

inhibition constitutes the ability to suppress or inhibit prepotent or automatic responses, and it encompasses motor inhibition, which is usually assessed with Go/NoGo or Stop Signal tasks (Chambers et al., 2009). On the other hand, interference control may be divided into two subtypes, cognitive inhibition, and the ability to focus on relevant information and inhibit the processing of irrelevant or distracting stimuli, commonly known as selective or focused attention (Diamond et al., 2013). Cognitive inhibition refers to the act of inhibiting or suppressing intrusive or unwanted thoughts or memories, also involving the intentionally attempting to forget them (Anderson & Levy, 2009). Additionally, cognitive inhibition also includes delayed gratification – i.e., the ability to exercise self-control by resisting the temptation of selecting smaller, immediate rewards in favor of larger rewards that are delayed in time (Tobin & Graziano, 2010). In sum, IC plays a vital role in optimizing behavior, regulating responses according to environmental demands, and aligning actions with long-term goals (Allom et al., 2016). In this regard, the integrity of this function can be intimately linked to the engagement in risky behaviors, such as drug or alcohol consumption (Lee et al., 2019; Smith et al., 2014). Therefore, research has predominantly centered on elucidating how behavioral inhibition may be impacted in individuals with alcohol or substance misuse, with the aim of comprehending the underlying mechanisms sustaining substance use.

Figure 1.

Inhibitory Control Subtypes



Note. Based on Diamond et al., 2013

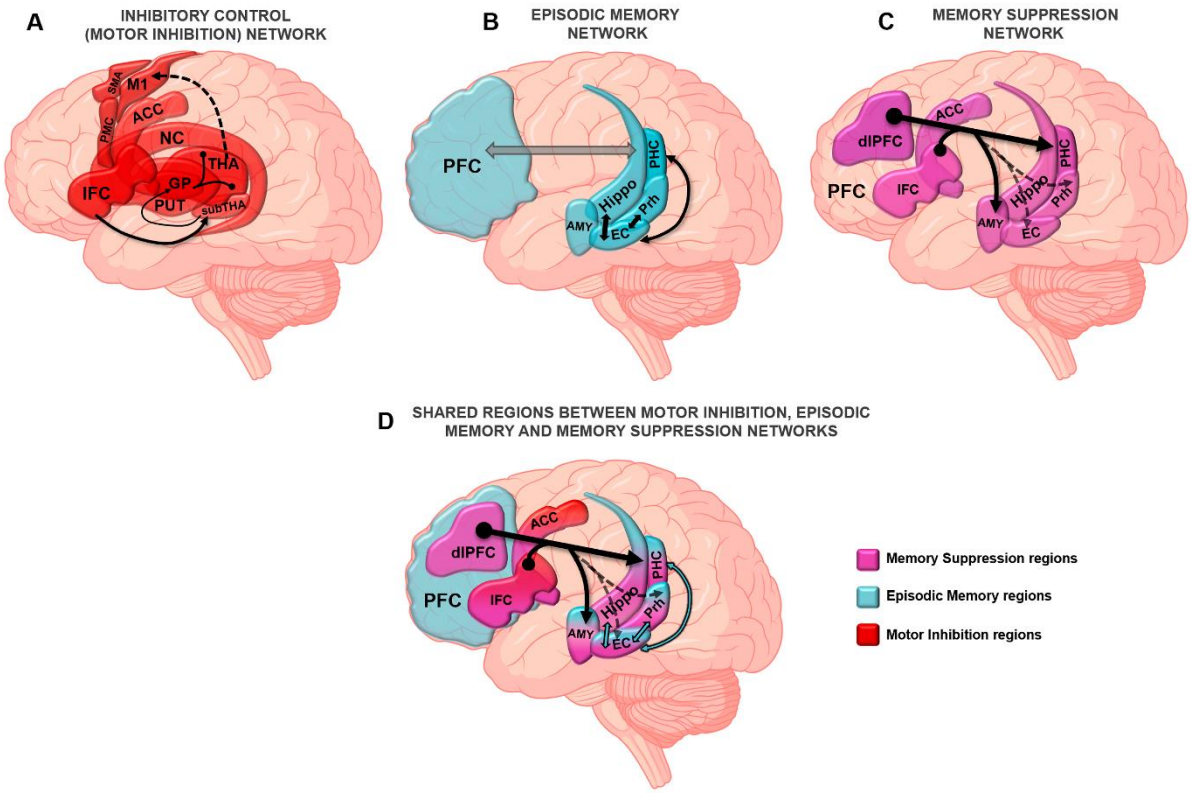
1.2.1. Brain Mechanisms Underlying IC

Evidence has revealed that behavioral inhibition involves a frontostriatal network (see Figure 2A), where the PFC - particularly the inferior frontal cortex (IFC) - plays a pivotal role for successful inhibition

(Aron et al., 2007; Aron et al., 2014; Chikazoe et al., 2009). Accordingly, the IFC is responsible for generating a signal to withhold actions, which then passes through a network of subcortical structures, such as the subthalamic nucleus and the globus pallidus, ultimately leading to the inhibition of the thalamus (Figure 2A). This, in turn, results in the suppression of motor responses in the primary motor cortex (Nambu et al., 2002; Aron & Poldrack, 2006). Structures from the dorsomedial PFC, such as the anterior cingulate cortex (ACC), supplementary motor area (SMA) and the pre-SMA, also showed to be involved in inhibitory processes (Aron, 2011; Chambers et al., 2009; Duann et al., 2009; Durston et al., 2002; Nachev et al., 2008; Obeso et al., 2013), with ACC being responsible for monitoring conflicts in information processing and signaling the need for adjustments in behavior (Botvinick et al., 2004).

Figure 2.

Schematic representation of the neural pathways involved in Motor Inhibition, Episodic Memory, and Memory Suppression.



Note. **(A)** During response inhibition, the inferior frontal cortex (IFC) transmits a "Stop" signal via the subthalamic nucleus (SubTHA). This nucleus then sends out stimulating signals to the globus pallidus (GP), leading to the suppression of extensive thalamic regions. Therefore, the thalamocortical connections associated with hand movements are inhibited, resulting in the suppression of the response (Based on López-Caneda, Rodríguez Holguín et al., 2014). **(B)** In episodic memory, the hippocampus (Hippo) serves as a central hub receiving inputs - through entorhinal cortex (EC) -from association cortices, the parahippocampal cortex (PHC), the perirhinal cortex (Prh), and the amygdala (AMY) to integrate various elements into unified

representations (Based on Nadel & Hardt, 2011). **(C)** During memory suppression, prefrontal regions, particularly DLPFC and IFC - downregulate brain areas supporting episodic recollection, particularly hippocampus, amygdala, and entorhinal, perirhinal and parahippocampal cortex (Based on Anderson & Floresco, 2022). **(D)** Overlapped regions between the three brain networks that are involved in memory suppression mechanisms. ACC: Anterior Cingulate Cortex; AMY: Amygdala; dlPFC: dorsolateral Prefrontal Cortex; EC: Entorhinal Cortex; GP: Globus Pallidus; Hippo: Hippocampus; IFC: Inferior Frontal Cortex; NC: Nucleus Caudatus; PFC: Prefrontal Cortex; PHC: Parahippocampal Cortex; PMC: Pre-Motor Cortex; Prh: Perirhinal Cortex; PUT: Putamen; SMA: Supplementary Motor Area; SubTHA: Subthalamic nucleus; THA: Thalamus.

1.2.2. The Impact of BD on IC

As mentioned before, IC and the underlying brain structures are still developing during adolescence and early adulthood, a period commonly associated with alcohol consumption initiation. Therefore, given the importance of IC in regulating alcohol consumption and the relative immaturity of this cognitive function during adolescence and youth, several studies have been concerned with the effects of alcohol on this capacity in order to better understand the causes and consequences of alcohol consumption during this developmental stage. Research revealed that impaired IC may be both the cause and consequence of excessive alcohol use (López-Caneda, Rodríguez Holguín, et al., 2014). Accordingly, the adolescents and youth's poor or underdeveloped IC ability may lead to difficulties regulating alcohol use, resulting in excessive drinking (Antón-Toro et al., 2021). In turn, this increased alcohol intake may compromise the healthy development of IC, which further weakens the ability to prevent alcohol consumption, creating a vicious cycle (López-Caneda, Rodríguez Holguín, et al., 2014; Wiers et al., 2007).

For this reason, several studies have also been concerned with the effects of BD on IC processes. Neuropsychological studies showed poor behavioral performance in young binge drinkers (BDs) during response inhibition. Specifically, BDs seem to commit more errors and react slowly during attempts to inhibit their responses (Carbia et al., 2018). Similarly, neuroimaging evidence revealed altered brain activity -mainly in prefrontal regions- in BDs during tasks involving response inhibition (for reviews see Lannoy et al., 2019; Pérez-García, Suárez-Suárez, et al., 2022). Globally, these findings suggest that BD have a negative impact on IC processes. Nevertheless, studies in BD as well as in substance use disorders (SUDs) have been almost exclusively focused on the motor domain of IC, paying scarce attention to the cognitive dimension of this ability, especially the ability to inhibit or suppress memories and thoughts, which will be further reviewed.

1.3. Memory: Episodic Memory System

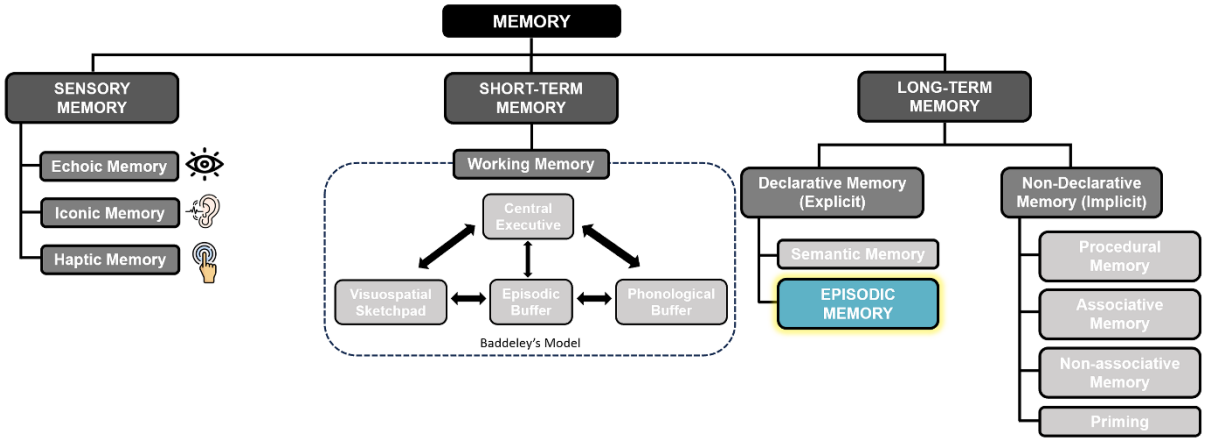
Memory is a remarkably intricate human capacity that has been a subject of attention from early on the literature. The experimental study of human memory has advanced beyond the initial idea of a

unified cognitive process, resulting in the identification of specific memory subsystems (Figure 3), often through the examination of neuropsychological patients (Squire et al., 2004). The three primary categories of memory encompass sensory, short-term, and long-term memory (Camina & Güel, 2017). Memory processing starts with sensory memory, which stores information from the surrounding environment through our senses for potential future access. Short-term memory handles information for brief periods, being facilitated by working memory. Long-term memory enables the storage of information over extended durations, which may be retrieved either consciously (explicit or declarative memory) or unconsciously (implicit or non-declarative memory) (Squire, 1992; Baddeley et al., 2020). The implicit/non-declarative memory covers memories that are not intentionally recalled, including various skills and abilities, and it can be categorized into four distinct types: procedural (habits and skills), associative (classical and operant conditioning), non-associative (habituation and sensitization), and priming (Baddeley et al., 2020; Camina & Güel, 2017). The explicit or declarative memory refers to information that is accessible through conscious effort. This type of memory is further divided into episodic memory and semantic memory, a division that was first proposed by Tulving (1972). Semantic memory comprises the broad understanding of the world, extending beyond word meanings to sensory details like colors or tastes, also including societal rules and knowledge (Squire et al., 2004; Baddeley et al., 2020). In contrast, episodic memory enables us to learn, retain, and recall specific personal experiences and events from our daily lives, encompassing details about when and where the event took place, as well as intricate information about the event itself (“what”) (Dickerson & Eichenbaum, 2010).

According to Tulving, the episodic memory system allows mental traveling by reexperiencing past events, which requires a subjective sense of self and time as well as autonoetic awareness (i.e., conscious recognition that the experience occurred in the past) (Tulving, 2002). The "events-in-context" approach highlights the fact that in episodic memory, events are linked to their spatial, temporal, and situational contexts. Accordingly, it meets three crucial behavioral criteria: (i) remembering the event/stimuli details and its context; (ii) integrating this information into a single representation; and (iii) applying the memory for adaptive behavior in new situations (Allen & Fortin, 2013). Apart from episodic memory serves the crucial function of providing memory-based predictions to guide adaptive behavior in the present and immediate future, it offers specific information about past experiences, allowing for informed decision-making. In addition, this memory system supports the ability to make novel inferences and plays a vital role in imagining plausible future scenarios (Allen & Fortin, 2013).

Figure 3.

Memory Classification



Note. The main divisions of memory include sensory, short-term, and long-term memory. Sensory memory briefly retains vast amounts of information from the environment through senses, including iconic (sight), echoic (auditory), and haptic (touch) memory, enabling potential future access. Short-term memory involves the temporary retention of a limited amount of information for brief periods. Working memory carries out this processing. The multi-storehouse model of working memory, proposed by Baddeley (2000), encompasses four subsystems - the central executive (responsible for attention control), phonological buffer (stores and consolidates recently acquired vocabulary), visuospatial sketchpad (constructs and retains visual-spatial representations), and episodic buffer (retains and combines information from various sources) - facilitating temporary storage and manipulation of information for complex cognitive tasks. Long-term memory encompasses the indefinite storage of information, categorized into declarative (explicit) memory, which involves the consciously recollection of events (episodic memory) and facts (semantic memory), and non-declarative (implicit) memory, which involves unconscious memories, including procedural (habits and skils), associative (classical and operant conditioning) and non-associative (habituation and sensitization) memories, and priming (Based on Camina & Güel, 2017).

1.3.2. Brain Mechanisms Underlying Episodic Memory

Animal and human neuroimaging research reveal that episodic memory system relies on a complex interplay of diverse brain regions (see Figure 2B) for effective encoding, consolidation, and retrieval (Dickerson & Eichenbaum, 2010). The hippocampus proves to assume the most prominent role in episodic memory network (Moscovitch et al., 2016). This structure acts as a central hub receiving multimodal inputs from widespread sensory regions in the neocortex to form associations among stimuli or between stimuli and their context by organizing distinct elements (e.g., time, place, and associated emotions) into a unified episodic representation (Baddeley et al., 2020; Moscovitch et al., 2016; Squire et al., 2015). The entorhinal cortex is responsible for facilitate the communication between the hippocampus and other brain areas, including the association cortices, the parahippocampal cortex, which receives spatial information (“where” pathway), the perirhinal cortex, which is focused on creating

detailed representations of objects ("what" pathway), and the amygdala, known to provide information about emotional elements (Allen & Fortin, 2013; Camina & Güel, 2017; Baddeley et al., 2020; Lipton & Eichenbaum, 2008). When episodic memories involve visual objects, the ventral temporal cortex, particularly the fusiform gyrus, is frequently activated, while the lateral temporal cortex, encompassing the superior temporal gyrus, is typically involved in processing auditory information during encoding (Dickerson & Eichenbaum, 2010). Regions such as the posterior cingulate, lateral temporal and parietal cortices also showed to be involved in episodic memory (Allen & Fortin, 2013; Dickerson & Eichenbaum, 2010)

Episodic retrieval occurs when an internal or external cue associated with the memory is presented, which activates the cortical regions responsible for the content of this memory representation (Baddeley et al., 2020). This cue input is relayed to the hippocampus, which then retrieves the entire memory trace. Subsequently, the hippocampus transmits backward signals to the parahippocampal region and other cortical associations areas (Allen & Fortin, 2013). This intricate feedback loop effectively reinstates the episodic memory in the neocortex, resulting in a vivid recollection of the past event/stimuli (Baddeley et al., 2020). The PFC is believed to play a crucial role in the process of using retrieved information to influence behavior. Specifically, this region seems to evaluate the retrieved information and formulate the suitable action plan, which is subsequently transmitted to the motor regions (Allen & Fortin, 2013).

In this vein, evidence showed the involvement of the prefrontal regions on episodic memory encoding and retrieval (Brand & Markowitsch, 2008; Dickerson & Eichenbaum, 2010). The DLPFC has been primarily associated with monitoring encoding and retrieval, while the ventrolateral region is implicated in strategic retrieval, information selection, and verification of the content (Brand & Markowitsch, 2008). Additionally, it integrates emotional and factual components to facilitate autobiographical memory retrieval (Brand & Markowitsch, 2008). On the other hand, the ventromedial prefrontal region plays a critical role in processing the emotional content of episodic memories, and the dorsomedial PFC show to be crucial for self-referential processing, which is integral to episodic memory and self-recollection (Brand & Markowitsch, 2008).

Overall, episodic memory neural system relies on higher association regions for sensory information processing (neocortex), intermediary regions for communication with the hippocampus (parahippocampal, entorhinal and perirhinal regions), the hippocampus for integrating and recalling episode-related information, and executive regions for generating the suitable behavioral response (PFC).

1.3.3. The Impact of BD on Episodic Memory

BD during adolescence and young adulthood has also been associated with episodic memory deficits. Studies have demonstrated that BD individuals exhibit difficulties in tasks assessing immediate and delayed recall, as well as retention in distinct episodic memory tests (Carbia et al., 2017; Parada et al., 2011; Winward et al., 2014). Furthermore, BD individuals have shown increased proactive interference (Parada et al., 2011) and higher rates of perseveration errors (Sanhueza et al., 2011) in verbal episodic memory tasks. Recently, a study also revealed compromised storage and retrieval processes associated with verbal episodic memory in young BDs (Gierski et al., 2020). Episodic memory deficits appear to persist over time, as evidenced by findings from follow-up studies (Carbia et al., 2017; Mota et al., 2013). Electrophysiological research has delved into the neural underpinnings of episodic memory in young BDs and revealed altered brain functioning during verbal episodic memory tasks in this population (Rodríguez Holguín et al., 2023; Smith et al., 2017). Additionally, BD behavior has been linked to impairments in prospective memory, a type of memory intimately linked to episodic memory since it involves the ability to use episodic memory to encode and retain intentions for future actions (Heffernan et al., 2010; Winward et al. 2014)

Altogether, these findings highlight the significant impact of BD on various facets of episodic memory, shedding light on both behavioral and neurophysiological correlates of this phenomenon. Surprisingly, despite evidence of compromised episodic memory and IC in individuals with BD, to the best of our knowledge, there has been no study to date exploring the memory suppression capacity in young BDs.

1.4. Memory Suppression

Memory suppression –also known as suppression-induced forgetting (SIF)- is distinguished by an intentional attempt to prevent a memory from entering conscious awareness, which involves a purposeful disruption of the retrieval process, resulting in a subsequent decrease in the accessibility of that memory (Anderson & Green, 2001). Thus, it is commonly described as the ability to voluntarily suppress unwanted or contextually relevant thoughts or memories (Anderson & Hulbert, 2021). This form of active forgetting has been commonly assessed through the Think/No-Think (TNT) task, an adaptation of the well-known paradigm designed to evaluate motor inhibition, the Go/No-Go task (Anderson & Green 2001; Anderson et al., 2004). In general, in the TNT task, participants are asked to remember and retain (Think) or prevent from entering awareness (No-Think) a paired item from cue-target pairs previously learned (Anderson & Hanslmayr, 2014; Levy & Anderson et al., 2012). Evidence has shown that suppressing retrieval

frequently decreases memory for No-Think items below that exhibited for Think and, most importantly, for Baseline items (i.e., items that were learned but that do not go through the Think/No-Think phase), yielding SIF (Anderson & Hulbert, 2021). This phenomenon has been observed in tasks using different types of content, such as words, images, complex scenes, abstract stimuli, motor actions, emotional and autobiographical memories, hypothetical scenarios, and fears about the future, revealing that memory suppression has a detrimental effect on the recollection of episodic memories (Anderson & Hulbert, 2021; Marsh & Anderson, 2022). Therefore, research seems to indicate that memory suppression processes may commonly impact the episodic memory system (Marsh & Anderson, 2022).

1.4.1. Brain Mechanisms Underlying Memory Suppression

Research demonstrated that memory suppression is a cognitively demanding mechanism that heavily depends on IC processes (Anderson & Green, 2001; Benoit et al., 2015; Catarino et al., 2015) – either in its quick deployment or in the ability to sustain it (Lin et al., 2021)- as well as on attention demands (Anderson & Hulbert, 2021). In this vein, studies exploring the neural mechanisms underlying memory suppression revealed that forgetting recruits brain regions similar to those implicated in motor inhibition (Figure 2D), involving predominantly right-lateralized areas (Anderson et al. 2004, 2016; Depue et al., 2007; Schmitz et al. 2017). Specifically, this ability has been associated with increased activation of prefrontal regions engaged in executive control, particularly the DLPFC and the inferior frontal gyrus, and deactivations of brain areas supporting episodic recollection, including the hippocampus and medial temporal cortex (Figure 2C) (Anderson et al., 2004; Benoit & Anderson, 2012; Depue et al., 2007; Gagnepain et al., 2014; Levy & Anderson, 2012; Paz-Alonso et al., 2013). In addition, stronger activation of DLPFC showed to be predictor of greater later forgetting (Anderson et al., 2004; Depue et al., 2007) and related to decreased activation of the hippocampus (Depue et al., 2007). In line with this evidence, subsequent studies of effective connectivity revealed a causal influence of the right DLPFC over the hippocampus during memory suppression (Apšvalka et al., 2022; Benoit & Anderson, 2012; Benoit et al., 2015; Benoit et al., 2016; Gagnepain et al., 2017; Mary et al., 2020; Schmitz et al., 2017), with this negative coupling being more pronounced when unwanted memories intruded into awareness and needed to be purged (Gagnepain et al., 2017; Mary et al., 2020). Interestingly, evidence showed that this top-down IC signal from the DLPFC not only targets the hippocampus but also other brain regions according to the content of the avoided memories, including the amygdala (emotional content) (see Figure 2C) (Gagnepain et al., 2017; Sacchet et al., 2017) and the fusiform cortex (visual objects) (Gagnepain et al., 2014; Mary et al., 2020). Recently, Crespo-García and colleagues (2022) shed light on the

mechanisms by which the DLPFC suppresses the hippocampus activity, suggesting that the ACC detects the emergence of unwanted content and triggers top-down IC processes for DLPFC, facilitating the communication between the DLPFC and hippocampus (Crespo-García et al., 2022).

1.4.2. Memory Suppression and Alcohol Misuse

As explained above, the main regions involved in memory suppression are also regions particularly vulnerable to the neurotoxic effects of alcohol (Jacobus & Tapert, 2010; Spear et al., 2018). Accordingly, studies in individuals with AUD reported increased DLPFC activation during alcohol-related cues exposure, which correlated with craving for alcohol and was associated with higher susceptibility to cue-induced relapse in AUDs, highlighting the crucial role of DLPFC in motivational reactions to alcohol-related cues (George et al., 2001; Goldstein & Volkow, 2011; Heinz et al., 2007; Myrick et al., 2004; Olbrich et al., 2006; Grüsser et al., 2004). In the same vein, neuroimaging studies in BD revealed structural and functional alterations in the DLPFC (Ames et al., 2014, Worbe et al., 2014; Sousa et al., 2017, 2019; Doallo et al., 2014) and the ACC (Ames et al., 2014, 2014; Arienzo et al., 2020; Doallo et al., 2014; Mashhoon et al., 2014; Brumback et al., 2015), showing that these structures are also especially sensitive to the impact of BD behaviors.

Although evidence reported that excessive alcohol use can have detrimental effects on brain regions associated with memory suppression, there is a lack of research exploring this capacity in individuals with alcohol-related problems, such as BD. To date, only two behavioral studies were conducted in detoxified alcohol dependent individuals (Nemeth et al., 2014) and healthy hazardous drinkers (Simeonov et al. 2022). Nemeth and colleagues (2014) revealed impaired memory suppression capability, which might entail difficulties to maintain long-term abstinence as detoxified AUD may be less able to inhibit intrusive alcohol-related memories. The study of Simeonov et al. (2022) -which used the task designed by López-Caneda, Crego et al., (2019) (see below)- showed that the use of reward-relevant alcohol cues diminishes memory suppression in hazardous drinkers, suggesting that the presence of alcohol-related information may compromise memory suppression mechanisms in individuals with alcohol misuse. Collectively, these findings indicate disrupted memory suppression abilities, including in the presence of alcohol-related cues, among individuals with alcohol-related problems. Importantly, evidence has shown that the retrieval of drug-related memories or thoughts leads to increased craving and, consequently, maintenance of the consumption (Kavanagh et al., 2005; May et al., 2015). Bearing this in mind, the incapacity to properly suppress alcohol-related memories could contribute to alcohol-seeking and taking behaviors, leading to the perpetuation of the drinking pattern. Therefore, exploring the memory inhibition processes, particularly

the suppression of alcohol-related memories in BDs may be a promising approach to understand how this pattern or another chronical/clinical one (i.e., AUD) may be interrupted or controlled, which could hold significant clinical and practical implications.

Once the two studies conducted in individuals affected by alcohol-related issues only explored memory suppression at the behavioral level, future studies should use techniques to measure brain functioning, such as EEG or fMRI recordings. These more comprehensive investigations could contribute to a more profound understanding of how alcohol may affect the mechanisms underlying this ability. Recently, López-Caneda and colleagues (2019) developed an adaptation of the TNT task –the Think/No-Think Alcohol (TNTA) task– using neutral objects paired with an alcohol-related or a non-alcohol-related image. This paradigm showed to be effective in examining the behavioral and EEG mechanisms underlying memory suppression in alcohol-related contexts (López-Caneda, Crego, et al., 2019) proving to be a useful instrument to measure the ability to suppress (alcohol-related) memories in a population with alcohol-related problems, such as BDs, allowing the study of potential behavioral and neural abnormalities associated with this consumption pattern.

1.5. Electroencephalography (EEG) and BD

Electrophysiological techniques have traditionally been the primary approach for measuring brain activity and continue to be the most widely available and extensively researched methods in the fields of basic and clinical neuroscience. The EEG –i.e., the recording of electrical activity in the human brain (Berger, 1929)- has resulted in significant scientific advancements and diverse clinical applications (Borck, 2005; Gloor, 1994). This non-invasive technique involves placing electrodes on the scalp to detect and amplify the small electrical signals produced by the neurons of the brain. These signals, known as brainwaves or neural oscillations, reflect the underlying neural activity and provide valuable insights into brain function and activity patterns. EEG, contrarily to other low-temporal resolution neuroimaging techniques (i.e., fMRI), offers the advantage of directly capturing neural activity with high precision in the order of milliseconds. This high-temporal resolution makes EEG an ideal method for studying the intricate neural processes involved in various cognitive stages between a stimulus and a response (Campanella, 2013; Luck, 2014).

EEG data can be analyzed in time-domain, using event-related potentials (ERPs), the frequency domain through spectral power, or in time-frequency domain using event-related oscillations (EROs). In addition, the brain electrical activity can also be analyzed using functional connectivity (FC) measures (e.g., coherence and phase-locking) at the estimated neural source level (Cohen, 2014). FC is defined as

the temporal dependency of neuronal activation patterns of anatomically separated brain regions and plays a significant role in advancing the understanding of the relationships between different brain regions (Friston, 1994). It also offers important information about the efficiency and integrity of brain resting-state networks as well as networks underlying specific cognitive functions of several psychiatric and neurological conditions, including addiction (Ahmadlou & Adeli, 2011; Bullmore & Sporns, 2009; Rubinov & Sporns, 2010 Tomasi et al., 2016).

In general, EEG provides direct and precise access to regional and global neural activity and can measure oscillatory communication within and between networks (Sadaghiani et al., 2022). In addition to self-report, behavioral performance, and clinical variables, EEG metrics can detect subtle risks or deficits (Houston & Schlienz, 2018; Jurado-Barba et al., 2020; Zhang et al., 2021). Besides it is a safe and relatively inexpensive technique that provides valuable information about brain function, EEG-derived metrics have demonstrated good test-retest reliability (Tenke et al., 2017; Ip et al., 2018; Roach et al., 2019; Vázquez-Marrufo et al., 2020; Cofresí et al., 2022).

Accordingly, EEG has been widely used for investigating the neural alterations caused by alcohol consumption and the measures provided by this neurophysiological technique have demonstrated high sensitivity to both the acute and chronic effects of alcohol consumption (Brion et al., 2016; Ingels et al., 2022; Rangaswamy et al., 2007). As a result, EEG has become an important tool for identifying subtle abnormalities that may not be evident at the behavioral level and for identifying potential neural indicators of risk for alcohol abuse (Kamarajan, 2019), particularly in cases of non-pathological populations, such as BDs (Lannoy et al., 2019). Consequently, this highlights the value of EEG in uncovering hidden aspects of alcohol-related brain activity and its potential in identifying individuals at risk for alcohol abuse. Furthermore, its reliability, accessibility, and ability to capture precise neural activity make it a valuable tool for advancing the understanding of BD pattern, which may foster the development of targeted interventions, prevention strategies, and effective treatments for alcohol-use problems.

In recent decades, there has been a growing interest in investigating the influence of the BD pattern on brain EEG activity, and some attempts have been made to provide an overview of the EEG profile associated with BD (Lannoy et al., 2019; Lees et al., 2019). Nevertheless, a comprehensive systematic review of the existing research on this field has not been conducted so far, despite the important insights that could provide for BD research. On the other hand, EEG studies exploring FC patterns associated with BD have been notably absent in the literature, regardless of the effectiveness of FC measures -as explored by fMRI studies- to detect alterations in brain networks of individuals with alcohol abuse (Courtney et al., 2013; Camchong et al.,2013; Müller-Oehring et al., 2015; Sion et al., 2020; Sullivan et al., 2013; Wang

et al., 2018) and those with BD (Arienzo et al., 2020; Correas et al., 2016; Kim et al., 2020; Sousa et al., 2019). Consequently, upcoming research should also focus on understanding the impact of BD on electrophysiological FC, particularly paying attention to the processes most affected by this pattern, such as alcohol attentional bias and IC. This avenue of investigation may provide relevant information about how this pattern may affect the communication of multiple brain regions throughout different cognitive processing stages. More importantly, this method holds great potential as a crucial approach for investigating, for the first time, the memory suppression mechanisms of BDs, offering a promising way to explore the interplay between heightened alcohol-cue reactivity and altered IC.

1.6. The Present Work

After considering the theoretical overview provided in the present chapter, the relevance of studying how BD affects the young adult brain becomes evident. Therefore, the present dissertation is positioned to make a significant and valuable contribution in this realm by filling some existing gaps in the literature and generating knowledge that can be an add-value for alcohol abuse research and clinical practice.

Firstly, given the growing literature examining the EEG impairments linked to BD and aiming to acquire a profound comprehension of the neurofunctional consequences of this alcohol consumption pattern in youth, a systematic review of the empirical evidence available between 2000 and 2020 regarding the effects of BD on the EEG activity of adolescents and young adults was conducted (Chapter 2: *Electroencephalographic signatures of the binge drinking pattern during adolescence and young adulthood: A PRISMA-driven systematic review*). This work provides, for the first time, a qualitative synthesis of the EEG studies exploring the effects of BD in the brain electrical activity elicited during different cognitive tasks as well as in resting state. Additionally, the relationship between EEG activity and alcohol consumption variables, the impact of BD on behavioral performance and sex-related effects are also addressed. Finally, the general strengths and limitations of the studies conducted so far are discussed in this systematic review, and areas of interest for future research on BD are recommended. One of the issues highlighted by this work is the need to strengthen the research on the interplay between altered IC and augmented alcohol reactivity, which -similarly to individuals with alcohol dependence- have shown to be characteristics of young BDs.

Research in BD and addictive behaviors in general has consistently been focused on the motor aspect of IC to understand the repeatedly substance intake, neglecting the cognitive dimension of this ability, which involves the suppression or inhibition of thoughts and/or memories. Accordingly, the study of memory suppression mechanisms can be a potential way to explore the combination of impaired IC

and heightened alcohol attentional bias, which may contribute to the maintenance of binge alcohol intake or even to the escalation towards alcohol dependence. In this regard, the last chapter of the Introduction, provides an insightful perspective about the potential role of memory suppression as a viable approach in the study of addictive behaviors (Chapter 3: *Tackling Addictive Behaviors Through Memory Suppression: A Narrative Review*). Despite the rising interest in the examination of memory suppression mechanisms, namely in psychiatric conditions such as post-traumatic stress disorder and anxiety, the study of this ability in addictive behaviors, BD or other substance-use problems has received scarce attention until now.

As the investigation in this field could have relevant insights for a deep knowledge of BD as well as bring significant contributions to addiction research and clinical practice, the second part of the current thesis (Part II: Method) presents a double-blind, randomized controlled trial (RCT) study that aims to fill this existing gap on the literature (Chapter 4: *Forgetting Alcohol: A Double-Blind, Randomized Controlled Trial Investigating Memory Inhibition Training in Young Binge Drinkers*). Specifically, the primary goal of this pre-registered protocol (ClinicalTrials.gov identifier: NCT05237414) is to examine the behavioral and EEG correlates of memory suppression, particularly those related to alcohol-related memories suppression, among college students with a BD pattern. Secondly, this work aims to evaluate an alcohol-specific memory suppression intervention protocol using cognitive training and transcranial direct-current stimulation (tDCS) while its effects on behavioral and EEG outcomes are assessed. In addition, the post-training effects on alcohol use and craving levels are also monitored through 10-days and 3-months follow-up assessments. Ultimately, this protocol also aims to assess the behavioral and EEG mechanisms associated with attentional bias towards alcoholic stimuli, before, and after the memory suppression training sessions. This protocol constitutes the major project where the current thesis is inserted, consequently, the methodology adopted here is entirely detailed in this work. As the present dissertation is embedded within the first part of this project, the post-training effects are not addressed in it.

The third part (Part III: Empirical Studies) comprises the two empirical studies accomplished during this doctoral thesis, which are focused on the pre-training evaluation outcomes of the protocol previously mentioned. In particular, the first empirical study aimed to shed light on the brain network interactions underlying alcohol attentional bias in young BDs, exploring the FC signatures linked to the processing of alcohol-related images in college students BDs (Chapter 5: *"It's a beer!": Brain functional hyperconnectivity during processing of alcohol-related images in young binge drinkers*). For this purpose, EEG activity was recorded in 54 college students (27 non/low-drinkers [N/LDs] and 27 BDs) while performing a visual alcohol cue-reactivity (ACR) task and the whole-brain FC was calculated during the

processing of alcoholic and non-alcoholic cues. Furthermore, the potential relationship between the FC profiles and alcohol craving levels were explored in this study. The second experimental study aimed to evaluate for the first time the potential behavioral and neurofunctional anomalies associated with memory inhibition, specifically those related to alcohol-related memories suppression, in college students BDs (Chapter 6: *Trying to Forget Alcohol: Brain mechanisms underlying memory 2 suppression in young binge drinkers*). Thus, EEG activity was recorded in 82 college students (40 N/LDS and 42 BDs) while they performed the TNTA task. Then, the FC levels between IC and memory networks, commonly involved in memory suppression, were assessed using a dynamic seed-based analysis.

The chapters summarized above are presented in article format according to the guidelines of the scientific journals where they were submitted/published. Therefore, each work will include its own theoretical introduction and discussion. At the beginning of each chapter, information regarding the journals where the articles were published or submitted (i.e., JCR and Scopus impact factors and their quartile) as well as the scientific events where the work was presented is provided.

Finally, in the last part (Part IV: Discussion), the present dissertation will end with a general discussion and integration of the main findings and conclusions of the studies (Chapter 7: *General Discussion*). In addition, in this chapter the main limitations of the works conducted within the scope of this thesis are mentioned and suggestions for future studies and potential practical implications are also addressed. At the end, an overall conclusion highlighting the contribution of the present work to the field of BD research is presented.

1.6. References

Addolorato, G., Vassallo, G. A., Antonelli, G., Antonelli, M., Tarli, C., Mirijello, A., Agyei-Nkansah, A., Mentella, M. C., Ferrarese, D., Mora, V., Barbàra, M., Maida, M., Cammà, C., Gasbarrini, A., Bruno, G., D'Angelo, G., Del Zompo, F., Di Rienzo, T., … Feliciani, D. (2018). Binge Drinking among adolescents is related to the development of Alcohol Use Disorders: results from a Cross-Sectional Study. *Scientific Reports, 8*(1). https://doi.org/10.1038/s41598-018-29311-y

Ahmadlou, M., & Adeli, H. (2011). Functional community analysis of brain: A new approach for EEG-based investigation of the brain pathology. *NeuroImage, 58*(2), 401–408. https://doi.org/10.1016/j.neuroimage.2011.04.070

Allen, T. A., & Fortin, N. J. (2013). The evolution of episodic memory. *Proceedings of the National Academy of Sciences, 110*(2), 10379–10386. https://doi.org/10.1073/pnas.1301199110

Allom, V., Mullan, B., & Hagger, M. (2016). Does inhibitory control training improve health behaviour? A meta-analysis. *Health Psychology Review, 10*(2), 168–186. https://doi.org/10.1080/17437199.2015.1051078

Ames, S. L., Wong, S. W., Bechara, A., Cappelli, C., Dust, M., Grenard, J. L., & Stacy, A. W. (2014). Neural correlates of a Go/NoGo task with alcohol stimuli in light and heavy young drinkers. *Behavioural Brain Research, 274*, 382–389. https://doi.org/10.1016/j.bbr.2014.08.039

Anderson, M. C., Bunce, J. G., & Barbas, H. (2016). Prefrontal–hippocampal pathways underlying inhibitory control over memory. *Neurobiology of Learning and Memory, 134*, 145–161. https://doi.org/10.1016/j.nlm.2015.11.008

Anderson, M. C., & Floresco, S. B. (2022). Prefrontal-hippocampal interactions supporting the extinction of emotional memories: the retrieval stopping model. *Neuropsychopharmacology, 47*(1), 180–195. https://doi.org/10.1038/s41386-021-01131-1

Anderson, M. C., & Green, C. (2001). Suppressing unwanted memories by executive control. *Nature, 410*(6826), 366-369. https://doi.org/10.1038/35066572

Anderson, M. C., & Hanslmayr, S. (2014). Neural mechanisms of motivated forgetting. *Trends in Cognitive Sciences, 18*(6), 279-292. https://doi.org/10.1016/j.tics.2014.03.002

Anderson, M. C., & Hulbert, J. C. (2021). Active Forgetting: Adaptation of Memory by Prefrontal Control. *Annual Review of Psychology, 72*, 1-36. https://doi.org/10.1146/annurev-psych-072720-094140

Anderson, M. C., & Levy, B. J. (2009). Suppressing unwanted memories. *Current Directions in Psychological Science, 18*(4), 189-194. https://doi.org/10.1111/j.1467- 8721.2009.01634.x

Anderson, M. C., Ochsner, K. N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S. W., Glover, G. H., & Gabrieli, J. D. (2004). Neural systems underlying the suppression of unwanted memories. Science (New York, N.Y.), 303(5655), 232-235. https://doi.org/10.1126/science.1089504

Antón-Toro, L. F., Bruña, R., Suárez-Méndez, I., Correas, Á., García-Moreno, L. M., & Maestú, F. (2021). Abnormal organization of inhibitory control functional networks in future binge drinkers. *Drug and Alcohol Dependence, 218*, 108401. https://doi.org/10.1016/j.drugalcdep.2020.108401

Apšvalka, D., Ferreira, C. S., Schmitz, T. W., Rowe, J. B., & Anderson, M. C. (2022). Dynamic targeting enables domain-general inhibitory control over action and thought by the prefrontal cortex. *Nature Communications, 13*(1). https://doi.org/10.1038/s41467-021-27926-w

Aron, A. R. (2011). From Reactive to Proactive and Selective Control: Developing a Richer Model for Stopping Inappropriate Responses. *Biological Psychiatry, 69*(12), e55–e68. https://doi.org/10.1016/j.biopsych.2010.07.024

Aron, A. R., Behrens, T. E., Smith, S., Frank, M. J., & Poldrack, R. A. (2007). Triangulating a Cognitive Control Network Using Diffusion-Weighted Magnetic Resonance Imaging (MRI) and Functional MRI. The Journal of Neuroscience, 27(14), 3743–3752. https://doi.org/10.1523/jneurosci.0519-07.2007

Aron, A. R., & Poldrack, R. A. (2006). Cortical and Subcortical Contributions to Stop Signal Response Inhibition: Role of the Subthalamic Nucleus. The Journal of Neuroscience, 26(9), 2424–2433. https://doi.org/10.1523/jneurosci.4682-05.2006

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2014). Inhibition and the right inferior frontal cortex: one decade on. *Trends in Cognitive Sciences, 18*(4), 177–185. https://doi.org/10.1016/j.tics.2013.12.003

Arienzo, D., Happer, J. P., Molnar, S. M., Alderson-Myers, A., & Marinkovic, K. (2019). Binge drinking is associated with altered resting state functional connectivity of reward-salience and top down control networks. *Brain Imaging and Behavior, 14*(5), 1731–1746. https://doi.org/10.1007/s11682-019-00107-6

Babor, T. F., Casswell, S., Graham, K., Huckle, T., Livingston, M., Österberg, E., Rehm, J., Room, R., Rossow, I., & Sornpaisarn, B. (2022). *Alcohol: No Ordinary Commodity.* https://doi.org/10.1093/oso/9780192844484.001.0001

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences*, 4(11), 417–423. https://doi.org/10.1016/s1364-6613(00)01538-2

Baddeley, A., Eysenck, M. W., Anderson, M. C. (2020). *Memory* (Third edition). Routledge, Taylor & Francis Group.

Bava, S., & Tapert, S. F. (2010). Adolescent brain development and the risk for alcohol and other drug problems. *Neuropsychology Review, 20*(4), 398-413.

Bari, A., & Robbins, T. W. (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology, 108*, 44–79. https://doi.org/10.1016/j.pneurobio.2013.06.005

Benoit, R. G., & Anderson, M. C. (2012). Opposing mechanisms support the voluntary forgetting of unwanted memories. *Neuron, 76*(2), 450-460. http://dx.doi.org/10.1016/j.neuron.2012.07.025

Benoit, R. G., Davies, D. J., & Anderson, M. C. (2016). Reducing future fears by suppressing the brain mechanisms underlying episodic simulation. *Proceedings of the National Academy of Sciences, 113*(52). https://doi.org/10.1073/pnas.1606604114

Benoit, R. G., Hulbert, J. C., Huddleston, E., & Anderson, M. C. (2015). Adaptive top-down suppression of hippocampal activity and the purging of intrusive memories from consciousness. *Journal of Cognitive Neuroscience, 27*(1), 96-111. https://doi.org/10.1162/jocn_a_00696

Berger, H. (1929). Über das elektroenkephalogramm des menschen. *Archiv für Psychiatrie und Nervenkrankheiten, 87*(1), 527-570.

Bjork, J. M., & Pardini, D. A. (2015). Who are those "risk-taking adolescents"? Individual differences in developmental neuroimaging research. *Developmental Cognitive Neuroscience, 11*, 56–64. https://doi.org/10.1016/j.dcn.2014.07.008

Boelema, S. R., Harakeh, Z., Ormel, J., Hartman, C. A., Vollebergh, W. A. M., & van Zandvoort, M. J. E. (2014). Executive functioning shows differential maturation from early to late adolescence: Longitudinal findings from a TRAILS study. *Neuropsychology, 28*(2), 177–187. https://doi.org/10.1037/neu0000049

Borck, C. (2005). Writing Brains: Tracing the Psyche With the Graphical Method. *History of Psychology, 8*(1), 79–94. https://doi.org/10.1037/1093-4510.8.1.79

Borsari, B., Murphy, J. G., & Barnett, N. P. (2007). Predictors of alcohol use during the first year of college: Implications for prevention. *Addictive Behaviors, 32*(10), 2062–2086. https://doi.org/10.1016/j.addbeh.2007.01.017

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciences, 8*(12), 539–546. https://doi.org/10.1016/j.tics.2004.10.003

Brady J. (2006). The association between alcohol misuse and suicidal behaviour. *Alcohol and alcoholism (Oxford, Oxfordshire), 41*(5), 473-478. https://doi.org/10.1093/alcalc/agl060

Brand, M., & Markowitsch, H. J. (2008). The role of the prefrontal cortex in episodic memory. *Handbook of Behavioral Neuroscience*, 18, 317-619. https://doi.org/10.1016/S1569-7339(08)00218-X

Brion, M., Pitel, A.-L., & D'Hondt, F. (2016). New Perspectives in the Exploration of Korsakoff's Syndrome: The Usefulness of Neurophysiological Markers. *Frontiers in Psychology, 7*. https://doi.org/10.3389/fpsyg.2016.00168

Brumback, T., Squeglia, L. M., Jacobus, J., Pulido, C., Tapert, S. F., & Brown, S. A. (2015). Adolescent heavy drinkers' amplified brain responses to alcohol cues decrease over one month of abstinence. *Addictive Behaviors, 46*, 45–52. https://doi.org/10.1016/j.addbeh.2015.03.001

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience, 10*(3), 186–198. https://doi.org/10.1038/nrn2575

Camchong, J., Stenger, A., & Fein, G. (2012). Resting-State Synchrony During Early Alcohol Abstinence Can Predict Subsequent Relapse. *Cerebral Cortex, 23*(9), 2086–2099. https://doi.org/10.1093/cercor/bhs190

Camina, E., & Güell, F. (2017). The Neuroanatomical, Neurophysiological and Psychological Basis of Memory: Current Models and Their Origins. *Frontiers in Pharmacology*, 8. https://doi.org/10.3389/fphar.2017.00438

Campanella, S. (2013). Why it is time to develop the use of cognitive event-related potentials in the treatment of psychiatric diseases. *Neuropsychiatric Disease and Treatment*, 1835. https://doi.org/10.2147/ndt.s53687

Carbia, C., Cadaveira, F., Caamaño-Isorna, F., Rodríguez-Holguín, S., & Corral, M. (2017). Binge drinking during adolescence and young adulthood is associated with deficits in verbal episodic memory. *PloS one, 12*(2), e0171393. https://doi.org/10.1371/journal.pone.0171393

Carbia, C., López-Caneda, E., Corral, M., & Cadaveira, F. (2018). A systematic review of neuropsychological studies involving young binge drinkers. *Neuroscience and Biobehavioral Reviews, 90*, 332-349. https://doi.org/10.1016/j.neubiorev.2018.04.013

Casey, B. J., Getz, S., & Galvan, A. (2008). The adolescent brain. *Developmental Review, 28*(1), 62–77. https://doi.org/10.1016/j.dr.2007.08.003

Casey, B. J., & Jones, R. M. (2010). Neurobiology of the adolescent brain and behavior: implications for substance use disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(12), 1189-1285. https://doi.org/10.1016/j.jaac.2010.08.017

Catarino, A., Küpper, C. S., Werner-Seidler, A., Dalgleish, T., & Anderson, M. C. (2015). Failing to forget: inhibitory-control deficits compromise memory suppression in posttraumatic stress disorder. *Psychological Science, 26*(5), 604-616. https://doi.org/10.1177/0956797615569889

Chambers, C. D., Garavan, H., & Bellgrove, M. A. (2009). Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neuroscience & Biobehavioral Reviews, 33*(5), 631–646. https://doi.org/10.1016/j.neubiorev.2008.08.016

Chikazoe, J., Jimura, K., Asari, T., Yamashita, K. -i., Morimoto, H., Hirose, S., Miyashita, Y., & Konishi, S. (2008). Functional Dissociation in Right Inferior Frontal Cortex during Performance of Go/No-Go Task. *Cerebral Cortex, 19*(1), 146–152. https://doi.org/10.1093/cercor/bhn065

Cofresí, R. U., Piasecki, T. M., Hajcak, G., & Bartholow, B. D. (2021). Internal consistency and test–retest reliability of the P3 event-related potential (ERP) elicited by alcoholic and non-alcoholic beverage pictures. *Psychophysiology, 59*(2). Portico. https://doi.org/10.1111/psyp.13967

Cohen, M. X. (2014). *Analyzing neural time series data: theory and practice*. MIT press.

Correas, A., Cuesta, P., López-Caneda, E., Rodríguez Holguín, S., García-Moreno, L. M., Pineda-Pardo, J. A., Cadaveira, F., & Maestú, F. (2016). Functional and structural brain connectivity of young binge drinkers: a follow-up study. *Scientific Reports, 6*(1). https://doi.org/10.1038/srep31293

Cortez-Pinto, H., Gouveia, M., dos Santos Pinheiro, L., Costa, J., Borges, M., & Vaz Carneiro, A. (2010). The burden of disease and the cost of illness attributable to alcohol drinking-results of a national study. *Alcoholism, Clinical and Experimental Research, 34*(8), 1442-1449. https://doi.org/10.1111/j.1530-0277.2010.01229.x

Courtney, K. E., Ghahremani, D. G., & Ray, L. A. (2012). Fronto-striatal functional connectivity during response inhibition in alcohol dependence. Addiction Biology, 18(3), 593–604. https://doi.org/10.1111/adb.12013

Crespo-García, M., Wang, Y., Jiang, M., Anderson, M. C., & Lei, X. (2022). Anterior Cingulate Cortex Signals the Need to Control Intrusive Thoughts during Motivated Forgetting. *The Journal of Neuroscience, 42*(21), 4342–4359. https://doi.org/10.1523/jneurosci.1711-21.2022

Crews, F. T., & Boettiger, C. A. (2009). Impulsivity, frontal lobes and risk for addiction. Pharmacology *Biochemistry and Behavior, 93*(3), 237–247. https://doi.org/10.1016/j.pbb.2009.04.018

Crews, F., He, J., & Hodge, C. (2007). Adolescent cortical development: A critical period of vulnerability for addiction. *Pharmacology Biochemistry and Behavior, 86*(2), 189–199. https://doi.org/10.1016/j.pbb.2006.12.001

Crews, F. T., Vetreno, R. P., Broadwater, M. A., & Robinson, D. L. (2016). Adolescent alcohol exposure persistently impacts adult neurobiology and behavior. *Pharmacological Reviews, 68*(4), 1074-1109.

Crone, E. A., & Richard Ridderinkhof, K. (2011). The developing brain: From theory to neuroimaging and back. *Developmental Cognitive Neuroscience, 1*(2), 101–109. https://doi.org/10.1016/j.dcn.2010.12.001

Cservenka, A., & Brumback, T. (2017). The Burden of Binge and Heavy Drinking on the Brain: Effects on Adolescent and Young Adult Neural Structure and Function. *Frontiers in Psychology, 8*, 1111. https://doi.org/10.3389/fpsyg.2017.01111

Day, E., & Rudd, J. H. F. (2019). Alcohol use disorders and the heart. *Addiction (Abingdon, England), 114*(9), 1670-1678. https://doi.org/10.1111/add.14703

Depue, B. E., Curran, T., & Banich, M. T. (2007). Prefrontal Regions Orchestrate Suppression of Emotional Memories via a Two-Phase Process. *Science, 317*(5835), 215–219. https://doi.org/10.1126/science.1139560

Diamond, A. (2013). Executive Functions. *Annual Review of Psychology, 64*(1), 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Dickerson, B. C., & Eichenbaum, H. (2010). The Episodic Memory System: Neurocircuitry and Disorders. *Neuropsychopharmacology, 35*(1), 86–104. https://doi.org/10.1038/npp.2009.126

Doallo, S., Cadaveira, F., Corral, M., Mota, N., López-Caneda, E., & Holguín, S. R. (2014). Larger mid-dorsolateral prefrontal gray matter volume in young binge drinkers revealed by voxel-based morphometry. *PloS One, 9*(5), e96380. https://doi.org/10.1371/journal.pone.0096380

Dormal, V., Bremhorst, V., Lannoy, S., Lorant, V., Luquiens, A., & Maurage, P. (2018). Binge drinking is associated with reduced quality of life in young students: A pan-European study. *Drug and Alcohol Dependence, 193*, 48-54. https://doi.org/10.1016/j.drugalcdep.2018.08.033

Duann, J.-R., Ide, J. S., Luo, X., & Li, C. R. (2009). Functional Connectivity Delineates Distinct Roles of the Inferior Frontal Cortex and Presupplementary Motor Area in Stop Signal Inhibition. The Journal of Neuroscience, 29(32), 10171–10179. https://doi.org/10.1523/jneurosci.1300-09.2009

Durston, S., Thomas, K. M., Worden, M. S., Yang, Y., & Casey, B. J. (2002). The effect of preceding context on inhibition: an event-related fMRI study. *Neuroimage*, *16*(2), 449-453.

ESPAD. (2020). ESPAD Report 2019: Results from the European School Survey Project on Alcohol and Other Drugs. Retrieved from: https://arrow.tudublin.ie/cgi/viewcontent.cgi?article=1000&context=tobacreports

Fadardi, J. S., & Cox, W. M. (2009). Reversing the sequence: Reducing alcohol consumption by overcoming alcohol attentional bias. *Drug and Alcohol Dependence, 101*(3), 137–145. https://doi.org/10.1016/j.drugalcdep.2008.11.015

Field, M., Schoenmakers, T., & Wiers, R. W. (2008). Cognitive processes in alcohol binges: a review and research agenda. *Current Drug Abuse Reviews, 1*(3), 263-279. https://doi.org/10.2174/1874473710801030263

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping, 2*(1–2), 56–78. https://doi.org/10.1002/hbm.460020107

Fuhrmann, D., Knoll, L. J., & Blakemore, S.-J. (2015). Adolescence as a Sensitive Period of Brain Development. Trends in Cognitive Sciences, 19(10), 558–566. https://doi.org/10.1016/j.tics.2015.07.008

Gagnepain, P., Henson, R. N., & Anderson, M. C. (2014). Suppressing unwanted memories reduces their unconscious influence via targeted cortical inhibition. *Proceedings of the National Academy of Sciences of the United States of America, 111*(13), E1310-E1319. https://doi.org/10.1073/pnas.1311468111

Gagnepain, P., Hulbert, J., & Anderson, M. C. (2017). Parallel Regulation of Memory and Emotion Supports the Suppression of Intrusive Memories. *The Journal of Neuroscience, 37*(27), 6423–6441. https://doi.org/10.1523/jneurosci.2732-16.2017

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier Development of the Accumbens Relative to Orbitofrontal Cortex Might Underlie Risk-Taking Behavior in Adolescents. *Journal of Neuroscience, 26*(25), 6885–6892. https://doi.org/10.1523/jneurosci.1062-06.2006

George W. H. (2019). Alcohol and Sexual Health Behavior: "What We Know and How We Know It". *Journal of Sex Research, 56*(4-5), 409-424. https://doi.org/10.1080/00224499.2019.1588213

George, M. S., Anton, R. F., Bloomer, C., Teneback, C., Drobes, D. J., Lorberbaum, J. P., Nahas, Z., & Vincent, D. J. (2001). Activation of Prefrontal Cortex and Anterior Thalamus in Alcoholic Subjects on Exposure to Alcohol-Specific Cues. *Archives of General Psychiatry, 58*(4), 345. https://doi.org/10.1001/archpsyc.58.4.345

Giedd, J. N. (2008). The Teen Brain: Insights from Neuroimaging. *Journal of Adolescent Health, 42*(4), 335–343. https://doi.org/10.1016/j.jadohealth.2008.01.007

Gierski, F., Stefaniak, N., Benzerouk, F., Gobin, P., Schmid, F., Henry, A., Kaladjian, A., & Naassila, M. (2020). Component process analysis of verbal memory in a sample of students with a binge drinking pattern. *Addictive Behaviors Reports*, 12, 100323. https://doi.org/10.1016/j.abrep.2020.100323

Gloor, P. (1994). Berger lecture. Is Berger's dream coming true? *Electroencephalography and Clinical Neurophysiology, 90*(4), 253–266. https://doi.org/10.1016/0013-4694(94)90143-0

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., Nugent, T. F., Herman, D. H., Clasen, L. S., Toga, A. W., Rapoport, J. L., & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences, 101*(21), 8174–8179. https://doi.org/10.1073/pnas.0402680101

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*(11), 652–669. https://doi.org/10.1038/nrn3119

Grayson, D. S., & Fair, D. A. (2017). Development of large-scale functional networks from birth to adulthood: A guide to the neuroimaging literature. *NeuroImage, 160*, 15–31. https://doi.org/10.1016/j.neuroimage.2017.01.079

Grüsser, S. M., Wrase, J., Klein, S., Hermann, D., Smolka, M. N., Ruf, M., Weber-Fahr, W., Flor, H., Mann, K., Braus, D. F., & Heinz, A. (2004). Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology, 175*(3), 296–302. https://doi.org/10.1007/s00213-004-1828-4

Hartley, D. E., Elsabagh, S., & File, S. E. (2004). Binge drinking and sex: effects on mood and cognitive function in healthy young volunteers. *Pharmacology Biochemistry and Behavior, 78*(3), 611–619. https://doi.org/10.1016/j.pbb.2004.04.027

Heffernan, T., Clark, R., Bartholomew, J., Ling, J., & Stephens, S. (2010). Does binge drinking in teenagers affect their everyday prospective memory? *Drug and Alcohol Dependence, 109*(1–3), 73–78. https://doi.org/10.1016/j.drugalcdep.2009.12.013

Heikkinen, N., Niskanen, E., Könönen, M., Tolmunen, T., Kekkonen, V., Kivimäki, P., Tanila, H., Laukkanen, E., & Vanninen, R. (2017). Alcohol consumption during adolescence is associated with reduced grey matter volumes. *Addiction, 112*(4), 604–613. Portico. https://doi.org/10.1111/add.13697

Heinz, A., Wrase, J., Kahnt, T., Beck, A., Bromand, Z., Grüsser, S. M., Kienast, T., Smolka, M. N., Flor, H., & Mann, K. (2007). Brain Activation Elicited by Affectively Positive Stimuli Is Associated With a

Lower Risk of Relapse in Detoxified Alcoholic Subjects. *Alcoholism: Clinical and Experimental Research, 31*(7), 1138–1147. https://doi.org/10.1111/j.1530-0277.2007.00406.x

Herrero-Montes, M., Alonso-Blanco, C., Paz-Zulueta, M., Pellico-López, A., Ruiz-Azcona, L., Sarabia-Cobo, C., Boixadera-Planas, E., & Parás-Bravo, P. (2022). Excessive alcohol consumption and binge drinking in college students. *PeerJ, 10*, e13368. Portico. https://doi.org/10.7717/peerj.13368

Hingson, R. W., Zha, W., & White, A. M. (2017). Drinking Beyond the Binge Threshold: Predictors, Consequences, and Changes in the U.S. *American Journal of Preventive Medicine, 52*(6), 717–727. https://doi.org/10.1016/j.amepre.2017.02.014

Hjarnaa, L., Møller, S. P., Curtis, A. B., Becker, U., Andersen, O., Torvik, F. A., & Tolstrup, J. S. (2023). Alcohol Intake and Academic Performance and Dropout in High School: A Prospective Cohort Study in 65,233 Adolescents. *Journal of Adolescent Health.* https://doi.org/10.1016/j.jadohealth.2023.07.008

Houston, R. J., & Schlienz, N. J. (2018). Event-Related Potentials as Biomarkers of Behavior Change Mechanisms in Substance Use Disorder Treatment. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 3*(1), 30–40. https://doi.org/10.1016/j.bpsc.2017.09.006

Howell, N. A., Worbe, Y., Lange, I., Tait, R., Irvine, M., Banca, P., Harrison, N. A., Bullmore, E. T., Hutchison, W. D., & Voon, V. (2013). Increased Ventral Striatal Volume in College-Aged Binge Drinkers. PLoS ONE, 8(9), e74164. https://doi.org/10.1371/journal.pone.0074164

Ingels, A., Fabry, L., Hanak, C., Hanard, F., Kajosch, H., Kornreich, C., & Campanella, S. (2022). Using Cognitive Event-Related Potentials in the Management of Alcohol Use Disorder: Towards an Individual Approach. *Archives of Clinical and Medical Case Reports, 06*(06). https://doi.org/10.26502/acmcr.96550561

Ip, C.-T., Ganz, M., Ozenne, B., Sluth, L. B., Gram, M., Viardot, G., l'Hostis, P., Danjou, P., Knudsen, G. M., & Christensen, S. R. (2018). Pre-intervention test-retest reliability of EEG and ERP over four recording intervals. *International Journal of Psychophysiology, 134*, 30–43. https://doi.org/10.1016/j.ijpsycho.2018.09.007

Jacobus, J., & Tapert, S. F. (2013). Neurotoxic Effects of Alcohol in Adolescence. Annual Review of Clinical Psychology, 9(1), 703–721. https://doi.org/10.1146/annurev-clinpsy-050212-185610

Jones, S. A., Lueras, J. M., & Nagel, B. J. (2018). Effects of Binge Drinking on the Developing Brain. *Alcohol Research: Current Reviews, 39*(1), 87–96.

Jurado-Barba, R., Sion, A., Martínez-Maldonado, A., Domínguez-Centeno, I., Prieto-Montalvo, J., Navarrete, F., García-Gutierrez, M. S., Manzanares, J., & Rubio, G. (2020). Neuropsychophysiological Measures of Alcohol Dependence: Can We Use EEG in the Clinical Assessment? *Frontiers in Psychiatry, 11*. https://doi.org/10.3389/fpsyt.2020.00676

Kamarajan, C. (2019). Brain Electrophysiological Signatures in Human Alcoholism and Risk. *Neuroscience of Alcohol*, 119–130. https://doi.org/10.1016/b978-0-12-813125-1.00013-1

Kavanagh, D. J., Andrade, J., & May, J. (2005). Imaginary Relish and Exquisite Torture: The Elaborated Intrusion Theory of Desire. *Psychological Review, 112*(2), 446–467. https://doi.org/10.1037/0033-295x.112.2.446

Kim, B.-M., Kim, M.-S., & Kim, J. S. (2020). Alterations of Functional Connectivity During the Resting State and Their Associations With Visual Memory in College Students Who Binge Drink. *Frontiers in Human Neuroscience, 14*. https://doi.org/10.3389/fnhum.2020.600437

Kolk, S.M., Rakic, P. (2022) Development of prefrontal cortex. *Neuropsychopharmacology, 47*, 41-57. https://doi.org/10.1038/s41386-021-01137-9

Kraus, L., Guttormsson, U., Leifman, H., Arpa, S., Molinaro, S., Monshouwer, K., et al. (2016). ESPAD Report 2015. Results from the European School Survey Project on Alcohol and Other Drugs. Lisbon: European Monitoring Centre for Drugs and Drug Addiction and the European School Survey Project

on Alcohol and Other Drugs. Available online at: http://www.espad.org/sites/espad.org/files/ESPAD_report_2015.pdf

Langbridge, J. E., Jones, R. D., & Canales, J. J. (2019). A Neurophysiological and Behavioral Assessment of Interventions Targeting Attention Bias and Sense of Control in Binge Drinking. *Frontiers in Human Neuroscience, 12*, 538. https://doi.org/10.3389/fnhum.2018.00538

Lannoy, S., Heeren, A., Dormal, V., Billieux, J., & Maurage, P. (2019). Is there room for attentional impairments in binge drinking? A commentary on Carbia et al. (2018). *Neuroscience & Biobehavioral Reviews, 98*, 58–60. https://doi.org/10.1016/j.neubiorev.2019.01.006

Lee, R. S. C., Hoppenbrouwers, S., & Franken, I. (2019). A Systematic Meta-Review of Impulsivity and Compulsivity in Addictive Behaviors. Neuropsychology Review, 29(1), 14–26. https://doi.org/10.1007/s11065-019-09402-x

Lees, B., Meredith, L. R., Kirkland, A. E., Bryant, B. E., & Squeglia, L. M. (2020). Effect of alcohol use on the adolescent brain and behavior. *Pharmacology, Biochemistry, and Behavior, 192*, 172906. https://doi.org/10.1016/j.pbb.2020.172906

Lees, B., Mewton, L., Stapinski, L. A., Squeglia, L. M., Rae, C. D., & Teesson, M. (2019). Neurobiological and Cognitive Profile of Young Binge Drinkers: a Systematic Review and Meta-Analysis. *Neuropsychology Review, 29*(3), 357-385. https://doi.org/10.1007/s11065-019-09411-w

Levy, B. J., & Anderson, M. C. (2012). Purging of memories from conscious awareness tracked in the human brain. *Journal of Neuroscience, 32*(47), 16785-16794. https://doi.org/10.1523/JNEUROSCI.2640-12.2012

Lin, X., Chen, D., Yao, Z., Anderson, M. C., & Hu, X. (2021). Observing the suppression of individual aversive memories from conscious awareness. *BioRxiv*. https://doi.org/10.1101/2021.10.17.464746

Lipton, P. A., & Eichenbaum, H. (2008). Complementary Roles of Hippocampus and Medial Entorhinal Cortex in Episodic Memory. *Neural Plasticity*, 2008, 1–8. https://doi.org/10.1155/2008/258467

López-Caneda, E., Cadaveira, F., & Campanella, S. (2019). Editorial: Binge Drinking in the Adolescent and Young Brain. Frontiers in Psychology, 9. https://doi.org/10.3389/fpsyg.2018.02724

López-Caneda, E., Crego, A., Campos, A. D., González-Villar, A., & Sampaio, A. (2019). The Think/No-Think Alcohol Task: A New Paradigm for Assessing Memory Suppression in Alcohol-Related Contexts. *Alcoholism, Clinical and Experimental Research, 43*(1), 36-47. https://doi.org/10.1111/acer.13916

López-Caneda, E., Rodríguez Holguín, S., Cadaveira, F., Corral, M., & Doallo, S. (2014). Impact of alcohol use on inhibitory control (and vice versa) during adolescence and young adulthood: a review. *Alcohol and alcoholism, 49*(2), 173-181. https://doi.org/10.1093/alcalc/agt168

Luck, S. J. (2014). *An introduction to the event-related potential technique*. MIT press.

Luna, B., Marek, S., Larsen, B., Tervo-Clemmens, B., & Chahal, R. (2015). An Integrative Model of the Maturation of Cognitive Control. *Annual Review of Neuroscience, 38*(1), 151–170. https://doi.org/10.1146/annurev-neuro-071714-034054

Mary, A., Dayan, J., Leone, G., Postel, C., Fraisse, F., Malle, C., Vallée, T., Klein-Peschanski, C., Viader, F., de la Sayette, V., Peschanski, D., Eustache, F., & Gagnepain, P. (2020). Resilience after trauma: The role of memory suppression. *Science, 367*(6479), eaay8477. https://doi.org/10.1126/science.aay8477

Mashhoon, Y., Czerkawski, C., Crowley, D. J., Cohen-Gilbert, J. E., Sneider, J. T., & Silveri, M. M. (2014). Binge Alcohol Consumption in Emerging Adults: Anterior Cingulate Cortical "Thinness" Is Associated with Alcohol Use Patterns. Alcoholism: *Clinical and Experimental Research, 38*(7), 1955–1964. Portico. https://doi.org/10.1111/acer.12475

Maurage, P., Lannoy, S., Mange, J., Grynberg, D., Beaunieux, H., Banovic, I., Gierski, F., & Naassila, M. (2020). What We Talk About When We Talk About Binge Drinking: Towards an Integrated

Conceptualization and Evaluation. *Alcohol and Alcoholism, 55*(5), 468–479. https://doi.org/10.1093/alcalc/agaa041

May, J., Kavanagh, D. J., & Andrade, J. (2015). The elaborated intrusion theory of desire: a 10-year retrospective and implications for addiction treatments. *Addictive Behaviors, 44*, 29-34.

Meda, S. A., Dager, A. D., Hawkins, K. A., Tennen, H., Raskin, S., Wood, R. M., Austad, C. S., Fallahi, C. R., & Pearlson, G. D. (2017). Heavy Drinking in College Students Is Associated with Accelerated Gray Matter Volumetric Decline over a 2 Year Period. *Frontiers in Behavioral Neuroscience, 11*. https://doi.org/10.3389/fnbeh.2017.00176

Mehta A. J. (2016). Alcoholism and critical illness: A review. *World Journal of Critical Care Medicine, 5*(1), 27-35. https://doi.org/10.5492/wjccm.v5.i1.27

Morris, L. S., Dowell, N. G., Cercignani, M., Harrison, N. A., & Voon, V. (2018). Binge drinking differentially affects cortical and subcortical microstructure. *Addiction Biology, 23*(1), 403-411. https://doi.org/10.1111/adb.12493

Moscovitch, M., Cabeza, R., Winocur, G., & Nadel, L. (2016). Episodic Memory and Beyond: The Hippocampus and Neocortex in Transformation. *Annual Review of Psychology, 67*(1), 105–134. https://doi.org/10.1146/annurev-psych-113011-143733

Mota, N., Parada, M., Crego, A., Doallo, S., Caamaño-Isorna, F., Rodríguez Holguín, S., Cadaveira, F., & Corral, M. (2013). Binge drinking trajectory and neuropsychological functioning among university students: A longitudinal study. *Drug and Alcohol Dependence, 133*(1), 108–114. https://doi.org/10.1016/j.drugalcdep.2013.05.024

Müller-Oehring, E. M., Jung, Y. C., Pfefferbaum, A., Sullivan, E. V., & Schulte, T. (2015). The resting brain of alcoholics. *Cerebral Cortex, 25*(11), 4155-4168. https://doi.org/10.1093/cercor/bhu134

Myrick, H., Anton, R. F., Li, X., Henderson, S., Drobes, D., Voronin, K., & George, M. S. (2003). Differential Brain Activity in Alcoholics and Social Drinkers to Alcohol Cues: Relationship to Craving. *Neuropsychopharmacology, 29*(2), 393–402. https://doi.org/10.1038/sj.npp.1300295

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience, 9*(11), 856–869. https://doi.org/10.1038/nrn2478

Nadel, L., & Hardt, O. (2010). Update on Memory Systems and Processes. *Neuropsychopharmacology, 36*(1), 251–273. https://doi.org/10.1038/npp.2010.169

Naqvi, N. H., & Bechara, A. (2010). The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain Structure & Function, 214*(5-6), 435-450. https://doi.org/10.1007/s00429-010-0268-7

National Institute of Alcohol Abuse and Alcoholism. (2004). NIAAA Council approves definition of binge drinking. NIAAA Newsletter No. 3:3. Retrieved from: https://www.niaaa.nih.gov/sites/default/files/publications/NIAAA_Binge_Drinking_3.pdf

National Institute of Alcohol Abuse and Alcoholism [NIAAA]. (2018). Alcohol Facts and Statistics. Report. Retrieved from: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics

Nemeth, V. L., Kurgyis, E., Csifcsak, G., Maraz, A., Almasi, D. A., Drotos, G., Szikszay, P., Ando, B., Janka, Z., & Must, A. (2014). The impact of intermediate-term alcohol abstinence on memory retrieval and suppression. *Frontiers in Psychology, 5*. https://doi.org/10.3389/fpsyg.2014.01396

Obeso, I., Robles, N., Marrón, E. M., & Redolar-Ripoll, D. (2013). Dissociating the Role of the pre-SMA in Response Inhibition and Switching: A Combined Online and Offline TMS Approach. *Frontiers in Human Neuroscience*, 7. https://doi.org/10.3389/fnhum.2013.00150

Olbrich, H. M., Valerius, G., Paris, C., Hagenbuch, F., Ebert, D., & Juengling, F. D. (2006). Brain Activation During Craving for Alcohol Measured by Positron Emission Tomography. *Australian & New Zealand Journal of Psychiatry, 40*(2), 171–178. https://doi.org/10.1080/j.1440-1614.2006.01765.x

Olsson, C. A., Romaniuk, H., Salinger, J., Staiger, P. K., Bonomo, Y., Hulbert, C., & Patton, G. C. (2016). Drinking patterns of adolescents who develop alcohol use disorders: results from the Victorian Adolescent Health Cohort Study. *BMJ Open, 6*(2), e010455. https://doi.org/10.1136/bmjopen-2015-010455

Palfai, T. P., & Luehring-Jones, P. (2021). How Alcohol Influences Mechanisms of Sexual Risk Behavior Change: Contributions of Alcohol Challenge Research to the Development of HIV Prevention Interventions. *AIDS and behavior, 25*(Suppl 3), 314-332. https://doi.org/10.1007/s10461-021-03346-1

Parada, M., Corral, M., Caamaño-Isorna, F., Mota, N., Crego, A., Holguín, S. R., & Cadaveira, F. (2011). Binge drinking and declarative memory in university students. Alcoholism, *Clinical and Experimental Research, 35*(8), 1475-1484. https://doi.org/10.1111/j.1530-0277.2011.01484.x

Patrick, M. E., & Schulenberg, J. E. (2010). Alcohol Use and Heavy Episodic Drinking Prevalence and Predictors Among National Samples of American Eighth-and Tenth-Grade Students. *Journal of Studies on Alcohol and Drugs, 71*(1), 41–45. https://doi.org/10.15288/jsad.2010.71.41

Paz-Alonso, P. M., Bunge, S. A., Anderson, M. C., & Ghetti, S. (2013). Strength of Coupling within a Mnemonic Control Network Differentiates Those Who Can and Cannot Suppress Memory Retrieval. *The Journal of Neuroscience, 33*(11), 5017–5026. https://doi.org/10.1523/jneurosci.3459-12.2013

Pennington, C. R., Shaw, D. J., Adams, J., Kavanagh, P., Reed, H., Robinson, M., Shave, E., & White, H. (2020). Where's the wine? Heavy social drinkers show attentional bias towards alcohol in a visual conjunction search task. *Addiction, 115*(9), 1650–1659. Portico. https://doi.org/10.1111/add.14997

Pérez-García, J. M., Cadaveira, F., Canales-Rodríguez, E. J., Suárez-Suárez, S., Rodríguez Holguín, S., Corral, M., Blanco-Ramos, J., & Doallo, S. (2022). Effects of Persistent Binge Drinking on Brain Structure in Emerging Adults: A Longitudinal Study. *Frontiers in Psychiatry, 13*. https://doi.org/10.3389/fpsyt.2022.935043

Pérez-García, J. M., Suárez-Suárez, S., Doallo, S., & Cadaveira, F. (2022). Effects of binge drinking during adolescence and emerging adulthood on the brain: A systematic review of neuroimaging studies. Neuroscience & Biobehavioral Reviews, 137, 104637. https://doi.org/10.1016/j.neubiorev.2022.104637

Pfefferbaum, A., Rohlfing, T., Pohl, K. M., Lane, B., Chu, W., Kwon, D., Nolan Nichols, B., Brown, S. A., Tapert, S. F., Cummins, K., Thompson, W. K., Brumback, T., Meloy, M. J., Jernigan, T. L., Dale, A., Colrain, I. M., Baker, F. C., Prouty, D., De Bellis, M. D., Voyvodic, J. T., Clark, D.B., Luna, B., Chung, T., Nagel, B.J., Sullivan, E. V. (2016). Adolescent Development of Cortical and White Matter Structure in the NCANDA Sample: Role of Sex, Ethnicity, Puberty, and Alcohol Drinking. *Cerebral Cortex, 26*(10), 4101-4121. https://doi.org/10.1093/cercor/bhv205

Pfefferbaum, A., Kwon, D., Brumback, T., Thompson, W. K., Cummins, K., Tapert, S. F., Brown, S.A., Colrain, I.M., Baker, F.C., Prouty, D., De Bellis, M.D., Clark, D.B., Nagel, B.J., Chu, W., Park, S.H., Pohl, K.M., & Sullivan, E. V. (2018). Altered brain developmental trajectories in adolescents after initiating drinking. *American Journal of Psychiatry, 175*(4), 370-380. https://doi.org/10.1176/appi.ajp.2017.17040469

Rangaswamy, M., Jones, K. A., Porjesz, B., Chorlian, D. B., Padmanabhapillai, A., Kamarajan, C., Kuperman, S., Rohrbaugh, J., O'Connor, S. J., Bauer, L. O., Schuckit, M. A., & Begleiter, H. (2007). Delta and theta oscillations as risk markers in adolescent offspring of alcoholics. International *Journal of Psychophysiology, 63*(1), 3–15. https://doi.org/10.1016/j.ijpsycho.2006.10.003

Raznahan, A., Lerch, J. P., Lee, N., Greenstein, D., Wallace, G. L., Stockman, M., Clasen, L., Shaw, P. W., & Giedd, J. N. (2011). Patterns of Coordinated Anatomical Change in Human Cortical

Development: A Longitudinal Neuroimaging Study of Maturational Coupling. *Neuron, 72*(5), 873–884. https://doi.org/10.1016/j.neuron.2011.09.028

Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y., & Patra, J. (2009). Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet, 373*(9682), 2223-2233. https://doi.org/10.1016/S0140-6736(09)60746-7

Ridderinkhof, K. R., van den Wildenberg, W. P. M., Segalowitz, S. J., & Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: The role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and Cognition, 56*(2), 129–140. https://doi.org/10.1016/j.bandc.2004.09.016

Roach, B. J., D'Souza, D. C., Ford, J. M., & Mathalon, D. H. (2019). Test-retest reliability of time-frequency measures of auditory steady-state responses in patients with schizophrenia and healthy controls. *NeuroImage: Clinical, 23*, 101878. https://doi.org/10.1016/j.nicl.2019.101878

Rodríguez Holguín, S., Folgueira-Ares, R., Crego, A., López-Caneda, E., Corral, M., Cadaveira, F., & Doallo, S. (2023). Neurocognitive effects of binge drinking on verbal episodic memory. An ERP study in university students. *Frontiers in Pharmacology*, 14. https://doi.org/10.3389/fphar.2023.1034248

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage, 52*(3), 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003

Sacchet, M. D., Levy, B. J., Hamilton, J. P., Maksimovskiy, A., Hertel, P. T., Joormann, J., Anderson, M. C., Wagner, A. D., & Gotlib, I. H. (2017). Cognitive and neural consequences of memory suppression in major depressive disorder. *Cognitive, Affective, & Behavioral Neuroscience, 17*(1), 77–93. https://doi.org/10.3758/s13415-016-0464-x

Sadaghiani, S., Brookes, M. J., & Baillet, S. (2022). Connectomics of human electrophysiology. *NeuroImage, 247*, 118788. https://doi.org/10.1016/j.neuroimage.2021.118788

Sanhueza, C., García-Moreno, L. M., & Expósito, J. (2011). Weekend alcoholism in youth and neurocognitive aging. *Psicothema,23*(2), 209-214.

Scaife, J. C., & Duka, T. (2009). Behavioural measures of frontal lobe function in a population of young social drinkers with binge drinking pattern. *Pharmacology Biochemistry and Behavior, 93*(3), 354–362. https://doi.org/10.1016/j.pbb.2009.05.015

Schmitz, T. W., Correia, M. M., Ferreira, C. S., Prescot, A. P., & Anderson, M. C. (2017). Hippocampal GABA enables inhibitory control over unwanted thoughts. *Nature Communications, 8*(1). https://doi.org/10.1038/s41467-017-00956-z

Silins, E., Horwood, L. J., Najman, J. M., Patton, G. C., Toumbourou, J. W., Olsson, C. A., Hutchinson, D. M., Degenhardt, L., Fergusson, D., Becker, D., Boden, J. M., Borschmann, R., Plotnikova, M., Youssef, G. J., Tait, R. J., Clare, P., Hall, W. D., & Mattick, R. P. (2018). Adverse adult consequences of different alcohol use patterns in adolescence: an integrative analysis of data to age 30 years from four Australasian cohorts. *Addiction, 113*(10), 1811–1825. Portico. https://doi.org/10.1111/add.14263

Simeonov, L., Peniket, M., & Das, R. (2022). No-think, No drink? Assessing the ability of reconsolidation interference by intentional forgetting to suppress alcohol 49 memories in hazardous drinkers. Behaviour research and therapy, 152, 104055. https://doi.org/10.1016/j.brat.2022.104055

Simon, J., Grogna, D., Rivard, M. C., Heck, M., Bouchard, S., & Quertemont, E. (2022). Assessing attentional bias for alcohol-related cues using eye tracking in a virtual reality environment. *Frontiers in Virtual Reality, 3*, 849840. https://doi.org/10.3389/frvir.2022.849840

Sion, A., Bruña Fernández, R., Martínez Maldonado, A., Domínguez Centeno, I., Torrado-Carvajal, A., Rubio, G., Pereda, E., & Jurado-Barba, R. (2020). Resting-state connectivity and network

parameter analysis in alcohol-dependent males. A simultaneous EEG-MEG study. *Journal of Neuroscience Research, 98*(10), 1857–1876. Portico. https://doi.org/10.1002/jnr.24673

Smith, J. L., De Blasio, F. M., Iredale, J. M., Matthews, A. J., Bruno, R., Dwyer, M., Batt, T., Fox, A. M., Solowij, N., & Mattick, R. P. (2017). Verbal Learning and Memory in Cannabis and Alcohol Users: An Event-Related Potential Investigation. *Frontiers in Psychology*, 8. https://doi.org/10.3389/fpsyg.2017.02129

Smith, J. L., Mattick, R. P., Jamadar, S. D., & Iredale, J. M. (2014). Deficits in behavioural inhibition in substance abuse and addiction: A meta-analysis. *Drug and Alcohol Dependence, 145*, 1–33. https://doi.org/10.1016/j.drugalcdep.2014.08.009

Sousa, S. S., Sampaio, A., López-Caneda, E., Bec, C., Gonçalves, Ó. F., & Crego, A. (2020). Increased Nucleus Accumbens Volume in College Binge Drinkers - Preliminary Evidence From Manually Segmented MRI Analysis. *Frontiers in Psychiatry, 10*. https://doi.org/10.3389/fpsyt.2019.01005

Sousa, S. S., Sampaio, A., Marques, P., López-Caneda, E., Gonçalves, Ó. F., & Crego, A. (2019). Functional and structural connectivity of the executive control network in college binge drinkers. *Addictive Behaviors, 99*, 106009. https://doi.org/10.1016/j.addbeh.2019.05.033

Sousa, S. S., Sampaio, A., Marques, P., Gonçalves, Ó. F., & Crego, A. (2017). Gray Matter Abnormalities in the Inhibitory Circuitry of Young Binge Drinkers: A Voxel-Based Morphometry Study. *Frontiers in Psychology, 8*. https://doi.org/10.3389/fpsyg.2017.01567

Spear, L. P. (2018). Effects of adolescent alcohol consumption on the brain and behaviour. *Nature Reviews Neuroscience, 19*(4), 197–214. https://doi.org/10.1038/nrn.2018.10

Squire, L. R. (1992). Declarative and Nondeclarative Memory: Multiple Brain Systems Supporting Learning and Memory. *Journal of Cognitive Neuroscience, 4*(3), 232–243. https://doi.org/10.1162/jocn.1992.4.3.232

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory, 82*(3), 171–177. https://doi.org/10.1016/j.nlm.2004.06.005

Squire, L. R., Genzel, L., Wixted, J. T., & Morris, R. G. (2015). Memory Consolidation. *Cold Spring Harbor Perspectives in Biology, 7*(8), a021766. https://doi.org/10.1101/cshperspect.a021766

Squeglia, L. M., Rinker, D. A., Bartsch, H., Castro, N., Chung, Y., Dale, A. M., Jernigan, T. L., & Tapert, S. F. (2014). Brain volume reductions in adolescent heavy drinkers. *Developmental Cognitive Neuroscience, 9*, 117-125. https://doi.org/10.1016/j.dcn.2014.02.005

Steinberg L. (2005). Cognitive and affective development in adolescence. *Trends in Cognitive Sciences, 9*(2), 69-74. https://doi.org/10.1016/j.tics.2004.12.005

Substance Abuse and Mental Health Services Administration. (December, 2022). Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health (HHS Publication No. PEP22-07-01-005, NSDUH Series H-57). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report

Sullivan, E. V., Brumback, T., Tapert, S. F., Brown, S. A., Baker, F. C., Colrain, I. M., Prouty, D., De Bellis, M. D., Clark, D. B., Nagel, B. J., Pohl, K. M., & Pfefferbaum, A. (2020). Disturbed Cerebellar Growth Trajectories in Adolescents Who Initiate Alcohol Drinking. *Biological Psychiatry, 87*(7), 632–644. https://doi.org/10.1016/j.biopsych.2019.08.026

Sullivan, E. V., Müller-Oehring, E., Pitel, A.-L., Chanraud, S., Shankaranarayanan, A., Alsop, D. C., Rohlfing, T., & Pfefferbaum, A. (2013). A Selective Insular Perfusion Deficit Contributes to Compromised Salience Network Connectivity in Recovering Alcoholic Men. *Biological Psychiatry, 74*(7), 547–555. https://doi.org/10.1016/j.biopsych.2013.02.026

Tamnes, C. K., Østby, Y., Fjell, A. M., Westlye, L. T., Due-Tønnessen, P., & Walhovd, K. B. (2009). Brain Maturation in Adolescence and Young Adulthood: Regional Age-Related Changes in Cortical

Thickness and White Matter Volume and Microstructure. *Cerebral Cortex, 20*(3), 534–548. https://doi.org/10.1093/cercor/bhp118

Telles-Correia, D., & Mega, I. (2015). Candidates for liver transplantation with alcoholic liver disease: Psychosocial aspects. *World Journal of Gastroenterology, 21*(39), 11027-11033. https://doi.org/10.3748/wjg.v21.i39.11027

Tenke, C. E., Kayser, J., Pechtel, P., Webb, C. A., Dillon, D. G., Goer, F., Murray, L., Deldin, P., Kurian, B. T., McGrath, P. J., Parsey, R., Trivedi, M., Fava, M., Weissman, M. M., McInnis, M., Abraham, K., E. Alvarenga, J., Alschuler, D. M., Cooper, C., Pizzagalli, D. A., Bruder, G. E. (2017). Demonstrating test-retest reliability of electrophysiological measures for healthy adults in a multisite study of biomarkers of antidepressant treatment response. *Psychophysiology, 54*(1), 34–50. Portico. https://doi.org/10.1111/psyp.12758

Tobin, R. M., & Graziano, W. G. (2010). Delay of gratification: A review of fifty years of regulation research. *Handbook of Personality and Self-Regulation*, 47-63.

Tomasi, D., Shokri-Kojori, E., & Volkow, N. D. (2016). Temporal Changes in Local Functional Connectivity Density Reflect the Temporal Variability of the Amplitude of Low Frequency Fluctuations in Gray Matter. *PLOS ONE, 11*(4), e0154407. https://doi.org/10.1371/journal.pone.0154407

Townshend, J. M., & Duka, T. (2001). Attentional bias associated with alcohol cues: differences between heavy and occasional social drinkers. *Psychopharmacology, 157*(1), 67-74. https://doi.org/10.1007/s002130100764

Trangenstein, P. J., Peddireddy, S. R., Cook, W. K., Rossheim, M. E., Monteiro, M. G., & Jernigan, D. H. (2021). Alcohol Policy Scores and Alcohol-Attributable Homicide Rates in 150 Countries. American *Journal of Preventive Medicine, 61*(3), 311-319. https://doi.org/10.1016/j.amepre.2021.03.020

Tulving, E. (2002). Episodic Memory: From Mind to Brain. Annual Review of Psychology, 53(1), 1–25. https://doi.org/10.1146/annurev.psych.53.100901.135114

van Duijvenvoorde, A. C. K., Peters, S., Braams, B. R., & Crone, E. A. (2016). What motivates adolescents? Neural responses to rewards and their influence on adolescents' risk taking, learning, and cognitive control. *Neuroscience & Biobehavioral Reviews, 70*, 135–147. https://doi.org/10.1016/j.neubiorev.2016.06.037

Vázquez-Marrufo, M., Caballero-Díaz, R., Martín-Clemente, R., Galvao-Carmona, A., & González-Rosa, J. J. (2020). Individual test-retest reliability of evoked and induced alpha activity in human EEG data. *PLOS ONE, 15*(9), e0239612. https://doi.org/10.1371/journal.pone.0239612

Verdejo-García, A., & Bechara, A. (2009). A somatic marker theory of addiction. *Neuropharmacology, 56*, 48–62. https://doi.org/10.1016/j.neuropharm.2008.07.035

Vogel, A. C., Power, J. D., Petersen, S. E., & Schlaggar, B. L. (2010). Development of the Brain's Functional Network Architecture. *Neuropsychology Review, 20*(4), 362–375. https://doi.org/10.1007/s11065-010-9145-7

Wang, Y., Zhao, Y., Nie, H., Liu, C., & Chen, J. (2018). Disrupted Brain Network Efficiency and Decreased Functional Connectivity in Multi-sensory Modality Regions in Male Patients With Alcohol Use Disorder. *Frontiers in Human Neuroscience, 12*. https://doi.org/10.3389/fnhum.2018.00513

Wang, Y., Zhao, Y., Nie, H., Liu, C., & Chen, J. (2018). Disrupted Brain Network Efficiency and Decreased Functional Connectivity in Multi-sensory Modality Regions in Male Patients With Alcohol Use Disorder. *Frontiers in Human Neuroscience, 12*. https://doi.org/10.3389/fnhum.2018.00513

Whelan, R., Watts, R., Orr, C. A., Althoff, R. R., Artiges, E., Banaschewski, T., Barker, G. J., Bokde, A. L. W., Büchel, C., Carvalho, F. M., Conrod, P. J., Flor, H., Fauth-Bühler, M., Frouin, V., Gallinat, J., Gan, G., Gowland, P., Heinz, A., Ittermann, B., Lawrence, C., Mann, K., Martinot, J., Nees, F., Ortiz, N., Paillère-Martinot, M., Paus, T., Pausova, Z., Rietschel, M., Robbins, T. W., Smolka, M. N., Ströhle, A., Schumann, G., Garavan, H., & Consortium. (2014). Neuropsychosocial profiles of

current and future adolescent alcohol misusers. *Nature, 512*(7513), 185–189. https://doi.org/10.1038/nature13402

Wierenga, L. M., Langen, M., Oranje, B., & Durston, S. (2014). Unique developmental trajectories of cortical thickness and surface area. *NeuroImage, 87*, 120–126. https://doi.org/10.1016/j.neuroimage.2013.11.010

Wiers, R. W., Bartholow, B. D., van den Wildenberg, E., Thush, C., Engels, R. C. M. E., Sher, K. J., Grenard, J., Ames, S. L., & Stacy, A. W. (2007). Automatic and controlled processes and the development of addictive behaviors in adolescents: A review and a model. *Pharmacology Biochemistry and Behavior, 86*(2), 263–283. https://doi.org/10.1016/j.pbb.2006.09.021

Winward, J. L., Hanson, K. L., Bekman, N. M., Tapert, S. F., & Brown, S. A. (2014). Adolescent Heavy Episodic Drinking: Neurocognitive Functioning during Early Abstinence. *Journal of the International Neuropsychological Society*, 20(2), 218–229. https://doi.org/10.1017/s1355617713001410

Worbe, Y., Irvine, M., Lange, I., Kundu, P., Howell, N. A., Harrison, N. A., Bullmore, E. T., Robbins, T. W., & Voon, V. (2014). Neuronal Correlates of Risk-Seeking Attitudes to Anticipated Losses in Binge Drinkers. *Biological Psychiatry, 76*(9), 717–724. https://doi.org/10.1016/j.biopsych.2013.11.028

World Health Organization (2018). Global status report on alcohol and health 2018. Geneva: Suisse. Available at: https://iris.who.int/bitstream/handle/10665/274603/9789241565639-eng.pdf?sequence=1 (Accessed September 29, 2023)

World Health Organization (2022, 9 May). Alcohol. Who. https://www.who.int/news-room/fact-sheets/detail/alcohol

Zhang, Y., Wu, W., Toll, R. T., Naparstek, S., Maron-Katz, A., Watts, M., Gordon, J., Jeong, J., Astolfi, L., Shpigel, E., Longwell, P., Sarhadi, K., El-Said, D., Li, Y., Cooper, C., Chin-Fatt, C., Arns, M., Goodkind, M. S., Trivedi, M. H., Marmar, C., R., Etkin, A. (2020). Identification of psychiatric disorder subtypes from functional connectivity patterns in resting-state electroencephalography. *Nature Biomedical Engineering, 5*(4), 309–323. https://doi.org/10.1038/s41551-020-00614-8

Zhao, Q., Sullivan, E. V., Honnorat, N., Adeli, E., Podhajsky, S., De Bellis, M. D., Voyvodic, J., Nooner, K. B., Baker, F. C., Colrain, I. M., Tapert, S. F., Brown, S. A., Thompson, W. K., Nagel, B. J., Clark, D. B., Pfefferbaum, A., & Pohl, K. M. (2021). Association of Heavy Drinking With Deviant Fiber Tract Development in Frontal Brain Systems in Adolescents. *JAMA Psychiatry, 78*(4), 407-415. https://doi.org/10.1001/jamapsychiatry.2020.4064

CHAPTER 2: Electroencephalographic signatures of the binge drinking pattern during adolescence and young adulthood: A PRISMA-driven systematic review

The work presented in Chapter 2 was published in NeuroImage: Clinical.

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

Journal indexed in JCR. Impact Factor (2022): 4.2

Citations number: Google Scholar: 27; ISI Web of Knowledge: 17

Cognitive Neuroscience: Q1; Neurology: Q1; Neurology (clinical): Q1

Reference:

Almeida-Antunes, N., Crego, A., Carbia, C., Sousa, S. S., Rodrigues, R., Sampaio, A., & López-Caneda, E. (2021). Electroencephalographic signatures of the binge drinking pattern during adolescence and young adulthood: A PRISMA-driven systematic review. *NeuroImage: Clinical*, *29*, 102537. https://doi.org/10.1016/j.nicl.2020.102537

In addition, this work was also presented at the Cognitive Neuroscience Society (CNS) 2020 Virtual Meeting.

Poster Presentation Reference:

Antunes, N., Rodrigues, R., Crego, A., Carbia, C., Sousa, S., Sampaio, A., Lopéz-Caneda, E. (2020, May 2-6). *Electrophysiological Consequences of Binge Drinking in Adolescents and Young Adults: A systematic Review* [Poster Presentation]. Cognitive Neuroscience Society (CNS) 2020 Virtual Meeting.

2.1. Abstract

Research on neurophysiological impairments associated with binge drinking (BD), an excessive but episodic alcohol use pattern, has significantly increased over the last decade. This work is the first to systematically review –following PRISMA guidelines- the empirical evidence regarding the effects of BD on neural activity –assessed by electroencephalography- of adolescents and young adults. A systematic review was conducted in 34 studies (N = 1723). Results indicated that binge drinkers (BDs) showed similar behavioral performance as non/ low drinkers. The most solid electrophysiological finding was an augmented P3 amplitude during attention, working memory and inhibition tasks. This increased neural activity suggests the recruitment of additional resources to perform the task at adequate/successful levels, which supports the neurocompensation hypothesis. Similar to alcoholics, BDs also displayed increased reactivity to alcohol-related cues, augmented resting-state electrophysiological signal and reduced activity during error detection –which gives support to the continuum hypothesis. Evidence does not seem to support greater vulnerability to BD in females. Replication and longitudinal studies are required to account for mixed results and to elucidate the extent/direction of the neural impairments associated with BD.

Keywords: binge drinking, electroencephalography, EEG, adolescents, young adults, event-related potentials, systematic review

2.2. Introduction

Alcohol use has an important social component among young people, since it is an essential part of academic traditions and parties (Dormal et al., 2019; Patrick et al., 2016). The excessive alcohol consumption that frequently occurs in these contexts is often associated with major social and health consequences, such as poor academic performance, motor vehicle accidents, sexual assault, liver and heart damage, and ultimately, death (Eurobarometer, 2010; National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2020). As such, alcohol misuse has been associated with more than 30% of deaths among American and European males aged between 15 and 29 years old (World Health Organization, 2011).

The detrimental effects of alcohol use on the brain have been broadly documented (Bernardin et al., 2014; Rangaswamy and Porjesz, 2014; Voon et al., 2020). Despite the focus has mainly been on alcohol dependence, the last decade has seen a significant increase in the studies concerning binge drinking (BD) (López-Caneda et al., 2019a). This pattern is commonly defined as the consumption of four (or more) drinks for women and five (or more) drinks for men in two hours, which results in a blood alcohol concentration of 0.08 g/dl or above (NIAAA, 2004). According to recent surveys from European and American national health agencies, BD is highly prevalent among adolescents and young adults, with around 35-40% of college students reporting at least one BD episode in the last month (Kraus et al., 2016; Substance Abuse and Mental Health Services Administration [SAMHSA], 2018).

These data become even more worrying when considering the special vulnerability of adolescence and youth to the neurotoxic effects of alcohol, particularly due to the undergoing structural and functional brain changes at this stage (Bava and Tapert, 2010; Jones et al., 2018). This developmental window is characterized by the maturation and refinement of several cognitive functions, especially higher order executive processes including cognitive flexibility, working memory and inhibitory control, which are mainly linked to the maturation of frontal areas (Boelema et al., 2014; Crone and Ridderinkhof, 2011; Luna et al., 2015).

Perhaps partially related to this increased vulnerability, BD during adolescence and youth has been associated with impaired cognitive performance, alterations in brain structure, and neurofunctional abnormalities (Carbia et al., 2018; Cservenka and Brumback, 2017; Jones et al., 2018; Lannoy et al., 2019; Lees et al., 2019; Petit et al., 2014a). In this sense, neuropsychological studies have reported that BD is mainly related to deficits in verbal memory and executive functions, particularly poor inhibitory control (Carbia et al., 2018). In addition, evidence from neuroimaging studies showed disruptions – reductions and/or increases- in the prefrontal cortex and subcortical structures (Kvamme et al., 2015;

Sousa et al., 2020; Squeglia et al., 2015; Doallo et al., 2014; Howell et al., 2013; Morris et al., 2018). At the functional level, neuroimaging data revealed impaired –frequently increased- neural activity during attentional, working memory and response inhibition tasks (Lees et al., 2019; Lannoy et al., 2019).

Another concerning aspect regarding this population is the possibility that BD and alcohol-dependence constitute two stages of the same phenomenon, a postulate known as the *continuum hypothesis* (Enoch, 2006; Parsons, 1998). This hypothesis has been supported by evidence showing that BDs exhibit impairments similar to those observed in alcoholics (Crego et al., 2010; López-Caneda et al., 2017b; Maurage et al., 2009; Petit et al., 2014a; Sanhueza et al., 2011), and that the engagement in this pattern during adolescence may constitute a first step towards the development of alcohol abuse during adulthood (Bonomo et al., 2004; McCambridge et al., 2011; McCarty et al., 2004). However, the validity of this proposal is still to be tested as, to the best of our knowledge, no neurophysiological study has directly explored the evolution –and its derivative effects- from BD to alcohol-dependence (Lannoy et al., 2014).

In the research on the potential cerebral effects of BD, the electroencephalography (EEG) –i.e., the study of the brain electrical activity by electrodes placed at the scalp- has gained considerable importance over the last decade. Contrarily to other imaging techniques, which have a coarse temporal resolution, EEG allows to explore the brain activity in the order of milliseconds, thus providing an optimal way for studying the neural dynamics that underlie the numerous cognitive stages occurring between a stimulus and a response (Campanella, 2013; Luck, 2014). The signal obtained can be analyzed in the time domain –e.g. event-related brain potentials (ERPs)-, the frequency domain -e.g. spectral power- or both –i.e. the time-frequency domain. Importantly, these measures have proven to be highly sensitive to the acute and chronic effects of alcohol (Brion et al., 2016; Kamarajan, 2019; Rangaswamy et al., 2007). Thus, given the subclinical nature of the BD pattern, EEG has emerged as a valuable approach for disentangling potential anomalies not observable at the behavioral level as well as for determining possible neural markers of risk for alcohol abuse.

Nevertheless, despite the importance of EEG for detecting underlying neural impairments associated with BD, the growing literature examining the electrophysiological impairments linked to this pattern and the previous efforts in providing an overview of the BD's EEG profile (Lees et al., 2019, Lannoy et al., 2019), no study to date has systematically reviewed the existing research on this topic. Thus, the main objective of the present study is to provide a qualitative synthesis of the available empirical evidence on the effects of BD in the brain electrical activity of adolescents and young adults. Additionally, we will

discuss the general strengths and limitations of these studies and recommend areas of interest for future research.

2.3. Methods

2.3.1. Search strategy and article selection

The present systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015), and the protocol was registered at PROSPERO International Prospective Register of Systematic Reviews of the University of York (registration number CRD42019118301). The literature review was conducted using PsycINFO, Web of Science, and PubMed databases. Articles were retrieved using the key terms: (binge/heavy/college drinking, binge/heavy/college/social drinkers, heavy episodic drinking, adolescen*, youth*, teen*, young, young adults and college/university students) and (ERP/ERPs, event-related, evoked potentials/evoked potential, electroencephalograph*, EEG and time-frequency). As additional inclusion criteria were defined: human observational studies, published in English between 2000 and 2020 (i.e. 1 January 2000 – 1 July 2020). Article's search, screening, eligibility and inclusion, was independently conducted by two of the authors using the Covidence systematic review software (Veritas Health Innovation, 2016). Authors resolved disagreements through discussion and consensus, and any remaining divergence (e.g. when one of the authors did not consider an inclusion/exclusion criteria) was resolved by a third author. Figure 3 represents the PRISMA flow diagram displaying the number of studies included at each phase of the selection process, and the reasoning for inclusion/exclusion.

The eligibility criteria are summarized in Table 1. Participants' age ranged from 12 to 30, namely from early adolescence to the end of young adulthood (Blakemore, 2012; Fuhrmann et al., 2015; Schulenberg et al., 2019). While variations in the definition of BD might exist (e.g. regarding frequency), we followed the standard definition of the NIAAA, which does not include a specific criterion regarding frequency (NIAAA, 2004). We excluded studies using other functional techniques such as functional magnetic resonance imaging (fMRI) or Magnetoencephalography (MEG). Additionally, we did not include studies whose main aim was to examine the relationship between psychiatric conditions (e.g. depression, anxiety) and the BD pattern or studies exploring other forms of alcohol consumption (e.g. acute ethanol effects).

The electrophysiological studies included in the present review are summarized in Table 2. The Cochrane-recommended National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to assess the methodological quality of the

studies (NHLBI, 2014) (for detailed information on assessment procedures see Table 3). Questions 5 and 14 of the NHLBI were adapted in order to better capture the strengths and weaknesses of the EEG studies (see supplementary Table A.1 for further details). There was a high total agreement (31/34 = 91.2%) between raters in the assessment of the studies. The inter-rater reliability, measured using Kappa coefficient of Cohen, was strong (K = 0.85) (McHugh, 2012).

Figure 4

PRISMA flow diagram of the study selection process

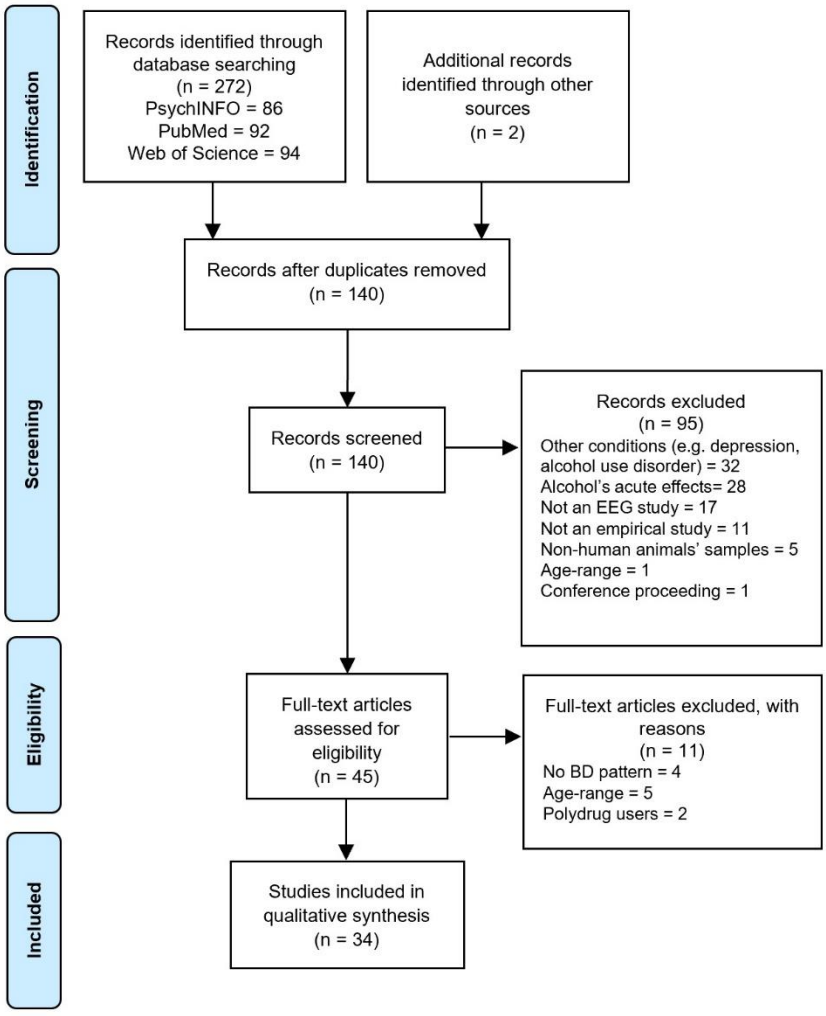


Table 1

Inclusion/Exclusion Criteria

1. Articles in English
2. Peer-reviewed journals indexed in Journal Citation Reports (JCR)
3. Published since January 2000
4. Human empirical studies
5. Participants aged between 12-30 years old
6. Participants must have a BD pattern as defined by NIAAA (2004), i.e. ≥ 4 (females) or 5 (males) drinks in two hours.
7. Healthy young people without an alcohol use disorder diagnosis or any substance use disorder
8. Participants must not be polydrug users, apart from tobacco and non-regular cannabis use
9. Healthy young people without history of psychiatric disorders (e.g. schizophrenia, depression)
10. Studies aimed at determining the neurofunctional impairments associated with BD assessed by EEG

Note. BD: Binge Drinking; EEG: Electroencephalography

2.4. Results

2.4.1. Main Findings

The database search resulted in the identification of 272 articles and Additional records identified through other sources. From these, 134 duplicated papers were excluded using the Zotero software (Ahmed and Bandar, 2011). The titles and abstracts of the remaining 140 articles were scrutinized and ninety-five studies were excluded (see Figure 4). In case of doubt, the manuscripts were submitted to full-text reading. Following the final screening of 45 full texts, a total of 34 articles fulfilled the inclusion criteria, being included a total of 1723 individuals (57.1% female).

Table 2

Summary of electrophysiological studies with adolescents and young adults BDs

Study & Design	Population (N)	Age (Mean ± SD)	BD criteria	Exclusion Criteria	Task	Main findings	Conclusions
Affan et al., 2018 Cross-sectional USA	N/LDs: 31 (16♂, 15♀) BDs: 30 (15♂, 15♀)	N/LDs: 23.3 ± 3.4 BDs: 23.4 ± 3.5	N/LDs: ≤ 1 BD episode in the previous 6 months BDs: ≥ 5 BD episodes [≥ 6(♂)/5(♀) SADs/2h] in the previous 6 months	Illicit drug or tobacco use at least one month prior to the study; History of brain injury, or other neuropsychiatric or medical problems; and Medications use at the time of the study	Resting state with eyes-open and eyes-closed	BDs: Alpha peak frequency was slower by 0.7 Hz; ↑ frontal theta and beta power Negative correlation between alpha peak frequency and drinking variables (e.g. n° of drinking days/week, n° of BD episodes in the previous 6 months) Positive correlation between theta power and drinking history during both resting conditions	BD among young adults is associated with augmented spontaneous electrophysiological signal
Bauer and Ceballos, 2014 Cross-sectional USA	Infrequent BDs: 55 ♀ (30 never and 25 less than monthly). Frequent BDs: 42 ♀ (28 monthly and 14 weekly).	Infrequent BDs: 19.5±1.3 Frequent BDs: 19.4±1.1	Infrequent BDs: infrequent episodes with ≥ 6 drinks/occasion at least once a month Frequent BDs: frequent episodes with ≥ 6 drinks/occasion at least once a week	Past year pregnancy; Psychosis; or Medical major disorders	Motor time estimation task	Frequent BD: ↑ Slow Potentials amplitude (more negative) in the right parietal cortex than infrequent BDs No group differences in Motor Potentials Negative correlation between Slow Potentials amplitude and AUDIT score	Augmented neural activity in BDs may reflect a compensatory over- activation of the circuit to perform the task at successful level
Blanco-Ramos et al., 2019 Cross-sectional Europe	N/LDs: 80 (28♂, 43♀) BDs: 71 (42♂, 38♀)	18-19	N/LDs: < 6 BD episodes over the last 6 months and cannabis consumption < 12 units over the last 3 months BDs: ≥ 6 BD episodes over the last 6 months and cannabis consumption < 12 units over the last 3 months	Chronic neurocognitive pathologies; History of neurological disorder or brain injury with LoC > 20 min; SCL-90-R > 90th percentile on GSI or ≥ 90 in 2 symptom dimensions; Family and/or personal history of psychopathology/alcoholism; Regular use of psychoactive drugs; Illegal drugs use (except cannabis) in the last 6 months; Non-corrected sensory/motor deficits	Go/NoGo task with alcoholic and non-alcoholic stimuli	BDs: ↑ N2-NoGo for non-alcoholic than for alcoholic stimuli; Similar P3-NoGo amplitude for non-alcoholic and for alcoholic stimuli (only in males) Negative correlation between: - N2-NoGo for non-alcoholic and the n° of BD episodes and total n° of alcoholic drinks in the last 180 days -P1 for Go-Alcohol and NoGo-NoAlcohol and age of onset drinking - n° of BD episodes and reaction time of false alarms Positive correlation between N2-NoGo for NoAlcohol and reaction time for false alarms	BDs seem to need increased activation to monitor conflict with the aim of compensate the affective-automatic system overactivation caused by alcohol-related bias

Table 2 *(continued)*

Study & Design	Population (N)	Age (Mean ± SD)	BD criteria	Exclusion Criteria	Task	Main findings	Conclusions
Courtney and Polich, 2010 Cross-sectional USA	N/LDs: 32 (16♂, 16♀) LBDs: 32 (16♂, 16♀) HBDs: 32 (16♂, 16♀)	N/LDs: ♂ 21.8 ± 0.8 ♀ 21.4 ± 1.3 LBDs: ♂ 20.5 ± 1.0 ♀ 20.4 ± 1.1 HBDs: ♂ 20.8 ± 2.0 ♀ 19.9 ± 1.1	N/LDs: 1-4 (♀)/5(♂) alcoholic drinks/<2h in the past 6 months LBDs: 5-4(♀)/7-6 (♂) alcoholic drinks/<2h at least once in the last 6 months HBDs: ≥ 10 alcoholic drinks/< 2h at least once in the last 6 months	Not use of alcohol, tobacco and psychiatric medication; Serious health problems (e.g. asthma, heart condition, etc.); Family and/or personal history of alcoholism; Neurologic/Psychiatric disorders; and Recent drug use	Resting state with eyes open	HBDs: ↑ spectral power in the delta (0-4 Hz) and fast beta (20-35 Hz) bands in comparison with N/LDs and LBDs	BDs exhibit augmented brain activity at rest similarly to alcohol-dependent individuals
Crego *et al.*, 2009 Cross-sectional Europe	N/LDs: 53 (27♂, 26♀) BDs: 42 (21♂, 21♀)	N/LDs: 18.7 ± 0.5 BDs: 18.9 ± 0.5	N/LDs: < 6 SADs/occasion and ≤ 2 SADs/hour BDs: ≥ 6 SADs/occasion at least once a month, ≥ 3 SADs/hour at least once a month	AUDIT > 20; Non-corrected sensory deficits; LoC > 20 minutes; History of traumatic brain injury or neurological disorder; Family and/or personal history of psychopathology; Drug use (except tobacco and cannabis); Alcohol use disorder; SCL-90-R > 90 on GSI or ≥ 2 symptom dimensions	Visual identical-pairs continuous performance task	BDs: ↑ N2 amplitude in central and parietal regions for the matching stimuli than N/LDs Cs: ↑ P3 amplitude in frontal, central and parietal regions for the matching than for the nonmatching stimuli (but not in BDs) No behavioral differences between groups	BDs require higher levels of attentional effort to perform the task at adequate levels. Also, they seem to have a deficiency in the electrophysiological differentiation between relevant and irrelevant information
Crego *et al.*, 2010 Cross-sectional Europe	N/LDs: 53 (27♂, 26♀) BDs: 42 (21♂, 21♀)	N/LDs: 18.7 ± 0.5 BDs: 18.9 ± 0.5	*(Same as above)*	*(Same as above)*	*(Same as above)*	BDs: ↓ LPC amplitude in frontal and central regions for matching condition than N/LDs, which was associated with hypoactivation of the right anterior prefrontal cortex No behavioral differences between groups	BDs display decreased electrophysiological activity during recognition and evaluation of the working memory processes
Crego *et al.*, 2012 Cross-sectional Europe	N/LDs: 53 (28♂, 25♀) BDs: 32 (17♂, 15♀)	N/LDs: 18.5 ± 0.5 BDs: 18.8 ± 0.6	(*Same as above)*	*Same as Crego et al. (2009)* and Left-handedness	Simple visual oddball task	BDs: ↑P3b amplitude in all regions (frontal, central and parietal) than N/LDs No significant differences in N2 No behavioral differences between groups	BDs seem to recruit broader brain areas linked to attentional processes to properly execute the task, which support the neurocompensation hypothesis

Table 2 *(continued)*

Study & Design	Population (N)	Age (Mean ± SD)	BD criteria	Exclusion Criteria	Task	Main findings	Conclusions
Folgueira-Ares *et al.*, 2017 Cross-sectional Europe	N/LDs: 25 (13♂, 12♀) BDs: 25 (14♂, 11♀)	N/LDs: 20.5 ± 0.6 BDs: 20.8 ± 0.7	*(Same as above)*	Non-corrected sensory deficits; LoC> 20 min; History of traumatic brain injury or neurological disorder; Family and/or personal history of psychopathology; Use of illegal drugs (except cannabis); and AUDIT > 20	Visual face–name association memory task	BDs: Similar neural activity for successful and unsuccessful encoding (no Dm effect); ↑ VPP amplitude at C3 and Cz electrodes than N/LDs Cs: Dm effect in posterior regions in the 350–650 ms latency range No significant differences in N170 No behavioral differences between groups	BDs display abnormal pattern of brain activity during the encoding phase, suggesting a different neural signature of successful memory encoding
Holcomb et al., 2019 CS USA	LDs: 32 (16♂, 16♀) BDs: 29 (14♂, 15♀)	LDs: 23.41 ± 3.4 BDs: 23.41 ± 3.5	LDs: < 1 BD episode in the past six months BDs: ≥ 3 BD episodes in the past 6 months with at least one episode in the last month	*Same as Affan et al. (2018)*	Visual Go/NoGo task	BDs: ↓ theta (4-7Hz) and early beta (15-25Hz) power during NoGo trials than LDs Negative correlation between NoGo theta power and n° BD episodes, daily alcohol intake, and the average n° of weekly drinking days No behavioral differences between groups	The results are consistent with deficits in the inhibitory control circuitry and are suggestive of allostatic neuroadaptive changes associated with BD
Huang *et al.*, 2018 CS USA	LDs: 32 (16♂, 16♀) BDs: 32 (16♂, 16♀) - LBDs: 17 (9♂) - HBDs: 15 (7♂)	LDs: 23.4 ± 3.4 BDs: 23.2 ± 3.3	LDs: 1 BD episode in the last 6 months. BDs: ≥ 5 BD episodes in the last 6 months. - LBDs: ≤ 10 BD episodes over the previous 6 months. - HBDs: ≥ 12 BD episodes over the previous 6 months	Drug or tobacco use for at least 1 month prior to the study; History of seizures, brain injury, neurological or neuropsychiatric disorders; Vision or hearing problems; learning difficulties; and Medications use at the time of the study	Emotional rating task	LDs: theta $power_{emotional}$ > theta $power_{neutral}$ (no differences in BDs) BDs: ↑ theta during erotic pictures compared to the other emotions HBDs: ↓ emotional modulation of theta and ↓ theta power to negative and positive photos in contrast with LDs Negative correlation between emotion-induced theta and n° of BD occasions within the past 6 months	BDs show diminished sensitivity of event-related theta to emotional salience, namely for negative and positive emotions
Kiat and Cheadle, 2018 CS USA	26 (6♂, 20♀) - 13: no BD episodes (past 30 days) - 13: 1-2 BD episodes (9 subjects) or 3-5 BD episodes (4 subjects)	20.0 ± 1.7	BD: > 5 alcoholic drinks in a row within a few hours	Not reported	Crocodile dentist (aversive risk-taking task)	↑ Late Positive Potential amplitude was associated with higher risk levels of BD	BD frequency seems to be linked to increased levels of anticipatory risk-taking reactivity

Table 2 *(continued)*

Study & Design	Population (N)	Age (Mean ± SD)	BD criteria	Exclusion Criteria	Task	Main findings	Conclusions
Kim and Kim, 2019 CS Asia	NBDs: 25♀ BDs: 25♀	NBDs: 21.7±2.4 BDs: 21.4±1.9	NBDs: AUDIT-K≤ 8, < 4 glasses in the last 2 weeks, and drank < 1 glass/hour. BDs: AUDIT-K= 12-26; ≥ 4 glasses more than once in the previous 2 weeks; and drank >2 glasses/hour	Left-handedness, Ambidexterity and History of psychiatric disorders	Flanker task (modified)	BDs: ↓ ERN amplitude than NBDs No differences in Pe amplitude or latency Positive correlation between ERN amplitude and total AUDIT-K and Alcohol Use Questionnaire scores <u>Behavioral</u>: BDs: ↑ error rates and ↓ reaction times in congruent and incongruent conditions than NBDs	BD seem to be associated with an impaired capacity to automatically monitor errors, reflected by decreased neural activity
Lannoy *et al.*, 2017 Cross-sectional Europe	N/LDs: 20 (7♂, 13♀) BDs: 20 (8♂, 12♀)	N/LDs: 21.2 ± 2.6 BDs: 20.3 ± 1.6	BD score formula: [(4*consumption speed) + drunkenness frequency + (0.2*drunkenness)] N/LDs: BD score ≤ 16 BDs: BD score > 16	Family and/or personal history of alcoholism; Positive psychological or neurological disorder; Current medication; Major medical problems; Past/current drug consumption (excepting alcohol and tobacco)	Visual speeded Go/NoGo task Balloon Analogue Risk task	BDs: ↑ ERN amplitude for false alarms than slow hits at Fz (not in N/LDs); ↑ Pe latency for slow hits at Cz during the Go/NoGo task No differences in FRN and P3 No behavioral differences between groups	BDs seem to have an impaired performance monitoring, showing an abnormal automatic processing of response errors and a decreased processing of their motivational significance
Lannoy et al., 2018 Cross-sectional Europe	N/LDs: 19 (11♂, 8♀) MDs: 17 (9♂, 8♀) BDs: 17 (10♂, 7♀)	N/LDs: 20.4 ± 2.8 MDs: 21.0 ± 2.7 BDs: 20.2 ± 1.6	N/LDs: BD score = 0, no consumption; MDs: BD score = 1-12; ≤3 doses/occasion; consumption speed 0.33-2; ≤3 drinking occasions/week. BDs: BD score ≥ 16; ≥ 6 doses/occasion; consumption speed ≥2; 2-4 drinking occasions/week	*Same as Lannoy et al. (2017)* and Non-corrected visual and auditory problems	Emotional crossmodal task	N/LDs: N1 latency$_{happiness}$ > N1 latency$_{anger}$ (no differences in BDs) BDs: <u>Congruent trials</u> SP3b amplitude for happy than anger faces (no differences in N/LDs and MDs); ↑P3b latency than MDs and N/LDs <u>Incongruent trials</u> ↑P3b amplitude than MDs; ↑ second positive component latency when anger voices were presented than MDs; ↑ third positive component amplitude when anger faces were presented than MDs	BDs present higher electrophysiological activity in the absence of behavioral deficits, which could be associated with a potential compensation process
Lannoy et al., 2020 Cross-sectional Europe	N/LDs: 25 (13♂, 12♀) BDS: 25 (10♂, 15♀)	N/LDs: 21.7 ± 1.8 BDs: 20.9 ± 1.7	N/LDs: BD score < 12; ≤ 4 drinking occasions/week; < 3 doses/occasion BDs: BD score ≥ 16; 2-4 drinking occasions/week; ≥ 6 doses/occasion	Severe alcohol use disorders; Family history of alcohol-use disorders; Psychological and neurological disorders; Past and current drug consumption (except alcohol and tobacco).	Go/NoGo task with alcoholic and non-alcoholic stimuli	BDs: ↓ NoGo-N2 amplitude for alcohol-related at F3 than F4 electrode. Behavioral: BDs: ↓ inhibition performance for explicit than implicit processing when compared to N/LDs	BD may be associated with impaired attentional/inhibitory processes in the presence of alcohol cues

Table 2 *(continued*

Study & Design	Population (N)	Age (Mean ± SD)	BD criteria	Exclusion Criteria	Task	Main findings	Conclusions
López-Caneda *et al.*, 2012 Longitudinal Europe	N/LDs: 25 (11♂, 14♀) BDs: 23 (13♂, 10♀)	1st evaluation N/LDs: 18.6 ± 0.5 BDs: 18.8 ± 0.5 2nd evaluation (2-year follow-up) N/LDs: 20.3 ± 0.5 BDs: 20.7 ± 0.6	N/LDs: < 6 SADs/occasion and ≤ 2 SADs/hour. BD: ≥ 6 SADs/occasion at least once a week or ≥ 6 SADs/occasion, ≥ 3 SADs/hour at least once a month	Family history of alcoholism; Family and/or personal history of psychopathology; drugs use (except cannabis); LoC> 20 minutes; history of traumatic brain injury or neurological disorder; non-corrected sensory deficits; and AUDIT> 20	Visual Go/NoGo Task	BDs: ↑Go-P3 amplitude in central and parietal regions in the 1st and 2nd evaluations ↑No/Go-P3 amplitude in all regions (frontal, central and parietal) in the 2nd evaluation, associated with hyperactivation of the right inferior frontal cortex during successful inhibition No significant differences in N2 No behavioral differences between groups	BDs show increased neural activity in inhibitory control regions during response inhibition, which could reflect a compensatory mechanism to perform the task efficiently
López-Caneda *et al.*, 2013 Longitudinal Europe	N/LDs: 31 (15♂, 16♀) BDs: 26 (15♂, 11♀)	1st evaluation N/LDs: 18.5±0.5 BDs: 18.8±0.5 2nd evaluation (2-year follow-up) N/LDs: 20.4±0.6 BDs: 20.8±0.6	*(Same as above)*	*(Same as above)*	Simple visual oddball task	BDs: ↑P3 amplitude at both evaluation times than N/LDs, with more pronounced differences in the follow-up evaluation Positive correlation between P3b amplitude and quantity and intensity of alcohol consumption No behavioral differences between groups	The increased neural activity linked to attentional/working memory processes, suggesting the recruitment of additional resources to perform the task at adequate levels
López-Caneda *et al.*, 2014b Longitudinal Europe	N/LDs: 25 (11♂, 14♀) BDs: 22 (11♂, 11♀) Ex-BDs: 10 (3♂, 7♀)	1st evaluation 18-19 2nd evaluation (2-year follow-up) 20-21	*(Same as above)* Ex-BDs: BD criteria in the 1st but not in the 2nd evaluation	*(Same as above)*	Visual Go/NoGo Task	BDs: ↑NoGo-P3 amplitudes in the 2nd evaluation than N/LDs; ↑Go-P3 amplitudes than N/LDs; Ex-BDs: intermediate position between BDs and N/LDs Frontal NoGo-P3 amplitude in the 2nd evaluation: - correlated negatively with the age of onset of regular drinking - correlated positively with speed of alcohol consumption and weekly quantity of alcohol consumed	BD lead to impairments in the neural functioning involved in inhibitory control, and the cessation of BD could act as a brake on the neurophysiological impairments related to response inhibition
López-Caneda et *al.*, 2017a Cross-sectional Europe	N/LDs: 40 (21♂, 19♀) BDs: 40 (20♂, 20♀)	N/LDs: 18.1 ± 0.3 BDs: 18.1 ± 0.3	Cs: never BAC ≥ 0.08 g/dL BDs: BAC ≥ 0.08 g/dL at least once during the last month	*(Same as above)* Use of medical drugs with psychoactive effects	Resting-state with eyes-open and eyes-closed conditions	BDs: ↑ beta power over the right temporal lobe (parahippocampal and fusiform gyri) during eyes-open resting state ↑ theta power over the bilateral occipital cortex (cuneus and lingual gyrus) during eyes-closed resting condition	BDs seem to present cortical hyperexcitability and potential difficulties in the information processing capacity

Table 2 *(continued)*

Study & Design	Population (N)	Age (Mean ± SD)	BD criteria	Exclusion Criteria	Task	Main findings	Conclusions
López-Caneda *et al.*, 2017b Cross-sectional Europe	N/LDs: 36 (17♂, 19♀) - Abstainers: 20 (12♂, 8♀) BDs: 36 (20♂, 16♀)	N/LDs: 18.1 ± 0.3 BDs: 18.1 ± 0.3	N/LDs: never reached a BAC of 0.08 g/dL. BDs: BAC ≥ 0.08 g/dL at least once during the last month	*Same as López-Caneda et al. (2012)* and use of psychoactive medical drugs during the week before the assessment	Visual equiprobable Go/NoGo Task	BDs: ↓ beta and theta during Go and NoGo conditions than N/LDs. No behavioral differences between groups	BDs appear to show decreased neural oscillations linked to motor inhibition and execution similar to those observed in alcohol-dependent subjects
Maurage *et al.*, 2009 Longitudinal Europe	N/LDs: 18 (7♂, 11♀) BDs: 18 (7♂, 11♀)	N/LDs: 18.2 ± 0.3 BDs: 18.2 ± 0.4	N/LDs: expected alcohol use 9 months after the 1st evaluation < 3 SADs/week. BDs: expected alcohol consumption 9 months after the 1st evaluation > 20 SADs/week	Family history of alcoholism; High past alcohol consumption or BD habits; Past or current drug use; Major medical problems; CNS disease; Auditory impairment; Moderate/high depression/anxiety; and Personal history of psychopathology	Auditory task based on emotional valence detection (negative or positive)	BDs: ↑ P1, N2 and P3b latency No differences in amplitude Positive correlation between mean alcohol intake and latency of each component No behavioral differences between groups	Short-term BD can produce marked cerebral dysfunction undetectable by behavioral measures alone. Specifically, BD seems to be associated with a slowed cerebral activity
Maurage *et al.*, 2012 Cross-sectional Europe	N/LDs: 20 (11♂, 9♀) DDs: 20 (11♂, 9♀) LBDs: 20 (11♂, 9♀) HBDs: 20 (11♂, 9♀)	N/LDs: 21.6 ± 2.4 DDs: 22.1 ± 2.2 LBDs: 21.0 ± 2.2 HBDs: 21.2 ± 2.0	N/LDs: non-drinkers DDs: 3-5 SADs/occasion, < 2 SADs/h, 5-7 times/week and 15-29 SADs/week LBDs: 5-12 SADs/occasion, > 3 SADs/h, 2-3 times/week and 15-29 SADs/week HBDs: > 10 SADs/occasion, > 3 SADs/h, 3-4 times/week and > 30 SADs/week	*(Same as above)*	Visual oddball task with face-detection	LBDs and HBDs: ↑P3b latency and ↓N1, P1, N2b amplitude than the other 3 groups; ↓P3b amplitude than N/LDs and DDs HBDs: ↑ N1, P1, N2b, P3a latency and ↓N170, P2 amplitude than the other 3 groups; ↑ P3b latency than DDs LBDs: ↓N170 amplitude than N/LDs; ↓P2 amplitude than N/LDs and DDs DDs: No significant differences with N/LDs	BDs present early and global electrophysiological impairments (characterized by reduced and slower activity), affecting low-level (perception and attention) as well as high-level (decision) cognitive stages
Na et al., 2019 Cross-sectional Asia	N/LDs: 23♀ BDs: 27♀	N/LDs: 22.0 ± 2.0 BDs: 21.4 ± 2.0	*(Same as Kim & Kim, 2019)*	AUDIT-K score > 26; No psychiatric disorder; Score ≥ 6 on the Children of Alcoholics Screening Test (family history of alcohol use disorder); Left-handed and ambidextrous	Iowa Gambling Task (modified)	BDs: ↓ ΔFRN than N/LDs; No differences in P3 amplitude <u>Behavioral</u>: BDs: ↓ total net score than the N/LDs	Female BDs seem to have difficulties in early evaluation of positive or negative feedback which seem to be associated with decision-making deficits

Table 2 *(continued)*

Study & Design	Population (N)	Age (Mean ± SD)	BD criteria	Exclusion Criteria	Task	Main findings	Conclusions
Park and Kim, 2018 Cross-sectional Asia	N/LDs: 25 (8♂, 17♀) BDs: 25 (8♂, 17♀)	N/LDs: 22.2± 2.4 BDs: 22.1±2.2	N/LDs: *same as above* BDs: AUDIT-K = 12-26; > 4(♀)/5(♂) glasses at least one time during the previous 2 weeks; > 2(♀)/3(♂) glasses/hour	CAST-K score > 6; Drug/alcohol abuse; Left-handed and ambidextrous; and History of neurological/psychiatric disorders	Spatial 2-back task with congruent, incongruent, and lure conditions	BDs: ↑P3 amplitude than N/LDs. NBDs: ↑P3 amplitude for congruent stimuli compared to the incongruent and lure stimuli (no differences in BDs) No group significant differences in N2.	BDs show increased cognitive effort to perform the task effectively. Additionally, they were less efficient in differentiating between relevant and irrelevant information
Petit *et al.*, 2012 Cross-sectional Europe	N/LDs: 18 (8♂, 10♀) BDs: 18 (12♂, 6♀)	N/LDs: 21.9±3.1 BDs: 21.3±1.7	N/LDs: <6 SADs/occasion and < 3 SADs/hour. BDs: ≥6 SADs/occasion, ≥ 3 SADs/h and ≥ 1-4 times/week	Major medical problems; History of CNS disease; Visual impairment, Past or current drug use; Family history of alcoholism; Very low alcohol consumption; BD habits before starting university studies	Visual oddball task with neutral stimuli and alcoholic and non-alcoholic pictures as target deviant stimuli.	BDs: ↑P1 amplitude for alcoholic pictures than for the non-alcoholic pictures Positive correlation between P1 amplitudes for alcoholic pictures and duration of BD habits, and n° of doses consumed/week No group significant differences in N2b and P3 No behavioral differences between groups	BDs exhibit signs of prioritizing processing of alcohol-related information
Petit *et al.*, 2013 Cross-sectional Europe	N/LDs: 27 (10♂, 17♀) BDs: 29 (15♂, 14♀)	N/LDs: ♂ 22.1 ± 2.5 ♀ 20.5 ± 1.2 BDs: ♂ 22.5 ± 3.7 ♀ 21.9 ± 2.3	*(Same as above)*	Major medical problems; CNS conditions; Visual impairment; Past or current drug consumption (except alcohol, cannabis and tobacco); and Alcohol abstinence	*(Same as above)*	BDs: ↑P3 amplitude for alcoholic pictures than for the non-alcoholic pictures (only in males) No behavioral differences between groups	BDs seem to present an enhanced motivational response to alcoholic stimuli
Petit *et al.*, 2014b Longitudinal Europe	Cs: 15 (4♂, 11♀) BDs: 15 (11♂, 4♀)	1st evaluation N/LDs: 22.0±2.13 BDs: 22.0±1.72 2nd evaluation (1-year follow-up) N/LDs: 23.0±2.2 BDs: 23.0±1.6	*(Same as above)*	*(Same as above)*	*(Same as above)*	BDs: ↓ P1 amplitude for both types of stimuli in the 2nd than in the 1st evaluation ↓ P3 amplitude for non-alcoholic cues in the 2nd than in the 1st evaluation No behavioral differences between groups	The continuation of BD over one year is associated with the development of brain functional abnormalities as well as ↑ reactivity to alcoholic stimuli and/or ↓ reactivity to non-alcoholic stimuli

Table 2 *(continued)*

Study & Design	Population (N)	Age (Mean ± SD)	BD criteria	Exclusion Criteria	Task	Main findings	Conclusions
Ryerson *et al.*, 2017 Cross-sectional USA	62 - 41: 1-8 BD episodes - 21: no BD episodes in the last month	18.9 ± 1.1	BDs: ≥ 5 SADs/occasion (males); ≥ 4 SADs/occasion (females)	Not reported	Alcoholic and neutral pictures following a global or local attentional scope manipulation	BD correlated positively with N1 amplitude to alcoholic pictures, but not to neutral pictures	Individuals with greater BD experience demonstrate increased neural response to alcoholic pictures, but not neutral pictures
Schroder *et al,* 2019 Cross-sectional Europe	N/LDs: 24 (11♂, 13♀) BDs: 25 (13♂, 12♀)	N/LDs: 26.8 ± 9.3 BDs: 24.0 ± 2.4	N/LDs: drank 1-30 days/month, but never > 5 SADs/occasion and ≤ 2 SADs/h BDs: ≥ 6 SADs occasion and ≥ 2 SADs/h	Major medical issues, CNS conditions (e.g. epilepsy and a prior history of brain injury); Visual impairments; and Past/current drug consumption	N-back task with numbers	BDs: ↑ P3 and P600 amplitude than N/LDs N/LDs: ↑ P2 and N4 amplitude than BDs No behavioral differences between groups	BDs require higher processing intensity throughout the information-processing stream to perform the task at the same level as controls.
Smith and Mattick, 2013 Cross-sectional Australia	N/LDs: 17 ♀ BDs: 13 ♀	N/LDs: 20.1 ± 1.2 BDs: 20.0 ± 1.2	N/LDs: no regular (less than once a month) consumption of ≥ 4 SADs/occasion BDs: ≥ 4 SADs/occasion at least once a month	Epileptic seizure, serious head injury or LoC; Uncorrected hearing/vision problems; and Regular (≥ 2/month) use of other drugs	Stop signal task	BDs: ↓P3 amplitude for failed inhibitions than N/LDs; ↑P3 amplitude in FCz for successful than failed inhibition trials; ↓ERN amplitude in Fz than N/LDs; Positive correlation between P3 amplitude at FCz with AUDIT scores <u>Behavioral</u>: BDs: ↑Stop signal reaction time than N/LDs	Young female BDs have large deficits in inhibitory control and performance monitoring, and they may have to work harder in order to successfully inhibit a response
Smith *et al.*, 2015 Cross-sectional Australia	N/LDs: 35 (18♂, 17♀) BDs: 31 (16♂, 15♀)	N/LDs: ♂ 22.1 ± 2.4 ♀ 21.4 ± 2 BDs: ♂ 23.0 ± 2.2 ♀ 21.0 ± 2.3	N/LDs: ≥ 5 SADs/occasion less than once a month BDs: ≥ 5 SADs/occasion at least once a month	Psychotropic medication; Epileptic seizure, head injury or LoC; Uncorrected vision problems; and Regular (>1/month) use of drugs (except for alcohol or tobacco)	Eriksen flanker task (Visual conflict monitoring task)	BDs: ↑conflict adaptation for N2 amplitude than N/LDs (females); ↓ N2 amplitude and no differences in the conflict adaptation effect than N/LDs (males); No differences in P3 (indexing inhibitory control) <u>Behavioral</u>: BDs: ↑errors than N/LDs	Results are suggestive of a compensatory response in female BDs, as they seem to need to increase their ongoing performance monitoring to properly execute the task

Table 2 *(continued)*

Study & Design	Population (N)	Age (Mean ± SD)	BD criteria	Exclusion Criteria	Task	Main findings	Conclusions
Smith *et al.*, 2016 Cross-sectional Australia	N/LDs: 37 (20♂, 17♀) BDs: 34 (21♂, 13♀)	N/LDs: ♂ 20.1 ± 1.1 ♀ 20.1 ± 1.2 BDs: ♂ 19.8 ± 1.2 ♀ 20.0 ± 1.2	N/LDs: no regular (less than once a month) consumption of ≥ 4 SADs/occasion BDs: ≥ 4 SADs/occasion at least once a month preceding 12 months	*(Same as Smith & Mattick, 2013)*	Visual stop-signal task	BDs: ↑P3 amplitude for successful than failed inhibition trials (marginally significant); ↑P3 latency for failed than successful inhibitions (only in females); ↓ERN amplitude than N/LDs (marginally significant) Behavioral: BDs: ↑ Stop signal reaction time than N/LDs (only in females)	Electrophysiological deficits during response inhibition and performance monitoring seem to be common to both sexes; however females also show to be more vulnerable at behavioral level
Smith *et al.*, 2017a Cross-sectional Australia	N/LDs: 35 (18♂, 17♀) BDs: 25 (12♂, 13♀)	N/LDs: 21.8 ± 2.2 BDs: 22.2 ± 2.5	*(Same as above)*	*(Same as Smith et al., 2015)*	Error awareness (Stroop Go/NoGo) task	No ERPs differences between groups Behavioral: BDS: ↑inhibitory errors	BDs commit more inhibitory errors, suggesting deficits in inhibitory control, but they not display failures in error awareness
Smith *et al.*, 2017b Cross-sectional Australia	Study 1: N/LDs: 13♂ BDs: 12♂ CU: 8♂ Study 2: N/LDs: 45 (25♂, 20♀) BDs: 39 (23♂, 16♀) Cannabis users: 20 (11♂, 9♀)	Study 1: 17.2±0.7 Study 2: N/LDs: ♂ 20.0 ± 1.1 ♀ 19.9 ± 1.2 BDs: ♂ 19.7 ± 1.2 ♀ 20.0 ± 1.2 Cannabis users: ♂ 20.6 ± 1.2 ♀ 20.1 ± 1.2	N/LDs: non-regular use of cannabis and non-regular heavy drinking BDs: ≥ 4 SADs per occasion at least once a month in the past year Cannabis < 2 times/month in the past year Cannabis users: Cannabis ≥ 2 times/month in the preceding 12 months	Regular use of drugs (except cannabis/tobacco); Uncorrected hearing/vision problems; Use of psychoactive medications; Seizure, serious head injury or LoC.	Rey Auditory Verbal Learning Test	BDs: ↑P540 than N/LDs. Cannabis users: ↓N340 than BDs Behavioral: BDs: poorer delayed recall relative to N/LDs (Study 2)	The results indicated alterations in recognition memory processing which, even in the absence of overt behavioral impairment, underline the potential for neural dysfunction with early exposure to alcohol

Note. AUDIT = Alcohol Use Disorders Identification Test; AUDIT-K = AUDIT - Korean; BAC = Blood Alcohol Concentration; BD = Binge Drinking; BDs = Binge Drinkers; CNS= Central Nervous System; DDs = Daily Drinkers; ERN = Error-Related Negativity; FRN = Feedback-related Negativity; GSI = Global Severity Index; HBDs = High Binge Drinkers; LBDs = Light Binge Drinkers; N/LDs= Non/Light Drinkers; LoC= Loss of Consciousness; LPC= Late Positive Component; MDs = Moderate Drinkers; N= sample size; NBDs= Non-Binge Drinkers; NDs= Non-Drinkers; Pe= Error-positivity; SCL-90-R= Symptom Checklist-90-Revised; SD= Standard Deviation; SADs= Standard Alcoholic Drinks; ↑= larger/higher; ↓= lower/reduced; ΔFRN= difference in amplitudes of feedback-related negativity between gain and loss feedback; VPP= Vertex Positive Potential

2.4.2. Study Characteristics

The majority of the studies included in this review (94.1%) were published after 2009, being 58.8% of them published between 2015 and 2020 (see Figure 5). More than half of the studies (55.9%) were conducted in Europe, 20.6% in the United States, 14.7% in Australia, and the remaining 8.8% in Asia. Five studies (14.7%) were longitudinal, involving two assessments, but only one of them began before BD onset. Studies' samples were mostly composed of college students. The cognitive processes most frequently assessed were inhibitory control (29.4%), attention (29.4%) and performance monitoring (23.5%). Figure 6 depicts the proportion of studies that evaluated different cognitive functions. Regarding attention, the oddball paradigm was the most widely used task (6 of 10 studies). Similarly, in the studies assessing inhibitory control the paradigm most frequently employed was the Go/NoGo task (7/10). More variability was observed in the performance monitoring studies, in which four paradigms were used, including the Go/NoGo (3/8), Stop-Signal (2/8), Iowa Gambling (1/8), and Flanker tasks (2/8).

From the studies reviewed, 29 explored ERPs, three studies analyzed EROs and three assessed the EEG rhythms during resting-state (see supplementary Figure A.1). The ERPs analyzed throughout the various studies are described in Table 4, including their time windows, cortical/subcortical sources and functional correlates. As reflected in Figure 7, P3 was the most studied component, being explored by 23 out of the 29 ERP studies. In addition, alterations in P3 amplitude were the most consistently reported ERP disruption in BDs (see Figure 8). For similar specifications regarding each cognitive function see supplementary Figure A.2.

Figure 5

Number of EEG studies exploring the neurofunctional impairments associated with BD conducted per year.

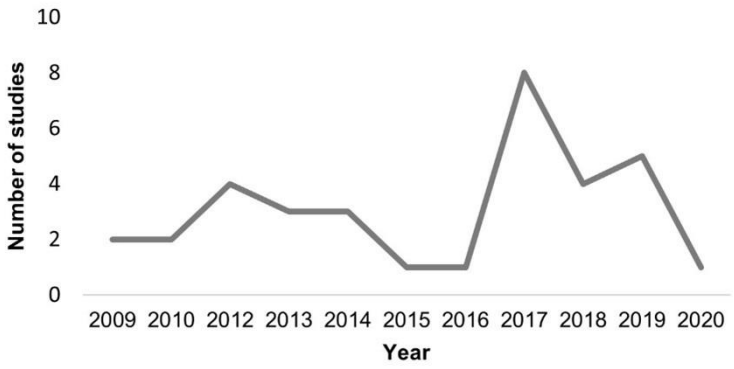


Figure 6

Number of articles included in the systematic review and the type of cognitive process analyzed.

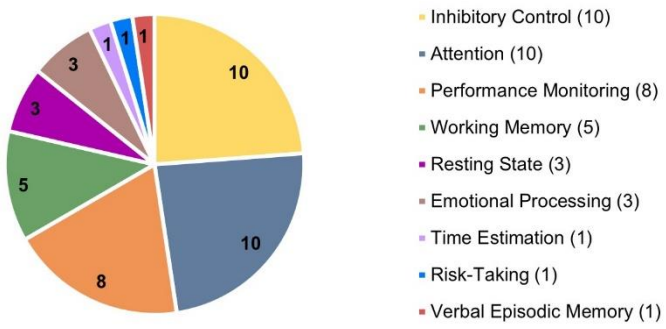
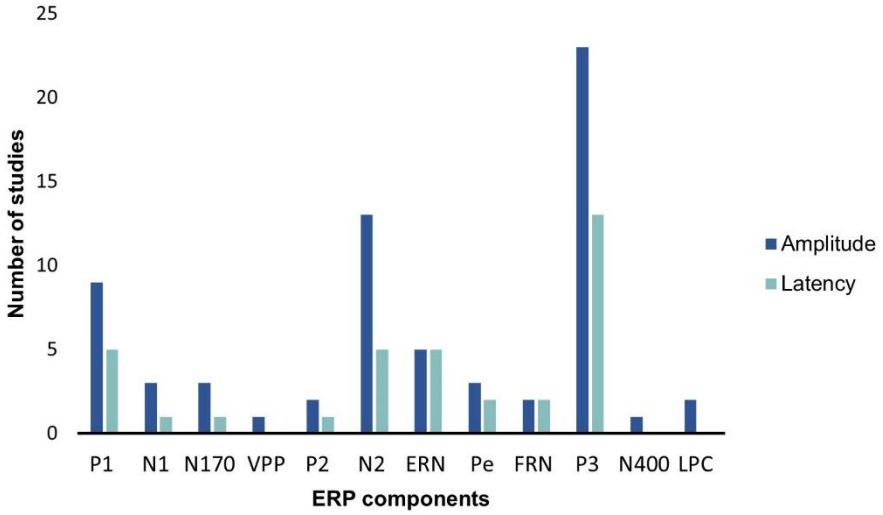


Figure 7

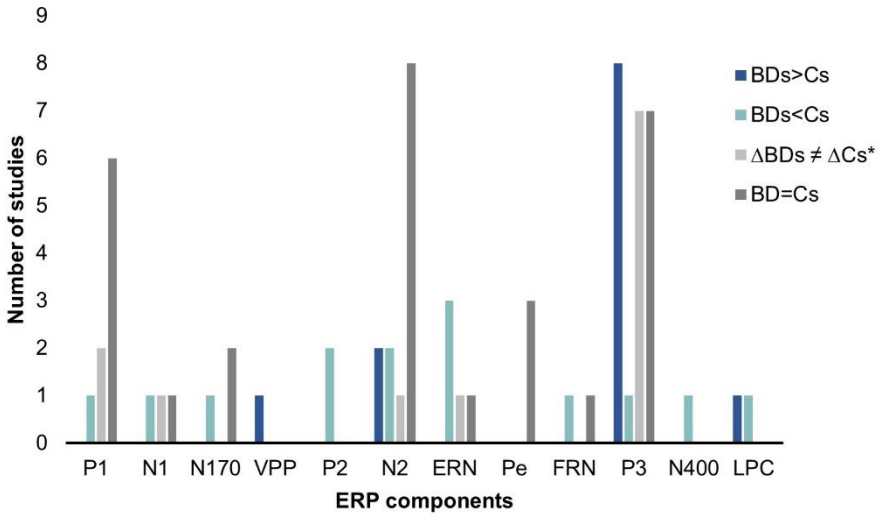
Number of studies exploring the amplitude and latency of each ERP component.



Note. VPP: Vertex Positive Potential; ERN: Error-Related Negativity; FRN: Feedback-Related Negativity; LPC: Late Positive Component; Pe: Error Positivity.

Figure 8

Number of studies, for each ERP component, that found increased (BDs>Cs), decreased (BDs<Cs), different (ΔBDs ≠ ΔCs), and similar (BDs=Cs) amplitude in BDs when compared to Cs (control group or non/low drinkers).



. *Significant differences between conditions only in one group.

2.4.3. Quality assessment

Most of the studies included were of high (44.1%) or intermediate quality (41.2%), while five studies were rated as having poor quality (14.7%). The main limitation of the studies was the disregard of potential confounding factors that could influence the results, such as not having relevant and clearly specified exclusion criteria, and lack of statistical control over confounders. The use of other drugs (including cannabis) and psychoactive substances as well as family history of alcoholism were the most common unspecified confounding factors. Specifically, a total of 13/34 studies (38.2%) did not mention or specifically clarify the consumption of illicit drugs in the sample.

Table 3

Quality assessment scores according to the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Study	Q1	Q2	Q3	Q4	Q5 *n* [a]/justification [b]	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Rating
Affan et al., 2018	Yes	No	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Bauer and Ceballos, 2014	Yes	Yes	NR	Yes	Yes/Yes	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Blanco-Ramos et al., 2019	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Good**
Courtney and Polich, 2010	Yes	Yes	NR	Yes	Yes/No	No	No	Yes	Yes	No	Yes	NR	NA	No	**Fair**
Crego et al., 2009	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Good**
Crego et al., 2010	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Good**
Crego et al., 2012	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Good**
Folgueira-Ares et al., 2017	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Good**
Holcomb et al., 2019	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Huang et al., 2018	Yes	No	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Kiat and Cheadle, 2018	Yes	No	NR	No	No (BD=13)/Yes	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Kim and Kim, 2019	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Lannoy et al., 2017	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Lannoy et al., 2018	Yes	Yes	NR	Yes	No (BD=17)/No	No	No	Yes	Yes	No	Yes	NR	NA	Yes	**Good**
Lannoy et al., 2020	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Good**
López-Caneda et al., 2012	Yes	Yes	NR	Yes	Yes/No	No	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	**Good**

Study	Q1	Q2	Q3	Q4	Q5 *n* [a]/justification [b]	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Rating
López-Caneda et al., 2013	Yes	Yes	NR	Yes	Yes/No	No	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	**Good**
López-Caneda, et al., 2014b	Yes	Yes	NR	Yes	Yes/No	No	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	**Good**
López-Caneda et al., 2017a	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
López-Caneda et al., 2017b	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Good**
Maurage et al., 2009	Yes	Yes	NR	Yes	No (BD=18)/No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	**Good**
Maurage et al., 2012	Yes	Yes	NR	Yes	Yes/No	No	No	Yes	Yes	No	Yes	NR	NA	Yes	**Good**
Na et al., 2019	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Park & Kim, 2018	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Petit et al., 2012	Yes	Yes	NR	Yes	No (BD=18)/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Fair**
Petit et al., 2013	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Good**
Petit et al., 2014b	Yes	Yes	NR	Yes	No/No	No	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	**Good**
Ryerson et al., 2017	Yes	Yes	NR	No	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Schroder et al., 2019	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Smith and Mattick, 2013	Yes	Yes	NR	Yes	No/No	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Smith et al., 2015	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Smith et al., 2016	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Smith et al., 2017a	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Smith et al., 2017b	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**

Note. n[a] = refers to having a reasonable sample size (≥20). Justification[b] = refers to statistical justification of sample size, estimates of effect size, etc. NA= not applicable; NR= not reported; NHLBI= National Heart, Lung, and Blood Institute

Table 4

Details of the main ERP components assessed by the studies included in the systematic review.

ERP	Time window	Polarity	Distribution	Source	Functional Meaning
[1]P1	Auditory ≈ 50 ms post-stimulus onset Visual ≈ 100 ms post-stimulus onset	Positive	Auditory: Fronto-Central Visual: Occipital	Auditory: superior temporal gyrus and medial frontal cortex Visual: extrastriate occipital cortex and posterior parietal regions	P1 represents a basic perceptual processing of the stimulus and provides a quantitative measure of the functional integrity of the sensory pathways. Additionally, it is usually interpreted as a neurophysiological indicator of preferential attention to sensory inputs and as an index of alertness status and attention.
[2]N1	Auditory: 75-150 ms post-stimulus onset Visual: 100-175 ms post-stimulus onset	Negative	Auditory: Fronto-Central Visual: Temporo-Occipital	Auditory: Primary auditory cortex and frontal regions. Visual: Inferior occipital cortex and the occipito-temporal junction	N1 is assumed to reflect selective attention to basic stimulus characteristics, an initial selection for later pattern recognition, which is modulated by the arousal and emotional salience of the stimulus.
[3]N170	125-225 ms post-stimulus onset	Negative	Occipito-Temporal	Posterior fusiform and inferior-temporal gyri	N170 is a component mainly associated with visual processing of human faces. It reflects the identification and structural encoding of faces and eyes, being considerably reduced for non-facial stimuli.
[4]VPP	140-180 ms post-stimulus onset	Positive	Central	Inferior temporal cortex	VPP is evoked during the processing of single images, exhibiting its largest amplitude response for faces. The functional similarity and the temporal coincidence with N170 have led to consider that both are flip sides of the same neural generators.
[5]P2	150-250 ms post-stimulus onset	Positive	Auditory: Central Visual: Frontal	Auditory: Primary and associative auditory cortex. Visual: inferior occipital cortex	P2 represents higher order perceptual processing modulated by attention and linked to memory. This component is part of a cognitive matching system that compares sensory inputs with stored memory, being involved in stimulus classification and attention modulation of nontarget stimuli.
N2	200-350 ms post-stimulus onset	Negative			N2 is considered to be a family of responses that differ in their distribution, source and interpretation, based on the features of the eliciting task, possibly reflecting task demands. However, all of them are part of the attentional processing and appear to indicate a detection of a deviation between a particular stimulus and the participant's expectation.
[6]*N2b*	200-350 ms post-stimulus onset	Negative	Fronto-Central	Anterior cingulate, frontal and superior temporal cortex	N2b is mainly elicited during the Stop Signal, Eriksen Flanker and Go/NoGo (NoGo-N2) tasks. It is associated with several processes such detection of response conflict (conflict monitoring), response inhibition or error detection. It is larger for non-targets (which do not require response) and it is usually observed along with the P3a component.
[7]*N2c*	200-350 ms post-stimulus onset	Negative	Auditory: Central Visual: Parieto-Occipital	Auditory: supratemporal auditory cortex Visual: occipito-temporal regions	N2c is most frequently elicited during the Continuous Performance and Oddball tasks. It partly reflects the conscious allocation of attentional resources to stimuli indicated as salient, as well as the voluntary switch of attention operated. It is larger for targets and observed along with P3b component.

Table 4 *(continued)*

ERP	Time window	Polarity	Distribution	Source	Interpretation
[8]ERN	80-150 ms after an erroneous response	Negative	Fronto-Central	Anterior cingulate cortex	ERN represents the early automatic detection of an error. This component is considered to reflect a process involved in evaluating the need for, or in implementing, control. The Flanker, Go/NoGo, Stop Signal and Stroop tasks (i.e. paradigms requiring speeded responses) are the most commonly used paradigms for assessing error processing.
[9]Pe	200-400 ms after response onset	Positive		Caudal and rostral portions of anterior cingulate cortex	Pe is a slow wave that reflects conscious error recognition. Similar to the ERN, the Flanker, Go/NoGo, Stop Signal and Stroop tasks are the most commonly used paradigms for eliciting this component.
[10]FRN	250-300 ms after feedback presentation	Negative	Fronto-Central	Anterior mid cingulate cortex	FRN follows the performance feedback, being linked to its valence and magnitude. Indexes an early evaluation, through a bottom-up mechanism of the feedback provided by the environment. It may also be an indicator of reward prediction and expectancy violation.
[11]P3	250-600 ms post-stimulus onset	Positive			P3 (or P300) is considered to index a wide variety of neurocognitive processes, including context processing, attention, working memory, response selection, stimulus salience, response inhibition and reward or emotional processing, depending on the type of cognitive processes required by the task. This component is usually divided into two subcomponents: P3a and P3b.
P3a	250-350 ms after the stimulus onset	Positive	Fronto-Central	Prefrontal cortex	P3a is mainly elicited by novelty oddball paradigms. This waveform has been associated with the involuntary attention orienting in response to changes in the environment. It reflects the bottom-up saliency that is determined by the novelty of the stimulus.
P3b	300-600 ms after the stimulus onset	Positive	Parietal	Temporo-parietal junction and deeper sources in the thalamus and hippocampus	P3b is frequently elicited by oddball and stimulus selection paradigms. This component has been associated with the voluntary attention and the *updating* of the stimulus representation in the working memory–usually indicating the top-down classification of the stimulus as relevant or target. In Go/NoGo paradigms, P3b elicited by NoGo stimulus may reflects response inhibition (NoGo-P3) and involve prefrontal regions. Sometimes this component is simply called P3.
[12]N400	300-600 ms post stimulus	Negative	Centro-Parietal	Anterior pre-frontal, superior temporo-parietal cortex and hippocampus and cingulate regions	N400 is a component commonly related to semantic incongruence in language paradigms, it is also typically observed in recognition–recall memory paradigms and is often referred to as an old–new effect. This component is associated with stimulus familiarity and memory trace strength.
[13]LPC	500-800 ms post stimulus	Positive	Centro-Parietal	Prefrontal cortex	LPC is related to higher order cognitive processes, such as recognition of the stimuli and decision accuracy/confidence. This component reflects the selection of a response category and the evaluation of the success of a category-related decision or memory match. Sometimes this component is also called P600.

2.4.4. Resting-State

Three studies explored resting-state brain activity –i.e. the electrophysiological recording of oscillatory brain activity while the person is relaxed- and all of them showed spontaneous EEG signal alterations associated with the BD pattern (Affan et al., 2018; Courtney and Polich, 2010; López-Caneda et al., 2017a). Courtney and Polich (2010) compared the brain activity of low-, high- and non-BDs during passive viewing. High-BDs (n = 32; M_{age_males} = 20.8; $M_{age_females}$ = 19.9) presented greater spectral power over the frontal, central and parietal regions (namely, the midline electrodes Fz, Cz and Pz) in the delta (0–4 Hz), and fast-beta (20–35 Hz) frequency bands, suggesting that high-BDs display an EEG spectral pattern similar to that observed in alcoholic patients.

The other two studies explored the neural activity of BDs during eyes-open and eyes-closed conditions. The results of López-Caneda et al. (2017a) showed that BDs (n = 40; M_{age} = 18.1) – comparatively to non/light drinkers- exhibited higher theta and beta power over the bilateral occipital cortex and the right temporal lobe respectively, which was suggestive of a potential neural disinhibition resulting from an excitatory-inhibitory imbalance. Similarly, Affan et al. (2018) found a slower Alpha Peak Frequency as well as increased frontal theta and beta power in the BD (n = 30; M_{age} = 23.4) relative to the light drinking group. According to the authors, the power increase in theta and beta bands might indicate disrupted excitatory-inhibitory homeostasis in BDs, resembling again the neural activity displayed by alcohol-dependent individuals (e.g. Rangaswamy et al., 2002, 2003).

Collectively, resting-state EEG studies seem to indicate that BDs, similarly to alcoholic individuals, present abnormal spontaneous EEG signal, mainly characterized by increased power in slow (delta/theta) and fast (beta) frequency bands. These results suggest that BD is associated with a brain overactivity eventually caused by an excitatory-inhibitory imbalance resulting from alterations in the neurotransmitter systems, including the GABAergic and glutamatergic systems (Ward et al., 2009).

2.4.5. Attention

Ten EEG studies included in this review examined attentional processes by mean of neutral (four studies) and alcohol-related (six studies) stimuli. Six of these studies used different versions of the visual oddball paradigm, which requires the detection of an unexpected stimulus among frequent/repetitive ones, involving bottom-up and top-down aspects of attention (Bledowski et al., 2004). While the former relates to the capacity of a salient stimulus to hold our attention regardless of our intentional goals, the top-down processes refer to our ability to screen the external information considering our current goals, and thus classifying the stimulus as a target (Katsuki and Constantinidis, 2013).

Crego et al. (2012) and López-Caneda et al. (2013) used a visual oddball task with neutral stimuli (stars and circles). Crego et al. (2012) explored the amplitude and latency of N2(7) and P3b(11) components (see Table 4) and showed that BDs (n = 32; M_{age} = 18.8) exhibited larger P3b amplitude than controls, specifically for the target condition, with no differences in the N2 component. In a follow-up study that used part of the sample of Crego et al.'s study, López-Caneda et al. (2013) also found larger P3b amplitude in BDs (n = 26; M_{age} = 18.8) when compared to the control group, a difference that was more pronounced after two years maintaining the BD pattern. According to the authors, these findings seem to indicate that, when compared to healthy subjects, BDs display abnormal neural activity associated with attentional processes (tentatively, an increased attentional resource allocation). Moreover, this anomalous activity tends to increase with the maintenance of BD over the years (López-Caneda et al., 2013).

Contrarily, Maurage et al. (2012) –using a visual oddball task with neutral faces-reported that BDs presented delayed latency and reduced amplitude in the ERP components associated with both early (perception and attention) and later (decision) stages of the cognitive processing. Specifically, when compared to controls, both low-BDs (n = 20) and high-BDs (n = 20; M_{age} = 21.2) exhibited lower (less negative) N1(2) and lower (less positive) P1(1) amplitude (with high-BDs showing in turn delayed latency in these components), suggesting an impaired early processing of visual stimuli in BDs. Both groups also had reduced N2b(6) amplitude relative to controls, and high-BDs exhibited larger N2b and P3a(11) latencies than the other three groups. These components are associated with adjustment of attention towards stimuli changes (Folstein and Petten, 2008), indicating that BD may lead to impairments in attentional control processes. Furthermore, delayed latency and reduced amplitude of the P3b component were also observed in both BD groups, reflecting impairments in the top-down (attentional/working memory) mechanisms involved in stimulus categorization. Lastly, low- and high-BDs displayed decreased N170(3)/P2(5) amplitude (an index of the perceptual processing of human faces), indicating diminished processing of high social value stimuli in BDs. However, the results of Folgueiras-Ares et al. (2017) –employing a memory paradigm instead of an attentional task- were not congruent with these findings as they reported absence of differences in N170 amplitude and increased amplitude in the vertex positive potential (VPP)(4), an ERP component also related to the processing of human faces.

Six studies –three from the same research group- tried to examine the attentional bias to alcohol stimuli. Petit et al. (2012, 2013, 2014b) used a visual oddball task with neutral pictures as standard stimuli and alcohol and non-alcohol-related pictures as target deviant stimuli. The first study (Petit et al., 2012) showed that in the BD group (n = 18; M_{age} = 21.3), alcoholic stimuli elicited larger P1 amplitude than non-alcoholic stimuli. This enhanced electrophysiological reactivity at early perceptual level was

considered an index of unconscious shift in attention (i.e. an attentional bias) toward alcohol pictures. Similarly, the study of Petit et al. (2013) showed that BDs (n = 29; $M_{age_females}$ = 21.9; M_{age_males} = 22.5) tended to elicit higher P3b amplitude to alcohol-related cues, which points again toward an enhanced motivational response to alcohol-related stimuli in these individuals. Finally, in order to explore the long-lasting influence of BD, Petit et al., (2014b) analyzed the alcohol attentional bias twice during a one-year period. The BD group (n = 15) displayed reduced P1 amplitude in the second (T2; M_{age} = 23.1) relative to the first (T1; M_{age} = 22.0) evaluation for both alcohol and non-alcohol-related cues, reflecting that the perpetuation of BD over one year may lead to a reduction in the mobilization of attentional resources towards visual information. Furthermore, non-alcoholic stimuli elicited lower P3b amplitude at T2 than in T1 only in the BD group, while P3b amplitudes in response to alcohol-related pictures remained identical. According to the authors, this non-reduction of P3b amplitudes to alcoholic stimuli would reflect the emergence of a bias in the processing of alcohol-related stimuli in youths with a BD pattern.

In the same vein, Ryerson et al. (2017) showed that BD was significantly associated with larger N1 amplitude to alcohol pictures but not to neutral ones, which was suggestive of increased attentional processing of alcohol-related stimuli. Recently, Blanco-Ramos et al. (2019) and Lannoy et al. (2020) also explored the attentional bias to alcoholic stimuli during a Go/NoGo task with alcoholic and non-alcoholic beverages. Contrarily to Petit et al. (2012), BDs did not reveal enhanced brain activity to alcohol pictures at the perceptual level (i.e., no differences regarding P1 amplitude).

Altogether, attention studies using neutral stimuli are not conclusive (as one of them observed reduced amplitudes in multiple ERP components including P3b, and the other two studies –conducted by the same research group- reported augmented P3b amplitude in BDs). Regarding the studies using alcohol-related stimuli, those that employed tasks designed to explore alcohol reactivity (4/6; 66.7%), revealed increased brain activity (greater attentional bias) for alcoholic images in BDs. Conversely, the two studies using inhibition tasks did not find significant differences; one explanation for this may be the use of tasks aiming at studying inhibitory processes instead of attentional ones. Additional studies exploring alcohol reactivity are still needed as three studies were conducted by the same group and another one only performed a correlational analysis.

2.4.6. Emotional Processing

Three studies explored the electrophysiological correlates linked to emotional processing in BDs. They used different tasks and all of them revealed alterations in BDs' brain activity (Huang et al., 2018; Lannoy et al., 2018; Maurage et al., 2009). Huang et al. (2018) used an emotional rating task and

analyzed the EEG signal in the time-frequency domain. High-BDs (n = 15; M_{age} = 23.2) displayed attenuated emotional modulation of event-related theta power and a weaker power in this frequency band to negative and positive pictures, when compared to light-drinkers. Furthermore, light-drinkers, contrary to high-BDs, exhibited higher theta power to emotional relative to neutral images. This was visible in early theta power (peaking at ~250ms), indicating that BDs may present difficulties in orientation of attention toward stimuli with emotional content, which could negatively influence the evaluation and integration of emotional and cognitive aspects of such stimuli.

In the study of Maurage et al. (2009), the participants were evaluated twice within a nine-month interval throughout an emotional valence judgment task. At the second session, BDs (n = 18; M_{age} = 18.2) revealed longer P1, N2 and P3b latency than controls (with no differences in terms of amplitude), suggesting that short-term BD, similarly to long-term alcoholism, was associated with a slowed cerebral activity during emotional processing.

Finally, Lannoy et al. (2018) employed an emotional crossmodal task requiring the identification of happiness and anger among three conditions (unimodal, crossmodal congruent, and crossmodal incongruent) and two modalities (visual and/or auditory). ERPs of early perceptual (P1 for visual and N1 for auditory), modality related (N170 for visual and N2 for auditory) and decisional (P3b) processes were analyzed. They found that while non-drinkers had longer N1 latency for happy versus anger voices, the BD group (n = 17; M_{age} = 20.2) presented no differences for this condition. This might suggest that the adaptive mechanism for processing anger quickly and with lower recruitment of resources seem to be diminished in BDs. Regarding later processes, BDs showed larger P3b amplitude for happy relative to anger faces during congruent trials, while non-drinkers and moderate drinkers did not show such differences. Consequently, BDs seem to benefit from different type of information (i.e. auditory and visual) and requiere more complex cognitive processes to more accurately discriminate emotional content. They also exhibited delayed P3b latency in comparison with moderate and non-drinkers, being suggestive of an impaired capacity to take advantage of crossmodal information. During incongruent trials, BDs displayed larger P3b amplitude than the other two groups, probably reflecting a neurocompensatory mechanism for emotional processing. Additionally, BDs seem to require more resources and take longer to integrate crossmodal information, which was indexed by delayed latency and increased amplitude in two frontal components (peaking between 150-260 ms and around 300-500 ms post-stimuli) during the processing of anger in incongruent trials.

Concluding, the studies exploring emotional processing –though scarce- suggest that BDs display difficulties in processing and directing attention toward visual and auditory information with emotional

cues (e.g. anger stimuli). Moreover, they seem to recruit more resources to properly process incongruent emotional stimuli (reflected as increased P3b amplitude), as well as to integrate incongruent emotional information (indexed by enhanced and slower frontal activity).

2.4.7. Working Memory

Working memory (WM) refers to the short-term maintenance and manipulation of information (Baddeley, 2001). Five studies –three from the same research group- examined the potential effects of BD on WM: four of them using n-back tasks and the fifth one using the Subsequent memory paradigm.

Crego et al. (2009) explored how BD affects brain functioning in college students during a visual identical-pairs continuous performance task, a paradigm similar to the one-back task, where participants are asked to maintain previous stimulus presentations actively in WM in order to detect whether the subsequent stimulus 'match' the previous one (Cornblatt et al., 1988; Shalev et al., 2011). In this study, BDs (n = 42; M_{age} = 18.9) displayed larger N2 amplitude for the matching stimuli in comparison with age-matched controls. Additionally, increased P3[11] amplitude was only observed in the control group for the matching when compared to the non-matching stimuli. The authors argued that the larger N2 amplitude observed in BDs was suggestive of higher allocation of attentional resources in order to be able to perform at successful/adequate levels. Furthermore, the absence of differences in the P3 amplitude between conditions in the BD group suggested a potential deficiency in the electrophysiological differentiation between relevant and irrelevant information.

Similar results were recently reported by Park and Kim (2018) using a modified spatial 2-back task which included congruent, incongruent, and lure conditions. Authors found enhanced P3 amplitude in BD (n = 25; M_{age} = 22.1) relative to control individuals, which might represent increased cognitive effort towards the classification and updating of information or in the allocation of attentional resources. Moreover, the non-BD group showed larger P3 amplitudes in response to the congruent stimuli compared to the incongruent and lure stimuli whereas the BD group did not differ significantly among the three conditions. Thus, similarly to Crego's et al study (2009), results suggested that BD individuals were less efficient in differentiating relevant and irrelevant stimuli due to difficulties in allocating attentional resources for relevant information.

Likewise, Schroder et al. (2019) used an n-back task with three conditions -control (N0), 2-back (N2) and 3-back (N3)- to compare the WM functioning of light-drinkers and BDs (n = 24; M_{age} = 24.0). To isolate the WM processes, they extracted difference waveforms by subtracting "N2 minus N0" and "N3 minus N0" for the P2/N2 complex, P3 and N400/P600 complex. Overall, young BDs exhibited a higher

processing intensity throughout the information-processing stream, reflected as increased P3 and P600[13] amplitude, while light drinkers displayed an increase in early visual attention (i.e. augmented P2 amplitude) in order to obtain a better memory trace (indicated by enlarged N400[12]). Again, and given that BDs performed the task at the same level as light drinkers, this increment in the neural resources can be interpreted as a compensation mechanism to perform at adequate levels in demanding tasks.

Conversely, Crego et al. (2010) observed lower amplitude in the late positive component (LPC[13] or P600) in BDs (n = 42; M_{age} = 18.9) relative to controls in the match condition of the identical-pairs continuous performance task. In this study, they combined both ERP and exact low-resolution brain electromagnetic tomography analysis (eLORETA). Results revealed that the reduced LPC was associated with a hypoactivation of the right anterior prefrontal cortex. According to the authors, these findings were indicative of functional alterations also in later stages of the cognitive processing stream such as recognition and self-monitoring of the WM process.

Folgueira-Ares et al. (2017) aimed to explore the brain activity during memory encoding using a Subsequent memory paradigm. This paradigm, which use a face–name pairs association task with subsequent memory testing, enables the evaluation of the *Difference due to memory effect* (Dm), an electrophysiological measure based on the comparison of the brain activity associated with subsequent successful and unsuccessful retrieval (Paller and Wagner, 2002). Contrary to controls, BDs (n = 25; M_{age} = 20.8) did not reveal a Dm effect, indicating a lack of electrophysiological differences between successful (subsequently remembered) and unsuccessful (subsequently forgotten) memory encoding.

Overall, findings seem to point to a number of electrophysiological anomalies linked to the performance of WM tasks in BDs, namely involvement of higher attentional/cognitive resources (as reflected by increased N2 and P3 amplitude), impaired differentiation between relevant and irrelevant information, as well as anomalous processing during memory encoding. However, results regarding later stages of WM have provided mixed evidence, so future studies will be needed to clarify the effects of BD on this cognitive process.

2.4.8. Cognitive Control

Cognitive control comprises a group of subprocesses, which recruit different regions of the prefrontal cortex (Miller, 2000). The goal-directed action selection, response execution/inhibition, performance monitoring, and reward-based learning are the main constituent processes of cognitive control (Ridderinkhof et al., 2004). Given that performance monitoring involves the adjustment of ongoing behavior in order to optimize subsequent performance (e.g. the execution and inhibition of a sequence of

responses), inhibitory control and performance monitoring are interrelated aspects of cognitive control (Chevrier et al., 2007; Verbruggen and Logan, 2008). As such, half of the studies exploring response inhibition in young BDs have also assessed ERP components linked to performance monitoring capacity.

2.4.8.1. Performance Monitoring. Successful goal-directed behavior involves not only correct selection and execution of a response but also the ability to flexibly adjust behavior when performance problems occur or the environment changes (Ullsperger et al., 2014). Performance monitoring, i.e. the ability to concurrently monitor and rapidly evaluate outcome of one's actions, plays a major role in everyday life by allowing behavioral adaptation in response to changing environment demands (Peterburs et al., 2015).

Potential impairments in performance monitoring associated with BD have been assessed in eight studies, four by the same research group. Seven of these studies pointed to abnormal neural activity in BDs in comparison with their control peers. Two studies used a Stop-Signal task (Smith and Mattick, 2013; Smith et al., 2016) to explore the Error-Related Negativity (ERN[8]) amplitude during successful and failed inhibition trials. Smith and Mattick (2013) compared two groups of females, BDs (n = 13; M_{age} = 20.0) and non-BDs, and observed lower ERN amplitude among the BD group, which might reflect difficulties in monitoring their ongoing performance. Smith et al. (2016) used the same sample of females and included a new sample of males (n = 21; M_{age} = 19.8). They also found – although marginally significant - decreased ERN (p = .06) in BDs when compared with controls, indicating that the electrophysiological alterations observed in the previous study probably are common markers of BD and not gender specific.

The ERN amplitude was also explored by Kim and Kim (2019) during a modified Flanker task (i.e. with higher level of difficulty) to assess error-monitoring mechanisms in female BDs. In the same line of Smith et al.'s results, female BDs (n = 25; M_{age} = 21.4) displayed a lower ERN amplitude when compared to non-BDs. This decreased ERN suggests that young females engaged in BD have an impaired capacity to automatically monitor errors, which may lead to difficulties in the adjustment of their internal performance. The authors also analyzed the error positivity (Pe[8]), but no significant effect of group was observed.

In contrast, Lannoy et al. (2017), using a Speeded Go/NoGo task, showed larger ERN amplitude during classical commission errors (false alarms) in comparison with slow hits (correct categorization that is performed beyond the response time) in BDs (n = 20; M_{age} = 20.3). According to the authors, BDs may have difficulties in judging their own errors as a failed response in NoGo trials (being reflected by the

recruitment of greater neural resources), and this impaired insight may in turn compromise the subsequent learning and adjustment processes. Furthermore, they exhibited a delayed Pe latency for slow hits compared to the control group, pointing to a slower error processing, i.e. BDs would need more time to adjust their behavior after a late response. Conversely, Smith et al., (2017a) used an error awareness task, where participants needed to signal the awareness of inhibitory errors on the subsequent trial. They also analyzed the Pe to explore conscious error detection and the ERN to assess early pre-conscious error detection. Despite BDs (n = 25; M_{age} = 22.2) had committed more inhibitory errors than controls, they exhibited no brain alterations when compared to controls, reflecting preserved error awareness.

Smith et al. (2015) explored the performance monitoring processes by an Eriksen Flanker task. The authors examined the conflict adaptation effect (a marker of well-adapted monitoring of ongoing performance) in RT, errors, and N2 amplitude and they observed a different pattern of results among females and males. While female BDs (n = 15; M_{age} = 21.0) exhibited larger conflict adaptation for N2 amplitude than the female controls, male BDs (n = 16; M_{age} = 23.0) showed decreased N2 amplitude and no differences in the conflict adaptation effect in comparison with the male controls. Once increased conflict adaptation is associated with efficient adaptive performance monitoring (Larson et al., 2014), this pattern of results may be suggestive of a compensatory response such that female BDs need to increase ongoing performance monitoring in order to achieve the same behavioral outcome as controls.

Likewise, Blanco-Ramos et al. (2019) analyzed the NoGo-N2 amplitude to assess conflict monitoring in BDs. As mentioned above, they employed a Go/NoGo task with alcohol and non-alcohol related pictures. The task has two conditions: the alcohol condition (Go-Alcohol), in which the Go stimuli were pictures of alcoholic drinks and the NoGo stimuli were pictures of non-alcoholic drinks; and the non-alcohol condition (Go-NoAlcohol) with the non-alcoholic drinks as Go stimuli. BDs (n = 71; age range: 18-19) revealed an enhanced NoGo-N2 amplitude for non-alcoholic than for alcoholic drinks. Considering the conflict monitoring theory, during the Go-Alcohol condition, alcoholic stimuli may turn the prepotent Go response more activated and thus increase the conflict between the prepotent response and its inhibition over NoGo trials (Blanco-Ramos et al., 2019). Consequently, this increased conflict leads BDs to recruit additional neural resources (as indexed by increased NoGo-N2) to successfully inhibit the primed (Go-Alcohol) response.

Performance monitoring is intimately linked to decision making and reward processing (Ullsperger and Cramon, 2004). Accordingly, some studies exploring performance monitoring used tasks that have decision making and reward sensitivity as underlying cognitive processes. As such, Lannoy et al. (2017)

examined the electrophysiological correlates linked to motivational (reward sensitivity) systems during performance monitoring, using the Balloon Analogue Risk Task. In this task participants are asked to pump a balloon in order to obtain a reward. This allowed them to explore the Feedback-Related Negativity (FRN[10]) and P3 waveforms. However, the results revealed intact feedback-related components in BDs (n = 20; M_{age} = 20.3).

The FRN amplitude was also explored in a recent study of Na et al. (2019) aiming at examining the early stages of feedback processing in female BDs. Specifically, they used a modified version of the original computerized Iowa Gambling Task (IGT) to analyze potential differences in the FRN amplitude between gain and loss feedback (ΔFRN). During IGT, participants were asked two choose one of four cards (two cards resulting in large immediate gains but greater long-term losses and two cards resulting in small immediate gains but reduced long-term losses) in order to earn as much money as possible over the task. The BD group (n = 27; M_{age} = 21.4) showed lower ΔFRN amplitudes than the non-BD group, revealing a deficit in early feedback evaluation, which may compromise their decision-making abilities and, consequently, lead them to choose more disadvantageous choices. Additionally, they analyzed ΔP3 (i.e. differences in the P3 amplitude between gain and loss feedback) and P3 amplitude to assess the late feedback processing as well as the allocation of attentional resources through top-down mechanisms; however, no group differences were observed in this component.

In sum, the enhanced N2 amplitude appears to support the idea that BDs need to recruit additional resources to compensate for potential neural anomalies/dysfunctions, in this case, during performance monitoring. Regarding ERN, BDs seem to exhibit decreased amplitude as reported by three of the five studies exploring this waveform. This reduced ERN may suggest that BDs have difficulties in automatically identify their errors, which could compromise their capacity to monitor/adapt their performance. However, studies are still required to give additional support to these findings.

2.4.8.2. Inhibitory control. Inhibitory control is crucial for behavior optimization as it enables the suppression and the control of inappropriate or impulsive responses and actions (Diamond, 2013; Ridderinkhof et al., 2004). This executive function allows people to regulate and adapt their behavior according to the demands of the surrounding environment and to long-term goals (Allom et al., 2016). Inhibitory control is particularly important in the study of BD, once its impairment may contribute to the maintenance of alcohol-seeking behavior (Field et al., 2010; López-Caneda et al., 2014a). In the present review, ten studies exploring inhibitory control were included (with a total of four different tasks) and seven of them reported electrophysiological alterations associated with BD. The studies by López-Caneda et al.

(2012, 2014b, 2017b) employed an equiprobably Go/NoGo task with two Go and two NoGo neutral stimuli. Results of the longitudinal study (López-Caneda et al., 2012) showed that BDs (n = 23; M_{age} = 18.8) displayed increased NoGo-P3 amplitude, which was associated with a greater activation of the right inferior frontal cortex. This enlarged activity linked to inhibitory control in BDs relative to controls was suggestive of the activation of additional neural mechanisms in order to compensate emerging functional alterations in the regions engaged in inhibition. Using part of the same sample and including an additional group of ex-BDs, López-Caneda et al. (2014b) observed that after maintaining a BD pattern for at least two years, BDs (n = 22; age range: 18-19) displayed significantly larger NoGo-P3 amplitude than controls, whereas ex-BDs (n = 10; age range: 18-19) were in an intermediate position between the two other groups (with no significant differences with respect to controls or BDs), suggesting that cessation of BD may act as a brake on the progression of the neurophysiological impairments related to response inhibition.

Similarly, the two studies of Smith et al.'s mentioned in the previous section (Smith et al., 2016; Smith and Mattick, 2013) also explored the P3 component for the successful and failed inhibition trials. The authors reported that females with a BD pattern showed lower P3 amplitude during failed inhibitions than the control ones, which together with the higher number of failed inhibitions may indicate that females engaged in BD have poorer inhibitory control than female controls (Smith and Mattick, 2013). Additionally, they displayed larger P3 amplitude during successful inhibition when compared with controls, suggesting that BDs need to trigger the inhibition process more strongly than controls to effectively inhibit their responses. Smith et al. (2016) also found a marginally significant successful > failed effect for the P3 amplitude (p = .08) in the BD group (i.e. females and males), suggesting that the neural abnormalities associated with inhibition presented in the previous study are common to both sexes. The other two studies conducted by this research group did not show alterations in BDs' brain activity relative to control individuals (Smith et al., 2015; Smith et al., 2017a).

Two studies used Go/NoGo tasks with alcoholic and non-alcoholic stimuli to explore how alcohol-related stimuli may modulate the inhibition of a prepotent response in BDs (Blanco-Ramos et al., 2019; Lannoy et al., 2020). Blanco-Ramos et al. (2019) analyzed the NoGo-P3 amplitude and the results showed larger amplitude in response to NoGo-NoAlcohol than in NoGo-Alcohol trials only in controls and female BDs. Conversely, male BDs did not show such differences. According to the authors, the absence of differences in male BDs suggests that the motivational value of the alcoholic stimuli may be interfering in their inhibitory processes. Using a similar task, Lannoy et al. (2020) observed that BDs (n= 25; M_{age} = 20.9) exhibited lower NoGo-N2 amplitude for alcoholic stimuli at left (F3) relative to right (F4) frontal sites, while non/light drinkers showed augmented NoGo-N2 amplitude. According to the authors' interpretation,

this reduced NoGo-N2 suggest that attentional/inhibitory processes of BDs may be impacted when alcohol cues are presented, which could be accounted for by an imbalance between the (underactivated) reflective system and the (overactivated) automatic system.

López-Caneda et al. (2017b) analyzed the Go-P3 and NoGo-P3 components and performed a time-frequency analysis to explore the brain oscillations linked to inhibition. Although BDs (n = 36; M_{age} = 18.1) did not show alterations in the ERP components, they exhibited reduced theta and beta power in comparison with the control group in the NoGo condition. These results were in line with those reported in studies with abstinent chronic alcoholics (e.g. Colrain et al., 2011; Pandey et al., 2016) and they are suggestive of dysfunctions in the oscillatory activity linked to response inhibition. Recently, Holcomb et al. (2019) has also reported decreased power in theta and early beta frequency bands during NoGo trials in BDs (n = 29; M_{age} = 23.4) when compared to low drinkers. The attenuated theta power may be suggestive of impaired top-down mechanisms involved in IC processes.

Taken together, BDs seem to present abnormal neural activity related to inhibitory control. More specifically, they show enhanced brain activity to successfully inhibit their responses. This overactivation likely reflects a neurocompensatory mechanism that allow BDs to counteract for an underlying deficit resulting from excessive alcohol drinking. Furthermore, these deficits in inhibitory control seem to be also supported by decreased oscillatory activity, particularly reduced theta power. Finally, additional studies exploring inhibitory control mechanisms with alcoholic and non-alcoholic stimuli are still needed to clarify the results of the two studies conducted so far.

2.4.9. Other Cognitive Functions

Some of the studies included in this review investigated the neural adversities of BD through tasks involving time perception, verbal episodic memory and risk-taking reactivity.

Bauer and Ceballos (2014) used a motor time estimation task and the results showed that frequent BDs (n = 42; M_{age} = 19.4) displayed an augmented (i.e. more negative) Slow Potential amplitude than the infrequent BDs. According to the authors, the enhanced Slow Potential observed in females with frequent episodes of BD seems to reflect a compensatory overactivation of the neural circuit responsible for time estimation (a region involving the right posterior parietal cortex).

Verbal episodic memory was explored by Smith et al. (2017b) during a modified version of the Rey Auditory Verbal Learning Task (RAVLT). They used a visual presentation modality of the words and examined the ERPs in the recall phase (P185), for remembered and not remembered words, and in the recognition phase (N340 and P540). While there were no behavioral differences neither in the recall nor

in the recognition phase, BDs (n = 39; $M_{age_females}$ = 20.0; M_{age_males} = 19.7) exhibited increased amplitude of the P540 waveform -an index of recollection also known as the classical parietal old/new effect (Rugg and Curran, 2007)- relative to drug-naïve controls, suggesting a greater need for recollection-based recognition during task execution in BDs.

Finally, Kiat and Cheadle (2018) assessed decision-free risk-reactivity as a function of BD frequency levels using the Crocodile Dentist task, a risk-taking game that allows the identification of *raw* risk-taking reactivity (i.e. isolated from decision making processes). Results revealed larger increase in the amplitude of the Late Positive Potential –a waveform equivalent to the P3 component- as participants transitioned from low- to high-risk levels of BD, suggesting enhanced risk-taking reactivity in individuals who are involved in excessive drinking.

2.4.10. Alcohol variables and ERPs

Nearby half of the studies of the present review (16/34; 47.1%) assessed whether a number of alcohol use variables were associated with electrophysiological dysfunctions. These variables were mainly related to the age of drinking onset and the quantity and intensity of drinking, such as speed of alcohol consumption, weekly amount of alcohol use, number of BD episodes and AUDIT score (see supplementary material for detailed results).

Overall, the results reported might reveal that different alcohol use variables are associated with some of the neural abnormalities observed in BDs. As such, though correlation-type analyzes should be carefully interpreted, results suggest that early onset of (regular) drinking could increase the vulnerability to display abnormal brain activity (e.g. enhanced P1 and P3 amplitude, slower spontaneous alpha peak frequency; Affan et al., 2018; Blanco-Ramos et al., 2019; López-Caneda et al, 2013, 2014b). Further, increased amounts of alcohol consumption as well as faster and hazardous drinking may enhance the susceptibility to exhibit disrupted neural activation during cognitive functioning and even at rest. Specifically, greater intensity and quantity of drinking was associated with enhanced neural activity during attentional and inhibitory processes (i.e. increased P3 amplitude; López-Caneda et al., 2013, 2014b; Smith and Mattick, 2013), performance monitoring (i.e., larger N2 amplitude; Blanco-Ramos et al., 2019; Smith et al., 2015), attention to alcohol-related information (i.e. higher P1 amplitude; Petit et al., 2012; 2014b) and during resting-state (i.e. greater theta power; Affan et al., 2018). Some studies showed, in turn, that more hazardous drinking was predictive of decreased electrophysiological activity during early pre-conscious error detection processes (as indexed by reduced ERN amplitude; Kim & Kim, 2019; Smith and Mattick, 2013) and during response inhibition (reflected by decreased theta power; Holcomb et al.,

2019). Four studies conducted regression analysis with alcohol-related variables and EEG measures (Blanco-Ramos et al., 2019; López-Caneda et al., 2014b; Petit et al., 2014b; Smith et al., 2016). Two of them found that alcohol quantity and drinking intensity as well as age of drinking onset may predict brain abnormalities in response inhibition, namely the recruitment of larger neural resources (i.e. increased NoGo-N2 and NoGo-P3; Blanco-Ramos et al., 2019; López-Caneda et al., 2014b).

2.4.11. Sex-related effects

The majority of the studies reviewed (23/34; 67.6%) explored differences between males and females. However, only five of them found dissimilar patterns of neural activity between sexes (Blanco-Ramos et al., 2019; Courtney and Polich, 2010; Petit et al., 2013; Smith et al., 2015, 2016).

In the study of Courtney and Polich (2010), during passive viewing, female BDs displayed an augmented power in delta, theta, and slow- and fast-beta bands relative to males, which may be caused by an increased sensitivity to high amounts of alcohol in females than males. Further, as mentioned above, female and male BDs presented an opposite pattern of results in the study of Smith et al. (2015), with females showing more affected EEG signal during performance monitoring. Similarly, Smith et al. (2016) only showed significant differences between BDs and controls in P3 latency in females, who revealed delayed P3 latency for failed relative to successful inhibitions.

Conversely, Petit et al. (2013) found that alcoholic stimuli evoked larger P3 amplitude in comparison with non-alcoholic stimuli only in male BDs. The results suggest that, contrary to females, males have an attentional bias to alcohol-related information. Likewise, as previously reported in the study by Blanco-Ramos et al. (2019), male BDs, unlike to females, revealed alterations in the neural activity associated with inhibitory control processes during a context of predominant alcoholic stimuli.

Overall, only five of the 23 studies exploring sex-related differences revealed a differential response between males and females. In addition, results from these five studies have provide mixed evidence, as three of them reported more pronounced abnormalities in female BDs, while the other two informed of electrophysiological anomalies only in BD males. In conclusion, results do not seem to support specific gender vulnerabilities to the effects of BD, at least at the electrophysiological level.

2.4.12. Behavioral Performance

The impact of BD on the behavioral performance was explored by 29 of the 31 studies (the remaining three studies analyzed the brain activity at rest). Remarkably, only seven of these 29 studies (24.1%) – four from the same research group - showed significant differences between BDs and non/low

drinkers during tasks involving inhibitory control, performance monitoring and verbal episodic memory (Kim and Kim, 2019; Lannoy et al., 2020; Na et al., 2019; Smith and Mattick, 2013; Smith et al., 2016, 2017a, 2017b).

According to these studies, BDs exhibited poor response inhibition ability in comparison with controls, being reflected by longer stop-signal reaction times (Smith and Mattick, 2013; Smith et al., 2016) and greater number of commission errors (to NoGo Stimuli) during an error awareness task (Smith et al., 2017a). Also, BDs showed poorer inhibition performance for explicit than implicit processing of alcohol-related information (Lannoy et al., 2020). Female BDs also exhibited more errors and shorter RT than non-BDs in a Flanker task, suggesting an impaired capacity to monitor their errors effectively and, consequently, adjust their performance (Kim and Kim, 2019). In the study of Na et al. (2019), females BDs presented a lower total net score in the IGT when compared to non-BDs, reflecting more disadvantageous choices. While non-BDs performance improved over the task, BDs persistently chose cards with more immediate gains even at greater potential risks. Therefore, according to the authors, young BD females seem to have deficits in decision-making, probably due to difficulties in adjusting their performance according to the goal underlying the task (i.e. maximize their profit) or a higher reward sensitivity. Concerning verbal episodic memory, BDs showed poor delayed recall in comparison with controls (Smith et al., 2017b).

Concluding, 22 out of 29 studies analyzing behavioral performance reported absence of significant differences between BDs and their control peers.

2.5. Discussion

The present work systematically reviewed the EEG signatures associated with a BD pattern in adolescents and young adults and provided a qualitative synthesis of the literature. Thirty-four studies fulfilled the inclusion criteria, including 28 ERPs studies, two EROs studies, one study examining both ERPs and EROs, and three resting-state EEG studies. Thirteen of the 29 ERP studies (44.8%) pointed to enhanced brain activity (i.e. increased ERP amplitude) in BDs when compared with non/low drinkers. In contrast, six of them (20.7%) found a reduced electrophysiological signal in BDs and ten studies (34.5%) found significant ERP differences between conditions (e.g. alcohol/non-alcohol stimuli, remembered/forgotten items) only in one group[1]. Finally, only three studies (10.3%) showed no differences in the ERP amplitude between groups nor between conditions (see supplementary Figure A.1).

[1] It should be noted that three studies reported both significant differences between groups (two revealing decreased amplitude in BDs and one increased amplitude in this group) and between conditions, and thus they are counted twice.

Regarding latencies, only four studies out of 29 (13.8%) found significant between-groups differences, with BDs exhibiting delayed latencies. All the EROs studies found reduced oscillatory brain activity in BDs when compared to controls, namely lower theta and beta power. Conversely, the three studies exploring resting-state reported augmented spontaneous EEG signal in young BDs.

2.5.1. The Compensation and Continuum Hypotheses

Considering the results highlighted in this review, the most solid electrophysiological finding is the augmented P3 amplitude observed in tasks involving attention, working memory and response inhibition, which could constitute an early biomarker for BD. Indeed, eight studies (34.8%) analyzing between-groups differences and three studies exploring between-conditions differences (13.0%) –i.e., a total of 47.8% of the 23 studies examining P3 –reported increased amplitude in this component in the BD group –in contrast to a single study (4.3%) reporting reduced P3 amplitude. This enlarged P3 has generally been interpreted in terms of a neurocompensatory mechanism enabling BDs to perform the tasks on par with their control peers.

Compensation is usually defined as a brain overactivation accompanied by a satisfactory level of functioning, i.e., an excess of neural activity not seen in the comparison group and associated with normal-level performance (Chanraud & Sullivan, 2014). Concordant with this approach, the findings reported here fall in line with the *neurocompensation* hypothesis, suggesting that BDs need to reallocate neural resources to compensate for an underlying neural deficit, which would allow them to successfully perform the task. In this sense, in the present review 13 studies showed enlarged electrophysiological activity (not only reflected in the P3 component, but also in other waveforms such as VPP, N2 or P600) in BDs when directly compared to control peers. Twelve of these studies compared the behavioral performance between groups and most of them (11/12; 91.7%) did not find significant between-groups differences. Conversely, from the seven studies reporting poor performance in the BD group, in five of them (71.4%) BDs displayed reduced ERPs amplitude relative to non/low drinkers. Collectively, these results suggest that compensation –in the form of increased neural activity/recruitment- may play an important role at least at the initial stages of BD. This proposal is in accordance with several neuroimaging studies which have showed enhanced activity in different brain areas in BDs when compared to controls, with no alterations in task performance (Brumback et al., 2015; Campanella et al., 2013; Correas et al., 2020; Molnar et al., 2018; Squeglia et al., 2011; Suárez-Suárez et al., 2020; Wetherill et al., 2013).

On the other hand, young BDs also seem to exhibit some neural alterations similar to those observed in alcohol-dependent individuals, which brings support to the proposition postulating that BD

and alcohol use disorder (AUD) are two successive steps of the same phenomenon –proposal known as the *continuum hypothesis* (Enoch, 2006; Lannoy et al., 2019). The suggestion that BD and AUD may lead to qualitatively analogous impairments is reinforced by several findings synthesized in the present review. First, resembling the typical cerebral hyperexcitability during resting states observed in alcoholics (Rangaswamy and Porjesz, 2014; Rangaswamy et al., 2002, 2003; Mumtaz et al., 2017), BDs also exhibited increased brain activity at rest, both in slow waves (primarily in the theta band) and fast waves (beta band) (Affan et al., 2018; Courtney and Polich, 2010; López-Caneda et al., 2017a). Despite the genesis of these anomalies has not been totally clarified yet, it has been suggested that this hyperexcitability may be due to an excitatory-inhibitory disequilibrium of the central nervous system (CNS) (Courtney and Polich, 2010; Porjesz and Begleiter, 2003). Given that alcohol acts as a CNS depressant, mainly reducing the glutamatergic excitatory neurotransmission and increasing the GABAergic inhibitory activity, repetitive heavy alcohol intake leads to adaptive changes (allostasis) resulting in downregulated GABA-mediated inhibition and upregulated glutamate-excitatory function (Abrahao et al., 2018; Roberto and Varodayan, 2017). When alcohol is withdrawn (for instance, during a period of abstinence), a rebound effect known as the *kindling* effect –and characterized by excessive brain excitability- occurs, which may result in brain damage (Becker, 1998; Stephens and Duka, 2008). Although BD is not associated with withdrawal symptoms as noticeable as those reported in alcoholics, the frequent alternation between excessive drinking episodes and abstinence might induce a kindling process leading to brain hyperexcitability. However, given that this brain overactivation has also been seen prior to the onset of alcohol drinking –e.g., in offspring of alcoholics (Kamarajan, 2019; Rangaswamy et al., 2004)-, the question of whether these impairments are present before the beginning of the excessive alcohol use or result from the neurotoxic effects of this substance still needs to be addressed through additional research.

Secondly, besides the increased resting (tonic) oscillations –mostly in the theta and beta bands- reported in both BDs and AUD individuals, decreased "active" (phasic) oscillations have also been observed in both groups –particularly in the theta band- during emotional/cognitive tasks (Correas et al., 2019; Kamarajan et al., 2004; Pandey et al., 2016; Holcomb et al., 2019; Huang et al., 2018; López-Caneda et al., 2017b). Again, these similarities between BDs and AUDs dovetail with the idea that BD may lead to consequences analogue to those of AUD, a thesis already pointed out by some neuropsychological studies (e.g., Sanhueza et al., 2011). In addition, these findings strengthen the notion that ERO measures –which contains not only brain oscillations not rigidly time- and phase-locked to the stimulus, but also nonphase-locked EEG activity (Pfurtscheller and Lopes da Silva, 1999)- may provide

additional information on brain functioning and thereby be more sensitive than the ERPs. However, further research analyzing EROs in the BD population are required to determine whether these anomalies are also mirrored in other cognitive processes (e.g., conflict monitoring, working memory).

Finally, another additional support to the *continuum* between BD and AUD is the augmented neural reactivity to alcoholic cues reported in both BDs and alcohol-dependent individuals. As such, several EEG studies indicate that the alcohol cue-reactivity typically observed in AUDs (Herrmann et al., 2000; Namkoong et al., 2004) is also present in young heavy and binge drinkers (Bartholow et al., 2007; Herrmann et al., 2001; Petit et al., 2012, 2013; Ryerson et al., 2017). Consistent with these findings, neuroimaging data have revealed amplified brain responses to alcohol cues in both BDs (Brumback et al., 2015) and AUDs (Huang et al., 2018; Tapert et al., 2004). This high motivational reactivity to alcohol-related cues deserves special attention in the initial stages of BD –or even before the transition to BD (Dager et al., 2013)-, as it is strongly related to craving (Bollen et al., 2020; Flaudias et al., 2019) and thus may greatly contribute to the perpetuation and/or escalation of alcohol consumption (Field and Eastwood, 2005; Manchery et al., 2017). Indeed, this evidence becomes even more worrying when the impairments in inhibitory control reported by EEG (Smith and Mattick, 2013; Smith et al., 2017a) and neuropsychological (Bø et al., 2016; Czapla et al., 2015) studies in young BDs are taken into consideration. The combination of altered inhibitory control together with augmented reactivity to alcoholic stimuli may constitute a risk factor for the escalation towards alcohol dependence. Accordingly, future studies should strengthen the research on the interplay of inhibition and alcohol bias, for example through still unexplored functions such as memory inhibition (López-Caneda et al., 2019b) or via neurocognitive stimulation (Dormal et al., 2020). Indeed, examining the extent to which BDs or individuals at early stages of alcohol abuse may have difficulties to inhibit alcohol-related information could hold important clinical implications.

Globally, the results reported in this systematic review appear to support both the compensation and the continuum hypothesis (see Figure 9). Thus, young BDs seem to display a similar profile as that of alcohol-dependent subjects in activities that require low cognitive effort, such as resting states or during visualization of alcohol pictures. Conversely, during tasks demanding a high involvement of cognitive resources, BDs would need to activate additional brain regions to counteract underpinning neural decline and to maintain performance. However, giving that some studies have also showed decreased electrophysiological activity in BDs during performance of cognitive tasks, one question that remains to be addressed is which impairments are compensated for –and for how long- and which ones not.

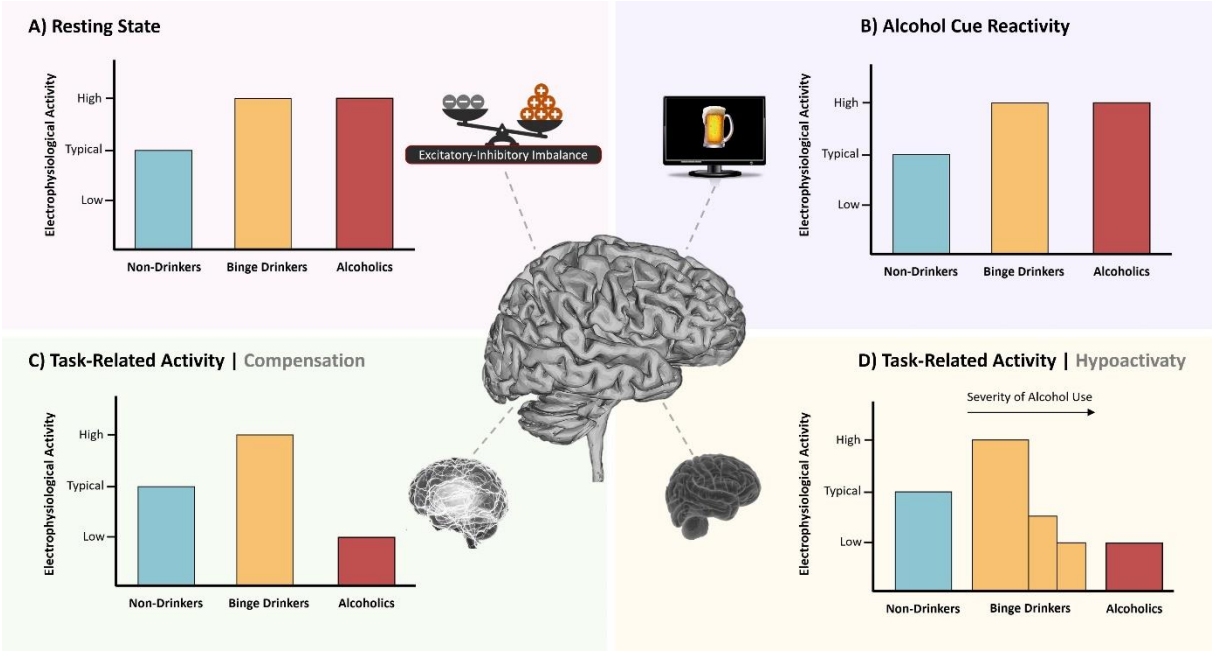
The preliminary findings from studies exploring performance monitoring suggest that BDs exhibit electrophysiological deficits (indexed as reduced ERN/FRN amplitude) during more automatic or even low demanding processes of error/feedback detection instead of during more cognitively demanding tasks. Noteworthy, this abnormal neural activity may underlie difficulties in monitoring internal behavior as most of the studies showing decreased ERN and FRN also reported the commission of more errors and poorer behavioral outcomes in BDs (Kim and Kim, 2019; Na et al., 2019; Smith and Mattick, 2013; Smith et al., 2016). Electrophysiological studies exploring acute alcohol consumption are consistent with these findings, also showing diminished ERN (Bailey et al. 2014; Bartholow et al. 2012; Easdon et al. 2005). Likewise, alcoholics (Kamarajan et al., 2010) and individuals with high family history density of alcohol problems (Fein and Chang, 2008) revealed reduced amplitude in feedback/outcome related negativity components. However, BD studies exploring conflict monitoring processes using experimental paradigms requiring greater cognitive resources –including a speeded Go/NoGo task, a beverage (alcoholic/non-alcoholic) Go/NoGo task, and a Stroop Go/NoGo task (Blanco-Ramos et al., 2019; Lannoy et al., 2017; Smith et al., 2017a) have failed to show alterations in the amplitude of ERN or N2 in BDs when directly compared to controls. Despite further replication is needed, this evidence may suggest that some electrophysiological deficits (e.g., decreased ERN) might remain hidden when a high allocation of resources is required (since BDs would be trying to compensate the underlying neural deficit), whereas in tasks lacking such behavioral difficulty these ERP anomalies would be apparent. Of course, this assumption deserves additional research, particularly because the question as to why other cognitive processes (e.g., working memory, inhibition) do not show this pattern of results remains elusive.

In this sense, besides the cognitive demands, other factors may underlie the apparent discrepancies between some studies, including the task characteristics/complexity (e.g., simple geometric stimuli *vs* faces processing in the attentional paradigms), or the sample composition/features –as the number of total standard alcoholic drinks per week might range from 7.3 to 42.9 drinks within the various BD profiles. Thus, it is possible that the P3 and other ERP components may vary from decreased to increased amplitude as a function of the consumption severity, showing the high-BDs an electrophysiological profile relatively equivalent to that of alcohol-dependent individuals (i.e. reduced neural activity) –as both displayed similar levels of alcohol consumption. Otherwise, BDs with lower alcohol use would still be able to compensate for the alcohol-related damage, thereby displaying increased neural activity. Accordingly, while BD studies reporting smaller amounts of alcohol consumed per drinking occasion (i.e., from 21 g to 56 g of alcohol) showed augmented brain activity (Crego et al., 2009; López-Caneda et al., 2012; Schroder et al., 2019), other studies where BDs drank larger amounts of alcohol

per occasion (i.e., from 81 g to 132 g of alcohol) revealed decreased brain activity (Lannoy et al., 2020; Maurage et al., 2012). However, this proposal clearly deserves further investigation, particularly with studies comparing BDs and AUD patients. Likewise, the absence, not only of a unified criterion to define BD (see below), but also of standardized measures to quantify alcohol use –e.g., no. of drinks per occasion (not reported in 35% of the studies) or no. of drinks per week (not reported in 59% of the studies)- makes it hard to extract reliable conclusions between the levels of alcohol use and the direction (increase *vs* decrease) of EEG activity.

Figure 9

Schematic depiction of the similarities and differences in the electroencephalographic (EEG) profile of binge drinkers (BDs) and alcohol-dependent individuals.



Note. Young BDs seem to display a similar profile as that of alcohol-dependent subjects during (A) resting state, and (B) visualization of alcohol-related pictures. Bottom left (C), representation of the brain overactivation observed in BDs during some cognitive tasks –accompanied by a satisfactory level of performance- presumably related to a neurocompensatory mechanism. Bottom right (D), illustration of how BDs' electrophysiological activity resembles that of alcoholics as the severity of alcohol use is sustained and/or increases over time.

2.5.2. Brain Functional Abnormalities – Cause or Consequence of BD?

It is important to note that some of the neurofunctional anomalies referred here might antecede the onset of the BD habits and not be a direct consequence of excessive alcohol use. As such, several neuroimaging studies have found abnormal brain functioning before the beginning of BD (Jones et al.,

2016; Norman et al., 2011; Squeglia et al., 2012; Wetherill et al., 2013), reflecting predisposing neural risk markers for excessive alcohol use. However, new anomalies associated with the onset and maintenance of BD seemed in turn to emerge years later (Squeglia et al., 2012; Wetherill et al., 2013). Thus, the pattern of results obtained from fMRI studies appear to point to both directions: 1) to a distinctive neural activity profile prior to the onset of alcohol drinking (i.e., reduced activity in frontoparietal regions), which may represent a predisposition to engage in future BD; and 2) to anomalies in brain function emerging as a consequence of BD, indexed by increased activity in frontoparietal regions once the BD pattern has been initiated.

With regard to ERP studies, reduced P3 amplitude has frequently been observed in offspring of alcoholics as well as in individuals with high risk for developing AUD, both prior to any alcohol exposure (Campanella et al., 2009; Fein and Chang, 2006; Holguín et al., 1999). These findings have led to the hypothesis that the low P3 amplitude may precede (and constitute a risk for) development of AUD, rather than being a consequence of alcohol abuse (Kamarajan, 2019; Perlman et al., 2009; Porjesz et al., 2005). Similarly to neuroimaging studies, both assumptions (cause *vs* consequence) are not mutually exclusive. Longitudinal evidence available concerning BD, although scarce, seem to point to a worsening and/or emergence of neurophysiological abnormalities with the maintenance or transition to this pattern (López-Caneda et al., 2012, 2013; Maurage et al., 2009; Petit et al., 2014b). Additionally, the fact that the age of drinking onset and the main variables defining BD (quantity, frequency and intensity of alcohol use) are correlated with the amplitude values of several ERP components (Affan et al., 2018; Blanco-Ramos et al., 2019; Holcomb et al., 2019; Kim & Kim, 2019; López-Caneda et al, 2013, 2014b; Petit et al., 2012; 2014b; Smith and Mattick, 2013; Smith et al., 2015), gives additional support the notion that certain alterations in brain function may constitute a consequence of the BD pattern. Of course, this does not rule out the hypothesis that some EEG anomalies may precede –and thus constitute markers of susceptibility for- BD. Unfortunately, to the best of our knowledge only one ERP study has assessed BDs before they started their drinking habits, and no significant electrophysiological differences were observed between groups (future BDs and non-BDs) at baseline (Maurage et al., 2009). Hence, despite that neuroimaging studies and EEG research in high-risk populations suggest that certain neurofunctional anomalies may precede alcohol consumption, the evidence to date does not allow to establish a clear EEG/ERP endophenotype of BD. Future longitudinal studies are thereby needed to disentangle potential risk markers for future BD from consequences of alcohol use.

In a related vein, the lack of longitudinal studies also precludes us to reliably determine the potential impairments caused by the perpetuation of BD or to conclude whether these impairments are cumulative

over the years. The recovery after BD clearly deserves further attention, as the only EEG study conducted suggested that the cessation of BD may act as a brake on electrophysiological impairments (López-Caneda et al., 2014b). Additional support for these observations comes from neuropsychological studies (Carbia et al., 2017a, 2017b; Mota et al., 2013; Winward et al., 2014a, 2014b) and a neuroimaging study (Brumback et al., 2015), demonstrating that abandoning the BD pattern may –at least partially- mitigate some of the alcohol-related dysfunctions. However, studies remain scarce and thus additional research should focus on this important and relatively unexplored topic.

2.5.3. EEG Signatures – The Role of Gender

The present systematic review also sheds light on the electrophysiological dissimilarities between sexes. As such, most of the studies (78.3%) failed to find significant differences in the EEG profile between male and female BDs. These results are consistent with those reported in a recent systematic review concerning neuropsychological studies in this population, where 70.6% of the studies did not identify sex-related differences (Carbia et al., 2018). Nevertheless, given that most of the studies did not report the drinking characteristics of females and males separately, it is difficult to conclude whether the absence of gender differences is due to the fact of females consuming fewer amounts of alcohol than males –which is common for the BD pattern (SAMHSA, 2018)- or if, indeed, there are no real differences at the neural level between male and female BDs. Thus, it would be helpful that the studies exploring sex-related differences describe the gender-specific drinking characteristics to better determine the effects of BD on males and females. In conclusion, and even with these limitations, the results suggest that both males and females are equally affected by BD (at least) at the electrophysiological level.

2.5.4. Methodological Considerations

Even though there has been a growing effort in recent years to understand the electrophysiological impact of BD, some methodological aspects represent a challenge to draw strong conclusions on this topic. For instance, most investigations were conducted by a few number of research groups, as 88.2% of the studies were carried out by only five research teams –with the Spanish and Belgian groups accounting for around 55.9% of all the studies. Consequently, there is a need for a broad replication.

Throughout the quality assessment of the papers, we observed that several studies did not clearly consider the consumption of other drugs (including cannabis; 13/34; 38.2%) and the family history of alcoholism (16/34; 47.1%). The lack of control over these variables might significantly impact the results (and therefore their interpretation), as it is known that both are associated with anomalies in

electrophysiological activity as well as in cognitive functioning (Crean et al., 2011; Kamarajan, 2019; Park and Schepp, 2015; Smith et al., 2014). Thus, future studies should clearly define the specific type and amount of drug used –if polydrug use is not an exclusion criterion- and include it in the models, as well as to control for the family history of drug abuse.

Additionally, the absence of a consensual BD conceptualization has led to excessive variability in experimental group selection and alcohol consumption evaluation (Maurage et al., 2020). As such, while most of the studies (25/34; 73.5%) have followed the NIAAA's BD definition for the quantity of alcohol use in a single occasion (5/4 alcoholic drinks), variability increase for speed and frequency of consumption –the latter not specified by the NIAAA. Indeed, some studies did not consider the intensity criterion defined by the NIAAA ("5/4 drinks in about 2h") and not all used the same frequency criterion. Half of the studies (50%) considered at least one episode in the past month, but others classified BDs as having at least one episode in the last week (e.g. Petit et al. 2012), in the last two weeks (e.g. Park and Kim, 2018), in the last six months (e.g. Courtney and Polich, 2010) or even did not refer any frequency criterion (e.g. Ryerson et al., 2017) (see Table 2). Consequently, the levels of alcohol use in the BD groups differ greatly across studies, which may have led to different results and might explain some of the discrepancies observed among the studies. These disparities undoubtedly constrain between-studies comparisons as well as the unified interpretation of the findings and place the focus on the need for targeting efforts in the search for a consensus on the definition of BD –considering (at least) the quantity, intensity and frequency criteria.

2.5.5. Clinical Implications

The present synthesis of the EEG signatures associated with BD could help to understand the processes underlying the transition from this pattern of excessive alcohol use to alcohol dependence. In this sense, some EEG correlates might constitute useful biological markers of cognitive and behavioral characteristics in alcohol dependence.

Evidence has shown that the persistence of binge alcohol consumption and/or alcohol abuse may lead to an abnormal bottom-up system (e.g., increased neural reactivity to alcohol-related cues) resulting in automatic action-tendencies to approach alcohol and craving (Herrmann et al., 2001; Schacht et al., 2012; Wiers et al., 2010; 2015). Furthermore, an impaired top-down cognitive control system –commonly observed in individuals with AUD- could also emerge if the BD pattern is maintained, as young BDs might not be able to compensate for the alcohol-related damage (Lannoy et al., 2019; López-Caneda et al., 2014a). Altogether, this imbalance between the automatic (bottom-up) and reflective (top-down) systems

may entail difficulties in the capacity to control alcohol drinking, resulting in the maintenance and/or escalation of the pattern (Peeters et al., 2012).

These findings highlight the importance of the EEG technique for understanding BD and indicate possible routes for prevention and intervention programs aiming at reducing alcohol misuse and mitigating potential detrimental effects on the brain and other organs. Indeed, EEG measures provide critical information that otherwise would not be apparent from psychological or behavioral assessments; for instance, in predicting (and preventing) relapse in alcohol-dependent patients (Campanella et al., 2019; Petit et al., 2015). Importantly, as ERPs have revealed a high sensitivity to change –e.g. along the treatment process (Campanella et al., 2020; Houston et al., 2018)-, they also constitute a valuable tool for monitoring interindividual alterations (Jurado-Barba et al., 2020). EEG assessment may also help to detect specific neurocognitive deficits associated with BD and to assist with cognitive stimulation (e.g., via cognitive training or by transcranial electrical stimulation), which might in turn facilitate early recovery before progression of these abnormalities, even in the absence of behavioral alterations (Di Lemma et al., 2020; Dormal et al., 2020).

2.5.6. Conclusion

Overall, the current literature suggests that BDs exhibit abnormal EEG signal during both cognitive performance and resting-state conditions. The most solid electrophysiological finding is the augmented P3 amplitude observed in tasks involving attention, working memory and response inhibition, which could constitute an early biomarker for BD. Accordingly, the increased neural activity during cognitive performance suggests the recruitment of additional resources to perform the task at adequate/successful levels, which supports the *neurocompensation hypothesis*. In contrast, BDs' EEG profile also resembles that of alcohol-dependent individuals in some paradigms, as they exhibited augmented spontaneous EEG signal at rest, increased reactivity to alcoholic cues, and reduced activity during error detection, which provides in turn additional support to the *continuum hypothesis* –suggesting that BD and alcohol dependence may share several common features.

Furthermore, the evidence collected in this review does not support the assumption that young females are particularly vulnerable to the effects of BD, at least at the electrophysiological level. Forthcoming studies should explore further those cognitive functions that have barely been assessed so far (e.g. verbal episodic memory, short- and long-term memory, emotional processing, and decision making), since results –although limited- point to neural alterations associated with the BD pattern.

2.6. References

Abrahao, K. P., Salinas, A. G., & Lovinger, D. M. (2017). Alcohol and the brain: neuronal molecular targets, synapses, and circuits. Neuron. 96, 1223-1238. https://doi.org/10.1016/j.neuron.2017.10.032

Affan, R. O., Huang, S., Cruz, S. M., Holcomb, L. A., Nguyen, E., & Marinkovic, K. (2018). High-intensity binge drinking is associated with alterations in spontaneous neural oscillations in young adults. Alcohol. 70, 51-60. https://doi.org/10.1016/j.alcohol.2018.01.002

Ahmed, K. M., & Al Dhubaib, B. (2011). Zotero: A bibliographic assistant to researcher. J. Pharm. Pharmacol. 2, 303-305. https://doi.org/10.4103/0976-500X.85940

Allom, V., Mullan, B., & Hagger, M. (2016). Does inhibitory control training improve health behavior? A meta-analysis. Health Psychol. Rev. 10, 168-186. https://doi.org/10.1080/17437199.2015.1051078

Baddeley, A., Chincotta, D., & Adlam, A. (2001). Working memory and the control of action: Evidence from task switching. J. Exp. Psychol. Gen. 130, 641. https://doi.org/10.1037//0096-3445.130.4.641

Bailey, K., Bartholow, B. D., Saults, J. S., & Lust, S. A. (2014). Give me just a little more time: Effects of alcohol on the failure and recovery of cognitive control. *J. Abnorm. Psychol. 123*, 152–167. https://doi.org/10.1037/a0035662

Bauer, L. O., & Ceballos, N. A. (2014). Neural and genetic correlates of binge drinking among college women. Biol. Psychol. 97, 43-48. https://doi.org/10.1016/j.biopsycho.2014.01.005

Bartholow, B. D., Henry, E. A., & Lust, S. A. (2007). Effects of alcohol sensitivity on P3 event-related potential reactivity to alcohol cues. Psychol. Addict. Behav. 21, 555. https://doi.org/10.1037/0893-164X.21.4.555

Bartholow, B. D., Henry, E. A., Lust, S. A., Saults, J. S., & Wood, P. K. (2012). Alcohol effects on performance monitoring and adjustment: Affect modulation and impairment of evaluative cognitive control. *J. Abnorm. Psychol. 121*, 173–186. https://doi.org/10.1037/a0023664

Bava, S., Tapert, S.F. (2010). Adolescent brain development and the risk for alcohol and other drug problems. Neuropsychol. Rev. 20, 398–413. http://dx.doi.org/10.1007/ s11065-010-9146-6.

Becker, H. C. (1998). Kindling in alcohol withdrawal. Alcohol Health Res. World, 22, 25.

Bernardin, F., Maheut-Bosser, A., & Paille, F. (2014). Cognitive impairments in alcohol-dependent subjects. Front. Psychiatry. 5, 78. https://doi.org/10.3389/fpsyt.2014.00078

Blakemore, S. J. (2012). Imaging brain development: the adolescent brain. Neuroimage. 61, 397-406. https://doi.org/10.1016/j.neuroimage.2011.11.080

Blanco-Ramos, J., Cadaveira, F., Folgueira-Ares, R., Corral, M., & Rodríguez Holguín, S. (2019). Electrophysiological correlates of an alcohol-cued go/nogo task: a dual-process approach to binge drinking in university students. Int. J. Environ. Res. Public Health. 16, 4550. https://doi.org/10.3390/ijerph16224550

Bledowski, C., Prvulovic, D., Goebel, R., Zanella, F. E., & Linden, D. E. (2004). Attentional systems in target and distractor processing: a combined ERP and fMRI study. Neuroimage. 22, 530-540. https://doi.org/10.1016/j.neuroimage.2003.12.034

Boelema, S. R., Harakeh, Z., Ormel, J., Hartman, C. A., Vollebergh, W. A., & van Zandvoort, M. J. (2014). Executive functioning shows differential maturation from early to late adolescence: Longitudinal findings from a TRAILS study. Neuropsychology. 28, 177. https://doi.org/10.1037/neu0000049

Bø, R., Billieux, J., & Landrø, N. I. (2016). Which facets of impulsivity predict binge drinking?. Addict. Behav. Rep. 3, 43-47. https://doi.org/10.1016/j.abrep.2016.03.001

Bollen, Z., Masson, N., Salvaggio, S., D'Hondt, F., & Maurage, P. (2020). Craving is everything: An eye-tracking exploration of attentional bias in binge drinking. J. Psychopharmacol. 34, 636-647. https://doi.org/10.1177/0269881120913131

Bonomo, Y. A., Bowes, G., Coffey, C., Carlin, J. B., & Patton, G. C. (2004). Teenage drinking and the onset of alcohol dependence: a cohort study over seven years. Addict. 99, 1520-1528. https://doi.org/10.1111/j.1360-0443.2004.00846.x

Brion, M., Pitel, A. L., & D'Hondt, F. (2016). New Perspectives in the Exploration of Korsakoff's Syndrome: The Usefulness of Neurophysiological Markers. Front. Psychol. 7, 168. https://doi.org/10.3389/fpsyg.2016.00168

Brumback, T., Squeglia, L. M., Jacobus, J., Pulido, C., Tapert, S. F., & Brown, S. A. (2015). Adolescent heavy drinkers' amplified brain responses to alcohol cues decrease over one month of abstinence. Addict. Behav. 46, 45-52. https://doi.org/10.1016/j.addbeh.2015.03.001

Campanella, S. (2013). Why it is time to develop the use of cognitive event-related potentials in the treatment of psychiatric diseases. Neuropsychiatr. Dis. Treat. 9, 1835. https://doi.org/10.2147/NDT.S53687

Campanella, S., Peigneux, P., Petit, G., Lallemand, F., Saeremans, M., Noël, X., ... & Ward, R. (2013). Increased cortical activity in binge drinkers during working memory task: a preliminary assessment through a functional magnetic resonance imaging study. PLOS ONE. 8. https://doi.org/10.1371/journal.pone.0062260

Campanella, S., Petit, G., Maurage, P., Kornreich, C., Verbanck, P., & Noël, X. (2009). Chronic alcoholism: insights from neurophysiology. Clin. Neurophysiol. 39, 191-207. https://doi.org/10.1016/j.neucli.2009.08.002

Campanella, S., Schroder, E., Kajosch, H., Hanak, C., Veeser, J., Amiot, M., ... & Kornreich, C. (2020). Neurophysiological markers of cue reactivity and inhibition subtend a three-month period of complete alcohol abstinence. Clin. Neurophysiol. 131, 555-565. https://doi.org/10.1016/j.clinph.2019.10.020

Campanella, S., Schroder, E., Kajosch, H., Noel, X., & Kornreich, C. (2019). Why cognitive event-related potentials (ERPs) should have a role in the management of alcohol disorders. Neurosci. Biobehav. Rev. 106, 234-244. https://doi.org/10.1016/j.neubiorev.2018.06.016

Carbia, C., Cadaveira, F., Caamano-Isorna, F., Rodriguez-Holguin, S., & Corral, M. (2017a). Binge drinking during adolescence and young adulthood is associated with deficits in verbal episodic memory. PLOS ONE. 12. https://doi.org/10.1371/journal.pone.0171393

Carbia, C., Cadaveira, F., López-Caneda, E., Caamaño-Isorna, F., Holguín, S. R., & Corral, M. (2017b). Working memory over a six-year period in young binge drinkers. Alcohol. 61, 17-23. https://doi.org/10.1016/j.alcohol.2017.01.013

Carbia, C., López-Caneda, E., Corral, M., & Cadaveira, F. (2018). A systematic review of neuropsychological studies involving young binge drinkers. Neurosci. Biobehav. Rev. 90, 332-349. https://doi.org/10.1016/j.neubiorev.2018.04.013

Chanraud, S., & Sullivan, E. V. (2014). Compensatory recruitment of neural resources in chronic alcoholism. In Handbook of clinical neurology (Vol. 125, pp. 369-380). Elsevier.

Chevrier, A. D., Noseworthy, M. D., & Schachar, R. (2007). Dissociation of response inhibition and performance monitoring in the stop signal task using event-related fMRI. Hum. Brain Mapp. 28, 1347-1358.

Colrain, I. M., Sullivan, E. V., Ford, J. M., Mathalon, D. H., McPherson, S. L., Roach, B. J., ... & Pfefferbaum, A. (2011). Frontally mediated inhibitory processing and white matter microstructure: age and alcoholism effects. Psychopharmacology. 213, 669-679. https://doi.org/10.1007/s00213-010-2073-7

Cornblatt, B. A., Risch, N. J., Faris, G., Friedman, D., & Erlenmeyer-Kimling, L. (1988). The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. Psychiatry Res. 26, 223-238. https://doi.org/10.1016/0165-1781(88)90076-5

Courtney, K. E., & Polich, J. (2010). Binge drinking effects on EEG in young adult humans. Int. J. Environ. Res. Public Health. 7, 2325-2336. https://doi.org/10.3390/ijerph7052325

Correas, A., Cuesta, P., Rosen, B. Q., Maestu, F., & Marinkovic, K. (2020). Compensatory neuroadaptation to binge drinking: Human evidence for allostasis. Addict. Biol. e12960. https://doi.org/10.1111/adb.12960

Correas, Á., López-Caneda, E., Beaton, L., Rodríguez Holguín, S., García-Moreno, L. M., Antón-Toro, L. F., ... & Marinkovic, K. (2019). Decreased event-related theta power and phase-synchrony in young binge drinkers during target detection: An anatomically-constrained MEG approach. J. Psychopharmacol. 33, 335-346. https://doi.org/10.1177/0269881118805498

Crean, R. D., Crane, N. A., & Mason, B. J. (2011). An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J. of Addiction Medicine. 5, 1. https://doi.org/10.1097/ADM.0b013e31820c23fa

Crego, A., Cadaveira, F., Parada, M., Corral, M., Caamaño-Isorna, F., & Holguín, S. R. (2012). Increased amplitude of P3 event-related potential in young binge drinkers. Alcohol. 46, 415-425. https://doi.org/10.1016/j.alcohol.2011.10.002

Crego, A., Holguín, S. R., Parada, M., Mota, N., Corral, M., & Cadaveira, F. (2009). Binge drinking affects attentional and visual working memory processing in young university students. Alcohol. Clin. Exp. Res. 33, 1870-1879. https://doi.org/10.1111/j.1530-0277.2009.01025.x

Crego, A., Rodriguez-Holguín, S., Parada, M., Mota, N., Corral, M., & Cadaveira, F. (2010). Reduced anterior prefrontal cortex activation in young binge drinkers during a visual working memory task. Drug Alcohol Depend. 109, 45-56. https://doi.org/10.1016/j.drugalcdep.2009.11.020

Crone, E.A., Ridderinkhof, K.R. (2011). The developing brain: from theory to neuroimaging and back. Dev. Cogn. Neurosci. 1, 101–109. http://dx.doi.org/10.1016/j.dcn. 2010.12.001.

Cservenka, A., & Brumback, T. (2017). The burden of binge and heavy drinking on the brain: effects on adolescent and young adult neural structure and function. Front. Psychol. 8, 1111. https://doi.org/10.3389/fpsyg.2017.01111

Czapla, M., Simon, J. J., Friederich, H. C., Herpertz, S. C., Zimmermann, P., & Loeber, S. (2015). Is binge drinking in young adults associated with an alcohol-specific impairment of response inhibition?. Eur. Addict. Res. 21, 105-113. https://doi.org/10.1159/000367939

Dager, A. D., Anderson, B. M., Stevens, M. C., Pulido, C., Rosen, R., Jiantonio-Kelly, R. E., ... & Wood, R. M. (2013). Influence of alcohol use and family history of alcoholism on neural response to alcohol cues in college drinkers. Alcohol.: Clin. Exp. Res. 37, E161-E171. https://doi.org/10.1111/j.1530-0277.2012.01879.x

Diamond, A. (2013). Executive functions. Annual Rev. of Psychology. 64, 135-168.

Di Lemma, L. C., Stancak, A., Soto, V., Fallon, N., & Field, M. (2020). Event-related and readiness potentials when preparing to approach and avoid alcohol cues following cue avoidance training in heavy drinkers. Psychopharmacology. 1-16. https://doi.org/10.1007/s00213-020-05462-7

Doallo, S., Cadaveira, F., Corral, M., Mota, N., López-Caneda, E., & Holguín, S. R. (2014). Larger mid-dorsolateral prefrontal gray matter volume in young binge drinkers revealed by voxel-based morphometry. PLOS ONE. 9. https://doi.org/10.1371/journal.pone.0096380

Dormal, V., Lannoy, S., Bollen, Z., D'Hondt, F., & Maurage, P. (2020). Can we boost attention and inhibition in binge drinking? Electrophysiological impact of neurocognitive stimulation. Psychopharmacology. 1-13. https://doi.org/10.1007/s00213-020-05475-2

Dormal, V., Lannoy, S., & Maurage, P. (2019). Impact of exchange stay on alcohol consumption: longitudinal exploration in a large sample of European students. Alcohol. Clin. Exp. Res. 43, 1220-1224. https://doi.org/10.1111/acer.14028

Easdon, C., Izenberg, A., Armilio, M. L., Yu, H., & Alain, C. (2005). Alcohol consumption impairs stimulus- and error-related processing during a Go/No-Go Task. Cogn. Brain Res. 25, 873-883. https://doi.org/10.1016/j.cogbrainres.2005.09.009

Enoch, M. A. (2006). Genetic and environmental influences on the development of alcoholism: resilience vs. risk. Ann. N. Y. Acad. Sci. 1094, 193-201. https://doi.org/10.1196/annals.1376.019

Eurobarometer S. (2010). EU Citizens' Attitudes Towards Alcohol. Brussels: European Commission. Retrieved from http://ec.europa.eu/public_opinion/archives/ebs/ebs_ 331_en.pdf

Fein, G., & Chang, M. (2006). Visual P300s in long-term abstinent chronic alcoholics. Alcohol.: Clin. Exp. Res. 30, 2000-2007. https://doi.org/10.1111/j.1530-0277.2006.00246.x

Fein, G., & Chang, M. (2008). Smaller feedback ERN amplitudes during the BART are associated with a greater family history density of alcohol problems in treatment-naive alcoholics. Drug Alcohol Depend. 92, 141-148. https://doi.org/10.1016/j.drugalcdep.2007.07.017

Field, M., & Eastwood, B. (2005). Experimental manipulation of attentional bias increases the motivation to drink alcohol. Psychopharmacology. 183, 350-357. https://doi.org/10.1007/s00213-005-0202-5

Field, M., Wiers, R. W., Christiansen, P., Fillmore, M. T., & Verster, J. C. (2010). Acute alcohol effects on inhibitory control and implicit cognition: implications for loss of control over drinking. Alcohol. Clin. Exp. Res. 34, 1346-1352. https://doi.org/10.1111/j.1530-0277.2010.01218.x

Flaudias, V., Heeren, A., Brousse, G., & Maurage, P. (2019). Toward a triadic approach to craving in addictive disorders: the metacognitive Hub Model. Harvard Rev. of Psychiatry. 27, 326-331. 10.1097/HRP.0000000000000225

Folgueira-Ares, R., Cadaveira, F., Rodríguez Holguín, S., López-Caneda, E., Crego, A., & Pazo-Álvarez, P. (2017). electrophysiological anomalies in Face–name Memory encoding in Young Binge Drinkers. Front. Psychiatry. 8, 216. https://doi.org/10.3389/fpsyt.2017.00216

Folstein, J. R., & Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: a review. Psychophysiology. 45, 152-170. https://doi.org/10.1111/j.1469-8986.2007.00602.x

Fuhrmann, D., Knoll, L. J., & Blakemore, S. J. (2015). Adolescence as a sensitive period of brain development. Trends Cogn. Sci. 19, 558-566. https://doi.org/10.1016/j.tics.2015.07.008

Herrmann, M. J., Weijers, H. G., Wiesbeck, G. A., Aranda, D., Böning, J., & Fallgatter, A. J. (2000). Event-related potentials and cue-reactivity in alcoholism. Alcohol.: Clin. Exp. Res. 24, 1724-1729. https://doi.org/10.1111/j.1530-0277.2000.tb01974.x

Herrmann, M. J., Weijers, H. G., Wiesbeck, G. A., Böning, J., & Fallgatter, A. J. (2001). Alcohol cue-reactivity in heavy and light social drinkers as revealed by event-related potentials. Alcohol Alcohol. 36, 588-593. https://doi.org/10.1093/alcalc/36.6.588

Holcomb, L. A., Huang, S., Cruz, S. M., & Marinkovic, K. (2019). Neural oscillatory dynamics of inhibitory control in young adult binge drinkers. Biol. Psychol. 146, 107732. https://doi.org/10.1016/j.biopsycho.2019.107732

Holguín, S. R., Porjesz, B., Chorlian, D. B., Polich, J., & Begleiter, H. (1999). Visual P3a in male subjects at high risk for alcoholism. Biological Psychiatry. 46, 281-291. Biol. Psychiatry. https://doi.org/10.1016/S0006-3223(98)00247-9

Howell, N. A., Worbe, Y., Lange, I., Tait, R., Irvine, M., Banca, P., ... & Voon, V. (2013). Increased ventral striatal volume in college-aged binge drinkers. PLOS ONE. 8. https://doi.org/10.1371/journal.pone.0074164

Houston, R. J., & Schlienz, N. J. (2018). Event-related potentials as biomarkers of behavior change mechanisms in substance use disorder treatment. Biol Psychiatry Cogn Neurosci Neuroimaging. 3, 30-40. https://doi.org/10.1016/j.bpsc.2017.09.006

Huang, S., Holcomb, L. A., Cruz, S. M., & Marinkovic, K. (2018). Altered oscillatory brain dynamics of emotional processing in young binge drinkers. Cogn. Affect. Behav. Neurosci. 18, 43-57. https://doi.org/10.3758/s13415-017-0551-7

Jones, S. A., Cservenka, A., & Nagel, B. J. (2016). Binge drinking impacts dorsal striatal response during decision making in adolescents. Neuroimage. 129, 378-388. https://doi.org/10.1016/j.neuroimage.2016.01.044

Jones, S. A., Lueras, J. M., & Nagel, B. J. (2018). Effects of binge drinking on the developing brain: studies in humans. Alcohol Res. Health. 39, 87.

Jurado-Barba, R., Sion, A., Martínez-Maldonado, A., Domínguez-Centeno, I., Prieto-Montalvo, J., Navarrete, F., ... & Rubio, G. (2020). Neuropsychophysiological Measures of Alcohol Dependence: Can We Use EEG in the Clinical Assessment?. Front. Psychiatry. 11. https://doi.org/10.3389/fpsyt.2020.00676

Kamarajan, C. (2019). Brain Electrophysiological Signatures in Human Alcoholism and Risk. Neuroscience of Alcohol (pp. 119-130). Academic Press. https://doi.org/10.1016/B978-0-12-813125-1.00013-1

Kamarajan, C., Porjesz, B., Jones, K. A., Choi, K., Chorlian, D. B., Padmanabhapillai, A., ... & Begleiter, H. (2004). The role of brain oscillations as functional correlates of cognitive systems: a study of frontal inhibitory control in alcoholism. Int. J. Psychophysiol, 51, 155-180. https://doi.org/10.1016/j.ijpsycho.2003.09.004

Kamarajan, C., Rangaswamy, M., Tang, Y., Chorlian, D. B., Pandey, A. K., Roopesh, B. N., ... & Porjesz, B. (2010). Dysfunctional reward processing in male alcoholics: an ERP study during a gambling task. J. Psychiatr. Res. 44, 576-590. https://doi.org/10.1016/j.jpsychires.2009.11.019

Katsuki, F., & Constantinidis, C. (2013). Bottom-up and top-down attention: different processes and overlapping neural systems. Neuroscientist. 20, 509-521. https://doi.org/10.1177/1073858413514136

Kiat, J. E., & Cheadle, J. E. (2018). Tick–tock goes the croc: a high-density EEG study of risk-reactivity and binge-drinking. Soc. Cogn. Affect. Neurosci. 13, 656-663. https://doi.org/10.1093/scan/nsy038

Kim, E. H., & Kim, M. S. (2019). An event-related potential study of error-monitoring deficits in female college students who participate in binge drinking. Clin. Psychopharmacol Neurosci. 17, 80. https://doi.org/10.9758/cpn.2019.17.1.80

Kraus, L., Guttormsson, U., Leifman, H., Arpa, S., Molinaro, S., Monshouwer, K., et al. (2016). ESPAD Report 2015. Results from the European School Survey Project on Alcohol and Other Drugs. Lisbon: European Monitoring Centre for Drugs and Drug Addiction and the European School Survey Project on Alcohol and Other Drugs. Available online at: http://www.espad.org/sites/espad.org/files/ESPAD_report_2015.pdf

Kvamme, T. L., Schmidt, C., Strelchuk, D., Chang-Webb, Y. C., Baek, K., & Voon, V. (2015). Sexually dimorphic brain volume interaction in college-aged binge drinkers. Neuroimage Clin. 10, 310-317. https://doi.org/10.1016/j.nicl.2015.12.004

Lannoy, S., Billieux, J., Dormal, V., & Maurage, P. (2019). Behavioral and cerebral impairments associated with binge drinking in youth: A critical review. Psychol. Belg. 59, 116. https://doi.org/10.5334/pb.476

Lannoy, S., Billieux, J., & Maurage, P. (2014). Beyond inhibition: A dual-process perspective to renew the exploration of binge drinking. Front. Hum. Neurosci., 8, 405. https://doi.org/10.3389/fnhum.2014.00405

Lannoy, S., Dormal, V., Billieux, J., Brion, M., D'Hondt, F., & Maurage, P. (2020). A dual-process exploration of binge drinking: Evidence through behavioral and electrophysiological findings. Addict. Biol. 25, 1-10. https://doi.org/10.1111/adb.12685

Lannoy, S., D'hondt, F., Dormal, V., Billieux, J., & Maurage, P. (2017). Electrophysiological correlates of performance monitoring in binge drinking: Impaired error-related but preserved feedback processing. Clin. Neurophysiol. 128, 2110-2121. https://doi.org/10.1016/j.clinph.2017.08.005

Lannoy, S., D'Hondt, F., Dormal, V., Blanco, M., Brion, M., Billieux, J., ... & Maurage, P. (2018). Electrophysiological correlates of emotional crossmodal processing in binge drinking. Cogn. Affect. Behav. Neurosci. 18, 1076-1088. https://doi.org/10.3758/s13415-018-0623-3

Larson, M. J., Clayson, P. E., & Clawson, A. (2014). Making sense of all the conflict: a theoretical review and critique of conflict-related ERPs. Int. J. Psychophysiol. 93, 283-297. https://doi.org/10.1016/j.ijpsycho.2014.06.007

Lees, B., Mewton, L., Stapinski, L. A., Squeglia, L. M., Rae, C. D., & Teesson, M. (2019). Neurobiological and cognitive profile of young binge drinkers: a systematic review and meta-analysis. Neuropsychol. Rev. 1-29. https://doi.org/10.1007/s11065-019-09411-w

López-Caneda, E., Cadaveira, F., & Campanella, S. (2019a). Binge drinking in the adolescent and young brain. Front. Psychol. 9, 2724. https://doi.org/10.3389/fpsyg.2018.02724

López-Caneda, E., Cadaveira, F., Correas, A., Crego, A., Maestú, F., & Rodríguez Holguín, S. (2017a). The brain of binge drinkers at rest: alterations in theta and beta oscillations in first-year college students with a binge drinking pattern. Front. Behav. Neurosci. 11, 168. https://doi.org/10.3389/fnbeh.2017.00168

López-Caneda, E., Cadaveira, F., Crego, A., Doallo, S., Corral, M., Gómez-Suárez, A., & Rodríguez Holguín, S. (2013). Effects of a persistent binge drinking pattern of alcohol consumption in young people: a follow-up study using event-related potentials. Alcohol and Alcohol. 48, 464-471. https://doi.org/10.1093/alcalc/agt046

López-Caneda, E., Cadaveira, F., Crego, A., Gómez-Suárez, A., Corral, M., Parada, M., ... & Rodríguez Holguín, S. (2012). Hyperactivation of right inferior frontal cortex in young binge drinkers during response inhibition: a follow-up study. Addiction. 107, 1796-1808. doi:10.1111/j.1360-0443.2012.03908.x

López-Caneda, E., Crego, A., Campos, A.D., González-Villar, A., & Sampaio, A (2019b). The Think/No-Think Alcohol Task: A New Paradigm for Assessing Memory Suppression in Alcohol-Related Contexts. (2019b). Alcohol. Clin. Exp. Res. 43, 36-47. https://doi.org/10.1111/acer.13916

López-Caneda, E., Holguín, S. R., Cadaveira, F., Corral, M., & Doallo, S. (2014a). Impact of alcohol use on inhibitory control (and vice versa) during adolescence and young adulthood: a review. Alcohol and Alcohol. 49, 173-181. https://doi.org/10.1093/alcalc/agt168

López-Caneda, E., Holguín, S. R., Corral, M., Doallo, S., & Cadaveira, F. (2014b). Evolution of the binge drinking pattern in college students: Neurophysiological correlates. Alcohol. 48, 407-418. https://doi.org/10.1016/j.alcohol.2014.01.009

López-Caneda, E., Holguín, S. R., Correas, Á., Carbia, C., González-Villar, A., Maestú, F., & Cadaveira, F. (2017b). Binge drinking affects brain oscillations linked to motor inhibition and execution. J. Psychopharmacol. 31, 873-882. https://doi.org/10.1177/0269881116689258

Luck, S. J. (2014). An introduction to the event-related potential technique. MIT press.

Luna, B., Marek, S., Larsen, B., Tervo-Clemmens, B., & Chahal, R. (2015). An integrative model of the maturation of cognitive control. Annu. Rev. Neurosci. 38, 151-170.

Manchery, L., Yarmush, D. E., Luehring-Jones, P., & Erblich, J. (2017). Attentional bias to alcohol stimuli predicts elevated cue-induced craving in young adult social drinkers. Addict. Behav. 70, 14-17. https://doi.org/10.1016/j.addbeh.2017.01.035

Maurage, P., Joassin, F., Speth, A., Modave, J., Philippot, P., & Campanella, S. (2012). Cerebral effects of binge drinking: respective influences of global alcohol intake and consumption pattern. Clin. Neurophysiol. 123, 892-901. https://doi.org/10.1016/j.clinph.2011.09.018

Maurage, P., Pesenti, M., Philippot, P., Joassin, F., & Campanella, S. (2009). Latent deleterious effects of binge drinking over a short period of time revealed only by electrophysiological measures. J. Psychiatry Neurosci. 34, 111.

McHugh, M. L. (2012). Interrater reliability: the kappa statistic. Biochem. Med. 22, 276-282. Retrieved from https://hrcak.srce.hr/89395

McCambridge, J., McAlaney, J., & Rowe, R. (2011). Adult consequences of late adolescent alcohol consumption: a systematic review of cohort studies. PLoS Med. 8, e1000413. https://doi.org/10.1371/journal.pmed.1000413

McCarty, C. A., Ebel, B. E., Garrison, M. M., DiGiuseppe, D. L., Christakis, D. A., & Rivara, F. P. (2004). Continuity of binge and harmful drinking from late adolescence to early adulthood. Pediatrics. 114, 714-719. https://doi.org/10.1542/peds.2003-0864-L

Miller, E. K. (2000). The prefontral cortex and cognitive control. Nat. Rev. Neurosci. 1, 59-65. https://doi.org/10.1038/35036228

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4. http://dx.doi.org/10. 1186/2046-4053-4-1.

Molnar, S. M., Beaton, L. E., Happer, J. P., Holcomb, L. A., Huang, S., Arienzo, D., & Marinkovic, K. (2018). Behavioral and brain activity indices of cognitive control deficits in binge drinkers. Brain Sci. 8, 9. https://doi.org/10.3390/brainsci8010009

Mota, N., Parada, M., Crego, A., Doallo, S., Caamaño-Isorna, F., Holguín, S. R., ... & Corral, M. (2013). Binge drinking trajectory and neuropsychological functioning among university students: a longitudinal study. Drug Alcohol Depend. 133, 108-114. https://doi.org/10.1016/j.drugalcdep.2013.05.024

Morris, L. S., Dowell, N. G., Cercignani, M., Harrison, N. A., & Voon, V. (2018). Binge drinking differentially affects cortical and subcortical microstructure. Addict. Biol. 23, 403-411. https://doi.org/10.1111/adb.12493

Mumtaz, W., Vuong, P. L., Xia, L., Malik, A. S., & Rashid, R. B. A. (2017). An EEG-based machine learning method to screen alcohol use disorder. Cogn. Neurodyn. 11, 161-171. https://doi.org/10.1007/s11571-016-9416-y

Na, E., Jang, K. M., & Kim, M. S. (2019). An event-related potential study of decision-making and feedback utilization in female college students who binge drink. Front. Psychol. 10. https://doi.org/10.3389/fpsyg.2019.02606

Namkoong, K., Lee, E., Lee, C. H., Lee, B. O., & An, S. K. (2004). Increased P3 amplitudes induced by alcohol-related pictures in patients with alcohol dependence. Alcohol.: Clin. Exp. Res. 28, 1317-1323. https://doi.org/10.1097/01.ALC.0000139828.78099.69

National Heart, Lung, and Blood Institute (NHLBI), 2014. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Available at: National Heart, Lung, and Blood Institute, Bethesda, MD. https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort.

National Institute of Alcohol Abuse and Alcoholism (2004). NIAAA Council Approves Definition of Binge Drinking. NIAAA Newsletter, 3. Available online at: https://pubs.niaaa.nih.gov/publications/Newsletter/winter2004/Newsletter_Number3.pdf

National Institute of Alcohol Abuse and Alcoholism (2020). College Drinking [Fact Sheet]. Available online at: https://pubs.niaaa.nih.gov/publications/CollegeFactSheet/CollegeFactSheet.pdf

Norman, A. L., Pulido, C., Squeglia, L. M., Spadoni, A. D., Paulus, M. P., & Tapert, S. F. (2011). Neural activation during inhibition predicts initiation of substance use in adolescence. Drug Alcohol Depend. 119, 216-223. https://doi.org/10.1016/j.drugalcdep.2011.06.019

Paller, K. A., & Wagner, A. D. (2002). Observing the transformation of experience into memory. Trends Cogn. Sci. 6, 93-102. https://doi.org/10.1016/S1364-6613(00)01845-3

Pandey, A. K., Kamarajan, C., Manz, N., Chorlian, D. B., Stimus, A., & Porjesz, B. (2016). Delta, theta, and alpha event-related oscillations in alcoholics during Go/NoGo task: Neurocognitive deficits in execution, inhibition, and attention processing. Prog. Neuropsychopharmacol. Biol. Psychiatry. 65, 158-171. https://doi.org/10.1016/j.pnpbp.2015.10.002

Park, S., & Kim, M. S. (2018). An event-related potential study of spatial working memory in binge drinking college students. PLOS ONE. 13. https://doi.org/10.1371/journal.pone.0203696

Park, S., & Schepp, K. G. (2015). A systematic review of research on children of alcoholics: Their inherent resilience and vulnerability. J. Child Fam. Stud. 24, 1222-1231. https://doi.org/10.1007/s10826-014-9930-7

Parsons, O. A. (1998). Neurocognitive deficits in alcoholics and social drinkers: a continuum?. Alcohol. Clin. Exp. Res. 22, 954-961. https://doi.org/10.1111/j.1530-0277.1998.tb03895.x

Patrick, M. E., Terry-McElrath, Y. M., Kloska, D. D., & Schulenberg, J. E. (2016). High-intensity drinking among young adults in the United States: Prevalence, frequency, and developmental change. Alcohol. Clin. Exp. Res. 40, 1905-1912. https://doi.org/10.1111/acer.13164

Peeters, M., Wiers, R. W., Monshouwer, K., van de Schoot, R., Janssen, T., & Vollebergh, W. A. (2012). Automatic processes in at-risk adolescents: the role of alcohol-approach tendencies and response inhibition in drinking behavior. Addiction. 107, 1939-1946. https://doi.org/10.1111/j.1360-0443.2012.03948.x

Perlman, G., Johnson, W., & Iacono, W. G. (2009). The heritability of P300 amplitude in 18-year-olds is robust to adolescent alcohol use. Psychophysiology. 46, 962-969. https://doi.org/10.1111/j.1469-8986.2009.00850.x

Peterburs, J., Thürling, M., Rustemeier, M., Göricke, S., Suchan, B., Timmann, D., & Bellebaum, C. (2015). A cerebellar role in performance monitoring–Evidence from EEG and voxel-based morphometry in patients with cerebellar degenerative disease. Neuropsychologia. 68, 139-147. https://doi.org/10.1016/j.neuropsychologia.2015.01.017

Petit, G., Cimochowska, A., Cevallos, C., Cheron, G., Kornreich, C., Hanak, C., ... & Campanella, S. (2015). Reduced processing of alcohol cues predicts abstinence in recently detoxified alcoholic patients in a three-month follow up period: An ERP study. Behav. Brain Res. 282, 84-94. https://doi.org/10.1016/j.bbr.2014.12.057

Petit, G., Maurage, P., Kornreich, C., Verbanck, P., & Campanella, S. (2014a). Binge drinking in adolescents: a review of neurophysiological and neuroimaging research. Alcohol and Alcohol. 49, 198-206. https://doi.org/10.1093/alcalc/agt172

Petit, G., Kornreich, C., Dan, B., Verbanck, P., & Campanella, S. (2014b). Electrophysiological correlates of alcohol-and non-alcohol-related stimuli processing in binge drinkers: A follow-up study. J. Psychopharmacol. 28, 1041-1052. https://doi.org/10.1177/0269881114545663

Petit, G., Kornreich, C., Maurage, P., Noël, X., Letesson, C., Verbanck, P., & Campanella, S. (2012). Early attentional modulation by alcohol-related cues in young binge drinkers: an event-related potentials study. Clin. Neurophysiol. 123, 925-936. https://doi.org/10.1016/j.clinph.2011.10.042

Petit, G., Kornreich, C., Verbanck, P., & Campanella, S. (2013). Gender differences in reactivity to alcohol cues in binge drinkers: A preliminary assessment of event-related potentials. Psychiatry Res. 209, 494-503. https://doi.org/10.1016/j.psychres.2013.04.005

Pfurtscheller, G., & Da Silva, F. L. (1999). Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin. Neurophysiol. 110, 1842-1857. https://doi.org/10.1016/S1388-2457(99)00141-8

Porjesz, B., & Begleiter, H. (2003). Alcoholism and human electrophysiology. Alcohol Res Health. 27, 153.

Porjesz, B., Rangaswamy, M., Kamarajan, C., Jones, K. A., Padmanabhapillai, A., & Begleiter, H. (2005). The utility of neurophysiological markers in the study of alcoholism. Clin. Neurophysiol. 116, 993-1018. https://doi.org/10.1016/j.clinph.2004.12.016

Rangaswamy, M., Jones, K. A., Porjesz, B., Chorlian, D. B., Padmanabhapillai, A., Kamarajan, C., ... & Schuckit, M. A. (2007). Delta and theta oscillations as risk markers in adolescent offspring of alcoholics. Int. J. Psychophysiol. 63, 3-15. https://doi.org/10.1016/j.ijpsycho.2006.10.003

Rangaswamy, M., & Porjesz, B. (2014). Understanding alcohol use disorders with neuroelectrophysiology. In Handbook of clinical neurology (Vol. 125, pp. 383-414). Elsevier. https://doi.org/10.1016/B978-0-444-62619-6.00023-9

Rangaswamy, M., Porjesz, B., Chorlian, D. B., Wang, K., Jones, K. A., Bauer, L. O., ... & Begleiter, H. (2002). Beta power in the EEG of alcoholics. Biol. Psychiatry. 52, 831-842. https://doi.org/10.1016/S0006-3223(02)01362-8

Rangaswamy, M., Porjesz, B., Chorlian, D. B., Wang, K., Jones, K. A., Kuperman, S., ... & Begleiter, H. (2004). Resting EEG in offspring of male alcoholics: beta frequencies. Int. J. Psychophysiol. 51, 239-251. https://doi.org/10.1016/j.ijpsycho.2003.09.003

Rangaswamy, M., Porjesz, B., Chorlian, D. B., Choi, K., Jones, K. A., Wang, K., ... & Begleiter, H. (2003). Theta power in the EEG of alcoholics. Alcohol. Clin. Exp. Res. 27, 607-615. https://doi.org/10.1111/j.1530-0277.2003.tb04397.x

Ridderinkhof, K. R., Van Den Wildenberg, W. P., Segalowitz, S. J., & Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain Cogn. 56, 129-140. https://doi.org/10.1016/j.bandc.2004.09.016

Roberto, M., & Varodayan, F. P. (2017). Synaptic targets: chronic alcohol actions. Neuropharmacology. 122, 85-99. https://doi.org/10.1016/j.neuropharm.2017.01.013

Rugg, M. D., & Curran, T. (2007). Event-related potentials and recognition memory. Trends Cogn. Sci. 11, 251-257. https://doi.org/10.1016/j.tics.2007.04.004

Ryerson, N. C., Neal, L. B., & Gable, P. A. (2017). Attenuating the alcohol allure: attentional broadening reduces rapid motivational response to alcohol pictures. Psychopharmacology. 234, 1247-1254. https://doi.org/10.1007/s00213-017-4557-1

Sanhueza, C., Moreno, L. M. G., & Expósito, J. (2011). Weekend alcoholism in youth and neurocognitive aging. Psicothema. 23, 209-214.

Schacht, J. P., Anton, R. F., & Myrick, H. (2012). Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. Addict. Biol. 18, 121-133. https://doi.org/10.1111/j.1369-1600.2012.00464.x

Schulenberg, J., Johnston, L., O'Malley, P., Bachman, J., Miech, R., & Patrick, M. (2019). Monitoring the Future national survey results on drug use, 1975-2018: Volume II, college students and adults ages 19-60.

Schroder, E., Dousset, C., Noel, X., Kornreich, C., & Campanella, S. (2019). Increased neural activity in hazardous drinkers during high workload in a visual working memory task: a preliminary assessment through event-related potentials. Front. Psychiatry. 10, 248. https://doi.org/10.3389/fpsyt.2019.00248

Shalev, L., Ben-Simon, A., Mevorach, C., Cohen, Y., & Tsal, Y. (2011). Conjunctive Continuous Performance Task (CCPT)—A pure measure of sustained attention. Neuropsychologia. 49, 2584-2591. https://doi.org/10.1016/j.neuropsychologia.2011.05.006

Sousa, S. S., Sampaio, A., López-Caneda, E., Bec, C., Gonçalves, Ó. F., & Crego, A. (2020). Increased Nucleus Accumbens Volume in College Binge Drinkers-Preliminary Evidence From Manually Segmented MRI Analysis. Front. Psychiatry. 10, 1005. https://doi.org/10.3389/fpsyt.2019.01005

Smith, J. L., De Blasio, F. M., Iredale, J. M., Matthews, A. J., Bruno, R., Dwyer, M., ... & Mattick, R. P. (2017b). Verbal learning and memory in cannabis and alcohol users: An event-related potential investigation. Front. Psychol. 8, 2129. https://doi.org/10.3389/fpsyg.2017.02129

Smith, J. L., Iredale, J. M., & Mattick, R. P. (2016). Sex differences in the relationship between heavy alcohol use, inhibition and performance monitoring: Disconnect between behavioral and brain functional measures. Psychiatry Res. Neuroimaging. 254, 103-111. https://doi.org/10.1016/j.pscychresns.2016.06.012

Smith, J. L., & Mattick, R. P. (2013). Evidence of deficits in behavioral inhibition and performance monitoring in young female heavy drinkers. Drug Alcohol Depend. 133, 398-404. https://doi.org/10.1016/j.drugalcdep.2013.06.020

Smith, J. L., Mattick, R. P., Jamadar, S. D., & Iredale, J. M. (2014). Deficits in behavioral inhibition in substance abuse and addiction: a meta-analysis. Drug Alcohol Depend. 145, 1-33. https://doi.org/10.1016/j.drugalcdep.2014.08.009

Smith, J. L., Mattick, R. P., & Sufani, C. (2015). Female but not male young heavy drinkers display altered performance monitoring. Psychiatry Res. Neuroimaging. 233, 424-435. https://doi.org/10.1016/j.pscychresns.2015.07.014

Smith, J. L., Mattick, R. P., & Sufani, C. (2017a). Error detection and behavioral inhibition in young heavy drinkers. Drug Alcohol Depend. 171, 20-30. https://doi.org/10.1016/j.drugalcdep.2016.11.016

Squeglia, L. M., Schweinsburg, A. D., Pulido, C., & Tapert, S. F. (2011). Adolescent binge drinking linked to abnormal spatial working memory brain activation: differential gender effects. Alcohol. Clin. Exp. Res. 35, 1831-1841. https://doi.org/10.1111/j.1530-0277.2011.01527.x

Squeglia, L. M., Sorg, S. F., Schweinsburg, A. D., Wetherill, R. R., Pulido, C., & Tapert, S. F. (2012). Binge drinking differentially affects adolescent male and female brain morphometry. Psychopharmacology. 220, 529-539. https://doi.org/10.1007/s00213-011-2500-4

Squeglia, L. M., Tapert, S. F., Sullivan, E. V., Jacobus, J., Meloy, M. J., Rohlfing, T., & Pfefferbaum, A. (2015). Brain development in heavy-drinking adolescents. Am. J. Psychiatry. 172, 531-542. https://doi.org/10.1176/appi.ajp.2015.14101249

Stephens, D. N., & Duka, T. (2008). Cognitive and emotional consequences of binge drinking: role of amygdala and prefrontal cortex. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 363, 3169-3179. https://doi.org/10.1098/rstb.2008.0097

Suárez-Suárez, S., Doallo, S., Pérez-García, J. M., Corral, M., Rodríguez Holguín, S., & Cadaveira, F. (2020). Response Inhibition and Binge Drinking During Transition to University: An fMRI Study. Front. Psychiatry. 11, 535. https://doi.org/10.3389/fpsyt.2020.00535

Substance Abuse and Mental Health Services Administration (SAMHSA). 2018 National Survey on Drug Use and Health (NSDUH). Table 2.20B - Binge Alcohol Use in Past Month among Persons Aged 12 or Older, by Age Group and Demographic Characteristics: Percentages, 2017 and 2018. Available at: https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2018R2/NSDUHDetTabsSect2pe2018.htm#tab2-1b

Tapert, S. F., Schweinsburg, A. D., Barlett, V. C., Brown, S. A., Frank, L. R., Brown, G. G., & Meloy, M. J. (2004). Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. Alcohol.: Clin. Exp. Res. 28, 1577-1586. https://doi.org/10.1097/01.ALC.0000141812.81234.A6

Ullsperger, M., & von Cramon, D. Y. (2004). Decision making, performance and outcome monitoring in frontal cortical areas. Nat. Neurosci. 7, 1173-1174. https://doi.org/10.1038/nn1104-1173

Ullsperger, M., Danielmeier, C., & Jocham, G. (2014). Neurophysiology of performance monitoring and adaptive behavior. Physiol. Rev. 94, 35-79. https://doi.org/10.1152/physrev.00041.2012

Verbruggen, F., & Logan, G. D. (2008). Response inhibition in the stop-signal paradigm. Trends Cogn. Sci. 12, 418-424. https://doi.org/10.1016/j.tics.2008.07.005

Veritas Health Innovation. (2016). Covidence systematic review software. Melbourne,
Australia. http://www.covidence.org

Voon, V., Grodin, E., Mandali, A., Morris, L., Weidacker, K., Kwako, L., ... & Momenan, R. (2020). Addictions NeuroImaging Assessment (ANIA): towards an integrative framework for alcohol use disorder. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2020.04.004

Ward, R. J., Lallemand, F., & De Witte, P. (2009). Biochemical and neurotransmitter changes implicated in alcohol-induced brain damage in chronic or 'binge drinking'alcohol abuse. Alcohol Alcohol. 44, 128-135. https://doi.org/10.1093/alcalc/agn100

Wetherill, R. R., Squeglia, L. M., Yang, T. T., & Tapert, S. F. (2013). A longitudinal examination of adolescent response inhibition: Neural differences before and after the initiation of heavy drinking. Psychopharmacology. 230, 663–671. https://doi.org/10.1007/s00213-013-3198-2

Wiers, R. W., Rinck, M., Kordts, R., Houben, K., & Strack, F. (2010). Retraining automatic action-tendencies to approach alcohol in hazardous drinkers. Addiction. 105, 279-287. https://doi.org/10.1111/j.1360-0443.2009.02775.x

Wiers, C. E., Stelzel, C., Gladwin, T. E., Park, S. Q., Pawelczack, S., Gawron, C. K., ... & Lindenmeyer, J. (2015). Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence. Am. J. Psychiatry. 172, 335-343. https://doi.org/10.1176/appi.ajp.2014.13111495

Winward, J.L., Bekman, N.M., Hanson, K.L., Lejuez, C.W., Brown, S.A. (2014a). Changes in emotional reactivity and distress tolerance among heavy drinking adolescents during sustained abstinence. Alcohol. Clin. Exp. Res. 38, 1761–1769. http://dx.doi.org/10.1111/acer.12415.

Winward, J.L., Hanson, K.L., Bekman, N.M., Tapert, S.F., Brown, S.A. (2014b). Adolescent heavy episodic drinking: neurocognitive functioning during early abstinence. J. Int. Neuropsychol. Soc. 20, 218–229. http://dx.doi.org/10.1017/S1355617713001410.

World Health Organization. (2011). Global status report on alcohol and health. Geneva. World Health Organization.

CHAPTER 3: Tackling Addictive Behaviors Through Memory Suppression: A Narrative Review

The work presented in Chapter 3 is under review

3.1. Abstract

Forgetting is often viewed as a human frailty; however, over the years, it has been considered an adaptive process that allows people to avoid retrieval of undesirable memories, preventing them from suffering and discomfort. Evidence has revealed that the ability to suppress memories is affected in several psychopathological conditions characterized by persistent unwanted thoughts, including anxiety and post-traumatic stress disorders. Nevertheless, memory suppression mechanisms in addiction - a clinical condition characterized by recurrent drug-related thoughts that contribute to repeated drug use – have received little attention so far. Addiction theories reveal that drugs change behavior by working on memory systems, particularly on declarative memory, which is related to the retrieval and encoding of drug-related memories. In this review, we show how this system is involved in the craving or anticipation/preoccupation stage of the addiction cycle. Subsequently, the study of memory suppression in the context of addictive behaviors is highlighted as a promising approach for gaining knowledge about the mechanisms contributing to the continuation of addiction. Finally, we discuss how interventions aiming to strengthen this ability might impact the anticipation/preoccupation stage by (i) reducing the accessibility of drug-related memories, (ii) decreasing craving and attention toward drug-related stimuli, and (iii) improving the overall inhibition abilities. Concluding, this review aims to illustrate how the study of memory suppression may be a valuable approach that may enhance understanding of substance use disorders by unveiling the underlying cognitive and neural mechanisms involved, which could have significant implications for addiction treatment.

Keywords: Memory Suppression, Addictive Behaviors, Drug-Related Memories, Anticipation/Preoccupation Stage, Craving

3.2. The Power of Letting Go: Forgetting as an adaptive process

How many events, situations, or actions would you like to have forgotten at some point in your life? Probably the answer is a considerable amount, and certainly consciously or unconsciously, you already tried to or forgot something. Forgetting is not always a failure in our memory, instead, it constitutes an adaptive process that allows people to discard irrelevant information and to avoid discomfort when reminded of undesirable events that cause guilt, shame, pain, and suffering. Over the past century, different terms for motivated forgetting have emerged in the literature (e.g., repression, directed forgetting, memory suppression), accompanied by distinct approaches aimed at exploring the underlying mechanisms contributing to this process.

Research has shown that controlling undesired memories from entering awareness may occur at different steps of mnemonic processing. The easiest way is truncating or limiting their encoding, which has been investigated using directed forgetting paradigms (Anderson & Hulbert, 2021; Bjork, 1989), where individuals are asked to forget recently encoded information. Despite the attempts to disrupt encoding, unwanted memories become stored in memory most of the time and, on that occasion, people might prevent its retrieval by avoiding reminders. However, this strategy is not always practicable, and when confronted with inescapable reminders, they often try to stop memory retrieval, a process known as memory suppression.

At the beginning of this century, Anderson and Green (2001) pioneered the field of voluntary memory suppression by developing the Think/No-Think (TNT) paradigm, an adaptation of the classical Go/No-Go task typically used to evaluate the suppression of motor responses (Huster et al., 2013). The TNT task tries to mirror situations when we are faced with a reminder of an unwelcome memory (Anderson & Hulbert, 2021). Initially, participants are asked to learn cue-target pairs to create the reminders and then, in the TNT phase, they are asked to exert control over retrieval. Specifically, individuals must remember and retain (Think reminder) or prevent from entering awareness (No-Think reminder) a paired item from the material previously learned. One of the main outputs of this task is the suppression-induced forgetting, measured by the recall of No-Think items *minus* the recollection exhibited for Baseline items - i.e., items that were initially memorized but were omitted from the TNT (recalling/suppression) phase. This phenomenon has been observed with distinct types of stimuli, including emotional (Anderson & Hanslmayr, 2014; Anderson et al., 2004; Anderson & Green, 2001; Levy & Anderson, 2012) and autobiographical memories (Stephens et al., 2013; Noreen & MacLeod, 2012), motor actions (Schmidt et al., 2023), and even personal fears about the future (Benoit et al., 2016). Within this context, suppressed-induced forgetting operates alongside mechanisms associated with episodic

explicit/declarative memory, which encompasses the deliberate retrieval of specific events, situations, or episodes (Baddeley et al., 2020).

Research documented that both motor inhibition and memory suppression share similar neural substrates –including the dorsolateral prefrontal cortex (DLPFC), the inferior frontal cortex (IFC), and the anterior cingulate (Anderson et al., 2004; Depue et al., 2007), thus pointing to a common inhibitory control mechanism for actions and memories. More specifically, functional magnetic resonance imaging (fMRI) studies have shown that suppressing retrieval is associated with increased activation of the DLPFC and the IFG, along with deactivations of brain areas supporting episodic recollection, such as the hippocampus and other cortical and subcortical regions (e.g., amygdala, precuneus, and fusiform cortex), which is consistent with a top-down regulation of memory (Apšvalka et al., 2022; Benoit & Anderson, 2012; Benoit et al., 2015, 2016; Gagnepain et al., 2017; Mary et al., 2020).

3.3. Memory Suppression in the Context of Psychopathological Disorders

With the emergence of compelling evidence demonstrating the ability to voluntarily suppress memories, it becomes pertinent to determine whether psychiatric disorders characterized by the persistence of intrusive and undesirable thoughts –such as post-traumatic stress disorder (PTSD), anxiety, and depression- may exhibit difficulties in this ability. Furthermore, the potential benefits of an efficient capacity to suppress intrusive or unwanted thoughts for individuals struggling with these conditions warrant further consideration.

As mentioned above, forgetting is an adaptive human feature that may allow people to achieve cognitive and emotional well-being. Therefore, individuals with psychological conditions where pervasive and unwanted thoughts, worries, or ruminations coupled with stopping deficits are hallmark symptoms, including PTSD, attention deficit hyperactivity disorder, and depressive and anxiety disorders, may face challenges in effectively using it. Accordingly, studies exploring suppression-induced forgetting in individuals with these clinical conditions, or with high scores on related symptoms, have revealed impaired recruitment of control mechanisms to efficiently prevent unwanted thoughts/memories (Catarino et al., 2015; Depue et al., 2010; Diwadkar, 2017; Joormann et al., 2009; Mary et al., 2020; Marzi et al., 2014; Waldhauser et al., 2018; Storm and White, 2010).

Although recent years have witnessed accumulating evidence regarding memory suppression in psychopathological illness (Constanzi et al., 2021; Stramaccia et al., 2019), insufficient attention has been paid to the study of this ability in addiction – a clinical condition marked by recurrent maladaptive drug-related thoughts that frequently lead to drug-seeking and taking behaviors (Di Ciano & Everitt, 2004;

Everitt & Robbins, 2005; Noël et al., 2013; Redish et al., 2008). Addiction is characterized by the compulsion to take drugs, which leads to excessive drug intake, loss of control in stopping consumption and emergence of adverse emotional states (American Psychiatric Association, 2014). Critically, addiction remains a pressing issue in modern society, mainly due to its significant economic and social costs (Patel et al., 2016). Furthermore, addiction's chronic and relapsing nature is a major problem for the individual and healthcare systems. The propensity to relapse can persist despite the adverse consequences and decreased satisfaction accompanying drug use, even after the initial signs of acute withdrawal have subsided (Koob & Volkow, 2016; Langleben et al, 2008; O'Brien & McLellan, 2013). In order to understand the reasons behind the perpetuation of this addiction cycle, extensive literature on this matter has been emerging over time, encompassing distinct conceptualizations, perspectives and theoretical models.

3.4. Neurobiological Models of Addiction

Drug use often starts with social drug-taking and immediate reinforcement, and in some cases, it progresses to escalating compulsive use, dependence, withdrawal, and extended periods of abstinence, which are commonly interrupted by the occurrence of relapse (Koob & Le Moal, 2005). Neurobiological research on addiction emerged to explore the neuroadaptive changes operating within specific brain circuits that lead to the progression from sporadic and controlled drug use to the inability to control drug-seeking and taking behaviors (Moal & Koob, 2007).

Initially, the literature was focused on the changes induced by drug use in the brain's reward system to explain the persistent urge to seek and consume drugs (Moal & Koob, 2007). In this sense, the incentive-sensitization perspective proposed that the sensitization of reward-related neural pathways, particularly dopamine neurons, leads to the attribution of incentive salience to drugs and subsequently, compulsive motivation to use them (Robinson & Berridge, 1993, 2001).

On the other hand, neurocognitive approaches have proposed an imbalance between an upregulated reward system and an impaired reflective control system located in the prefrontal cortex (Bechara et al., 2005). In this vein, the contemporary dual model known as iRISA (*impaired Response Inhibition and Salience Attribution*) comes to emphasize the impairment in response inhibition and salience attribution as the key elements contributing for the intoxication, craving, bingeing, and withdrawal addiction cycle (Goldstein & Volkow, 2002; Goldstein & Volkow, 2011; Zilverstand et al., 2018). Accordingly, in this model, addiction is characterized by significant changes in salience processing, specifically by the increased attention given to drug-related stimuli and a blunted motivational value for

non-drug-related information (Goldstein & Volkow, 2002). Supporting this view, evidence revealed that individuals with substance abuse exhibited heightened activation of the salience network (i.e., insula, dorsal anterior cingulate cortex, and inferior parietal cortex) when processing drug-related stimuli, indexing increased motivational reactivity to drug cues (Goldstein & Volkow, 2002, Zilverstand et al., 2018). Additionally, hyperactivity of this network has been usually accompanied by reduced activity of the executive network (i.e., DLPFC and ventrolateral PFC) during tasks involving behavioral inhibition in drug-addicted individuals (Harlé et al., 2014; Hu et al., 2015; Kober et al., 2014), with these dysfunctions being associated with augmented addiction severity and higher risk for relapse (Cousijn et al., 2012; Costumero et al., 2017; Harlé et al., 2014; Moeller et al., 2016). These prefrontal alterations are intimately linked to the relapsing nature of addiction since they are associated with impaired impulse control and inability to delay gratification – two characteristic traits of addictive behaviors – that lead to the incapacity to avoid inappropriate drug-seeking and taking behaviors (Garrison & Potenza, 2014, Goldstein & Volkow, 2011).

According to a perspective emphasizing reward related learnings, the evolution from intentional and recreational drug use to compulsive drug-seeking behavior occurs through Pavlovian and instrumental learning processes (Everitt & Robbins, 2005, 2016). Therefore, addiction results from the development of associations between environmental stimuli and drug highs and withdrawal states, which create persistent drug-related memories and maladaptive behaviors and habits (Everitt et al., 2001; Everitt & Robbins, 2005; Milton & Everitt, 2012). At a neural level, this shift is driven by changes in the control mechanisms underlying drug-seeking behavior, with a transition from prefrontal to striatal control and a progression from the ventral to the dorsal striatum (Everitt & Robbins, 2005).

Koob and Le Moal (2005) tried to integrate the perspectives mentioned above. According to the authors, addiction is conceptualized as a condition that progresses from impulsivity to compulsivity, and, as this progression occurs, the drug-seeking behavior changes from being driven by pleasant sensations, such as pleasure, relief, and gratification (i.e., positive reinforcement), to being motivated by avoiding aversive feelings, such as anxiety and stress (i.e., negative reinforcement) (Koob & Le Moal, 1997; Le Moal & Koob, 2007). This transition takes place through a spiraling cycle of three stages, binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (or craving), which are mediated by specific neural circuits that explain the uncontrollable and increasing drug use and difficulty quitting (Koob & Le Moal, 1997). The craving or preoccupation/anticipation stage has been pointed out as a critical factor contributing to relapse (Koob & Le Moal, 2005; Koob & Volkow, 2016). Indeed, the increased attention or sensitivity to drug-associated cues – including emotional states – leads to this

stage, which is distinguished by an intensified craving and difficulties in executive control (Koob & Volkow, 2010). Craving is conceived as learned responses that associates drug use and its surroundings with a pleasant or overwhelming experience that leads to drug-seeking behavior (Goldstein & Volkow, 2002). It is a complex phenomenon that can be triggered by external or internal cues, such as the retrieval of memories. Therefore, the retrieval of substance-related memories can result in the subjective feeling of craving, which may subsequently lead to the retrieval of additional memories associated with the consumption, originating a continuous excitatory cycle (Ekhtiari et al., 2016). Accordingly, research has revealed that cue-elicited craving and drug intoxication lead to increased activation of the hippocampus (Langleben et al., 2008; Li et al., 2012, 2015; Volkow et al., 2004; Wei et al., 2020), which is involved in the retrieval of drug-related memories.

Regarding the underlying neural substrates, the preoccupation/anticipation network comprises a widely distributed neurocircuitry encompassing the orbitofrontal cortex, dorsal striatum, PFC, basolateral amygdala, hippocampus, and insula, which play a role in augmenting craving levels (Koob & Volkow, 2010). Additionally, the preoccupation/anticipation stage involves the cingulate gyrus, DLPFC, and inferior frontal cortex, whose reduced activity has been linked to impaired inhibitory control (Koob & Volkow, 2010). Specifically, this stage involves the action of the basolateral amygdala in processing the conditioned reinforcement, and the hippocampus in processing the contextual information. Furthermore, the PFC managing executive control is responsible for representing contingencies and outcomes as well as their value and controlling the subjective states linked to the substance, including craving (Koob & Volkow, 2010). In general, this stage comprises most of the regions involved in the executive and salience networks as well as the main regions involved in memory systems (e.g., hippocampus and amygdala).

3.5. Unraveling the Connection between Memory Suppression and Addiction

Memory and learning systems seem to be strongly involved in the progression of addiction (Everitt & Robbins, 2005, 2016). As such, development of drug-related memories has been pointed as a key factor in the persistence of drug use and the high relapse rates observed in individuals with substance use disorders (SUDs) (Milton & Everitt, 2012; Wise & Koob, 2014). In this sense, addictive behaviors can be (at least partially) attributed to the diverse and simultaneous reinforcement effects of the drug on memory systems responsible for mediating different types of learning, including conditioned-incentive learning (i.e., nucleus accumbens and amygdala), habit learning (i.e., caudate and putamen), and declarative learning (i.e., hippocampus) (Koob & Volkow, 2010; White, 1996). The declarative memory system is known to play a crucial role in obtaining relevant information about drug-related situations,

being thus responsible for the encoding and retrieval of drug-related memories (White, 1996). Specifically, this system - mainly supported by the hippocampus – mediates the effects of drugs on behavior by allowing individuals to learn about the relationship between contextual cues and internal affective states elicited by the drug, by withdrawing the drug, or by the presence of conditioned cues (Everitt & Robbins, 2005, 2016; White, 1996). Consequently, the hippocampal system is also associated with the motivating effect of aversive withdrawal symptoms as it is responsible for acquiring information about how to alleviate these aversive states (White, 1996; Kutlu et al., 2016; Robbins et al., 2008). As a result, this system is intimately related to the craving experience and, according to mentioned above, it is also highly involved in the preoccupation/anticipation stage of the addiction cycle.

Importantly, most of addictive drugs may enhance memory for the information acquired by the hippocampus, increasing the likelihood of recalling contextually relevant details associated with drug use (Kutlu & Gould, 2016). In this way, drug-related thoughts and behaviors become more prevalent, while thoughts and actions related to other contexts diminish in significance (Kutlu & Gould, 2016). Thus, the declarative memory system is also involved in increasing the focus on drug-related situations. This augmented processing of substance-related cues commonly leads to higher craving levels, which may, in turn, intensify the salience and focused attention toward this type of stimuli (Franken, 2003).

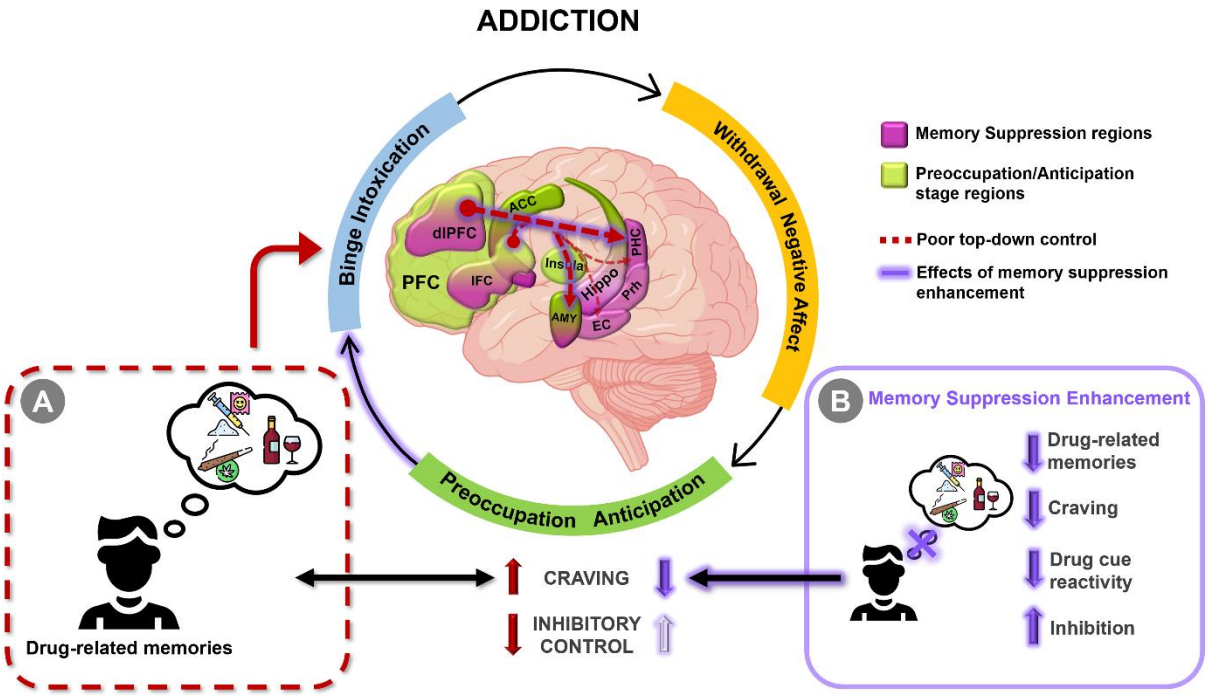
Overall, persistent drug-related memories became a major concern in addiction, since they can be triggered by drug-associated environmental cues and contribute to the perpetuation of the cycle by originating cravings, spontaneous behaviors, and diminished self-control involvement (Di Ciano & Everitt, 2004; Everitt & Robbins, 2016; Hogarth, 2020; Luscher et al., 2020; Noël et al., 2023).

Despite research has recurrently revealed that individuals with drug addiction have reduced executive (top-down) control as well as structural and functional alterations in regions implicated in memory suppression (Goldstein & Volkow, 2011; Zilverstand et al., 2018), no study so far has explored whether impairments in the executive network (i.e., DLPFC, IFC) in addiction may compromise the control of drug-associated thoughts or memories. This ability to regulate or suppress memories could be of particular relevance for addiction research since the control exerted by prefrontal regions over memory structures may modulate or even remove the retrieval of substance-related thoughts or images in the presence of external or internal drug use reminders. Therefore, the suppression of these maladaptive memories might impact the subjective states associated with drug use, including craving and other feelings that maintain drug-seeking and taking behaviors, which may ultimately lead to the reduction of such behaviors. In this regard, the suppression of substance-related memories could have a substantial effect on the addiction cycle by impacting the craving or anticipation/preoccupation stage (see Figure

10). Consequently, understanding the processes through which it may occur, might entail significant implications for the development of more effective treatments and approaches to reduce substance use and the risk for relapse.

Figure 10

Scheme depicting how ***(1)*** *drug-related memories and memory suppression mechanisms are involved and may contribute to the perpetuation of the addiction cycle and* ***(2)*** *how memory suppression enhancement may impact the Preoccupation/Anticipation stage.*



Note. Green brain regions represent the areas involved during the Preoccupation/Anticipation stage, characterized by increased craving and reduced prefrontal executive control. During memory suppression mechanisms, some of these regions are also recruited (regions with a color gradient between fuchsia and green). **(A)** The craving experience is closely related to drug-related memories/thoughts (bottom left bidirectional black arrow). The hypofunction of the prefrontal cortex (PFC) may reduce the control over memory regions, such as the hippocampus and amygdala (dashed red line depicted in the brain). Consequently, this stage of the addiction cycle may also involve increased retrieval of drug-related memories, which frequently lead to drug-seeking and taking behaviors and, thus, to the binge/intoxication phase (red arrow). **(B)** Memory suppression enhancement through cognitive training might decrease the retrieval of alcohol-related memories and, subsequently, the craving and the drug cue reactivity. Ultimately, and given that stopping motor actions and thoughts or memories share common neural regions, it may lead to improved inhibitory control in general. These potential effects may reduce drug-seeking and taking behaviors, weakening the transition to the binge/intoxication stage (black arrow brightened in purple). ACC: anterior cingulate cortex; AMY: amygdala; EC: Entorhinal Cortex: dlPFC: dorsolateral prefrontal cortex; Hippo: hippocampus; PHC: Parahipocampal Cortex; PFC: prefrontal cortex; Prh: Perirhinal Cortex

3.6. Empowering Memory Suppression: The Impact of Training

The persistent maladaptive drug-associated memories have already been addressed as a significant challenge for the maintenance of abstinence and the development of interventions aiming to

edit these memories (i.e., make a previously formed memory trace labile again) have been proposed as a promising way for the treatment of individuals with addictive disorders (Lee et al., 2005; Nöel, 2023). Research has shown that memories can be disrupted following their initial acquisition and consolidation by interfering with the process of reconsolidation (Lee et al., 2008; Lee et al., 2005). However, the development of memory editing/reconsolidation interventions may face some challenges given the various forms that learning, and memory can assume in general and, particularly, in addiction (i.e., habits, episodic events, and subjective feelings). As mentioned above, suppression induced forgetting has been observed in a variety of forms, including words, images, complex scenes, abstract stimuli, motor actions, emotional content, autobiographical memories, hypothetical scenarios, and fears about the future (Anderson & Hulbert, 2021; Marsh & Anderson, 2022). Nevertheless, despite the generalization of suppression-induced forgetting makes the interventions focused on memory suppression improvement a potential way to deal with the variability of (drug-related) memories, no study has explored the potential effects of training on the ability to suppress drug-associated memories in SUDs (Almeida-Antunes et al., 2022).

Recently, evidence has shown that training to suppress unpleasant personal thoughts about feared future events improves mental health in individuals suffering from anxiety and PTSD symptoms, reducing the consciousness of the inhibited content as well as the capacity to access details and imagery of those events (Mamat & Anderson, 2023). As a result, suppression enhancement also led to a reduction in the distinct forms of repetitive thinking (e.g., rumination) that characterize anxiety, depression, and PTSD (Mamat & Anderson, 2023). Given that recurring thoughts and memories about drug consumption are at the core of addiction, the interventions aiming at improving memory suppression abilities may constitute a powerful new tool for the treatment of addictive behaviors as it may reduce the persistence and strength of these maladaptive memories.

Although further research is still needed, cognitive training has shown to be efficient at improving impaired cognitive functions as well as clinical symptoms in SUDs (Nardo et al., 2022; Verdejo-Garcia, 2016). In addition, the inclusion of substance-related cues has been pointed as a potential strategy to enhance the transfer of cognitive improvements to clinical outcomes and to better integrate this type of intervention with conventional addiction therapies, with the goal of achieving long-term effects (Bartsch et al., 2016; Wiers et al., 2018). Accordingly, research showed that drug-specific inhibition training effectively decreases alcohol use in heavy drinkers (Houben et al., 2012; Jones & Field, 2013) and increases the abstinent days in individuals with severe alcohol use disorder (Stein et al., 2022). This

evidence supports the promising valuable effects that drug-specific memory suppression training may have on clinical outcomes in SUDs.

Considering the neurobiological models discussed above, the encoding and retrieval of drug-associated memories or thoughts seem to be intimately associated with the craving or anticipation/preoccupation stage of the addiction cycle (see Figure 10). Therefore, the development of drug-specific memory suppression training may have powerful effects in this stage. Specifically, the improvement of memory suppression mechanisms may reduce the retrieval and strength of drug-related memories, thoughts, or images that may be evoked in the presence of internal or external drug use reminders. Consequently, the reduction of these maladaptive memories may lead to decreased craving and lower attention toward this type of stimuli. Ultimately, enhancing memory suppression ability may also affect the inhibitory ability in general since these cognitive functions are supported by common neural substrates (i.e., DLPFC and IFC) (Apšvalka et al., 2022). Altogether, these potential effects of a (drug-specific) memory suppression training might lead to a reduction in the drug-seeking and taking behaviors and thus deserve further attention in future addiction research

3.7. Conclusion

Substance addiction is a chronic relapsing disorder that poses an ongoing struggle for healthcare providers and individuals with SUDs and, subsequently, requires ongoing treatment and management (Borson et al., 2013; Marlatt & Donovan, 2005). While pharmacological and behavioral interventions may be partially effective in reducing drug use, the persistent tendency for relapse remains a major obstacle in addiction treatment (Koob & Volkow, 2016; O'brien, 2005; Volkow & Li, 2004). Persistent maladaptive memories that associate contextual cues with the drug effects have been identified as a significant contributor for the persistence of addiction cycle and relapse. The encoding and retrieval of these memories depends on the declarative memory system, which is particularly involved in the craving or anticipation/preoccupation stage of the addiction cycle, a critical step contributing to relapse. As such, exploring the psychological and neural processes underlying the control over substance-associated memories may provide meaningful insights about the mechanisms associated with the perpetuation of the addiction cycle and lead to the development of more effective strategies to prevent and treat this disorder. The development of interventions aiming to improve the ability to suppress drug-related memories might represent a powerful way to intervene in addictive behaviors, particularly in the anticipation/preoccupation stage, by reducing the accessibility of drug-related memories, and, consequently, the craving levels and the attention toward drug-related stimuli as well as by enhancing the

overall inhibition abilities. In this way, drug-specific memory suppression trainings could be effective in reducing drug consumption and/or preventing relapse, by impacting an important step of the addiction cycle, and thus serve as an adjunct to other interventions employed in addiction treatment.

3.8. References

Almeida-Antunes, N., Vasconcelos, M., Crego, A., Rodrigues, R., Sampaio, A., & López-Caneda, E. (2022). Forgetting Alcohol: A Double-Blind, Randomized Controlled Trial Investigating Memory Inhibition Training in Young Binge Drinkers. *Frontiers in Neuroscience*, 16. https://doi.org/10.3389/fnins.2022.914213

American Psychiatric Association, D. S. M. T. F., & American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5, No. 5). Washington, DC: American psychiatric association.

Anderson, M. C., Ochsner, K. N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S. W., Glover, G. H., & Gabrieli, J. D. E. (2004). Neural Systems Underlying the Suppression of Unwanted Memories. *Science, 303*(5655), 232–235. https://doi.org/10.1126/science.1089504

Anderson, M. C. & Green, C. Suppressing unwanted memories by executive control. *Nature 410*, 366–369 (2001). https://doi.org/10.1038/35066572

Anderson, M. C. & Hanslmayr, S. Neural mechanisms of motivated forgetting. *Trends in Cognitive Sciences*. *18*, 279–292 (2014). https://doi.org/10.1016/j.tics.2014.03.002

Anderson, M. C., & Hulbert, J. C. (2021). Active Forgetting: Adaptation of Memory by Prefrontal Control. *Annual Review of Psychology, 72*(1), 1–36. https://doi.org/10.1146/annurev-psych-072720-094140

Anderson, M. C., Ochsner, K. N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S. W., Glover, G. H., & Gabrieli, J. D. (2004). Neural systems underlying the suppression of unwanted memories. *Science, 303*(5655), 232-235. https://10.1126/science.1089504

Apšvalka, D., Ferreira, C. S., Schmitz, T. W., Rowe, J. B., & Anderson, M. C. (2022). Dynamic targeting enables domain-general inhibitory control over action and thought by the prefrontal cortex. *Nature Communications, 13*(1). https://doi.org/10.1038/s41467-021-27926-w

Baddeley, A., Eysenck, M. W., Anderson, M. C. (2020). *Memory* (Third edition). Routledge, Taylor & Francis Group.

Bartsch, A. and Kothe, E. and Allom, V. and Mullan, B. and Houben, K. (2016). The Effect of Non-specific Response Inhibition Training on Alcohol Consumption: An Intervention. *Journal of Addiction Research & Therapy. 7*(1), 260-260.https://doi.org/10.4172/2155-6105.1000260

Benoit, R. G., & Anderson, M. C. (2012). Opposing mechanisms support the voluntary forgetting of unwanted memories. *Neuron, 76*(2), 450-460. https://doi.org/10.1016/j.neuron.2012.07.025

Benoit, R. G., Hulbert, J. C., Huddleston, E., & Anderson, M. C. (2015). Adaptive top–down suppression of hippocampal activity and the purging of intrusive memories from consciousness. *Journal of cognitive neuroscience, 27*(1), 96-111. https://doi.org/10.1162/jocn_a_00696

Benoit, R. G., Davies, D. J., & Anderson, M. C. (2016). Reducing future fears by suppressing the brain mechanisms underlying episodic simulation. *Proceedings of the National Academy of Sciences, 113*(52), E8492-E8501. https://doi.org/10.1073/pnas.1606604114

Bjork, R. A. (1989). Retrieval inhibition as an adaptive mechanism in human memory. In H. L. Roedinger ITI & F. I. M. Craik (Eds.), *Varieties of memory and consciousness* (pp. 309-330). Hillsdale, NJ: Erlbaum

Brorson, H. H., Ajo Arnevik, E., Rand-Hendriksen, K., & Duckert, F. (2013). Drop-out from addiction treatment: A systematic review of risk factors. *Clinical Psychology Review, 33*(8), 1010–1024. https://doi.org/10.1016/j.cpr.2013.07.007

Catarino, A., Küpper, C. S., Werner-Seidler, A., Dalgleish, T., & Anderson, M. C. (2015). Failing to Forget. *Psychological Science, 26*(5), 604–616. https://doi.org/10.1177/0956797615569889

Costanzi, M., Cianfanelli, B., Santirocchi, A., Lasaponara, S., Spataro, P., Rossi-Arnaud, C., & Cestari, V. (2021). Forgetting Unwanted Memories: Active Forgetting and Implications for the Development of Psychological Disorders. *Journal of Personalized Medicine, 11*(4), 241. https://doi.org/10.3390/jpm11040241

Costumero, V., Bustamante, J. C., Rosell-Negre, P., Fuentes, P., Llopis, J. J., Ávila, C., & Barrós-Loscertales, A. (2015). Reduced activity in functional networks during reward processing is modulated by abstinence in cocaine addicts. *Addiction Biology, 22*(2), 479–489. Portico. https://doi.org/10.1111/adb.12329

Cousijn, J., Goudriaan, A. E., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., & Wiers, R. W. (2012). Approach-Bias Predicts Development of Cannabis Problem Severity in Heavy Cannabis Users: Results from a Prospective FMRI Study. *PLoS ONE, 7*(9), e42394. https://doi.org/10.1371/journal.pone.0042394

den Uyl, T. E., Gladwin, T. E., Lindenmeyer, J., & Wiers, R. W. (2018). A Clinical Trial with Combined Transcranial Direct Current Stimulation and Attentional Bias Modification in Alcohol-Dependent Patients. *Alcoholism, clinical and experimental research*, *42*(10), 1961-1969. https://doi.org/10.1111/acer.13841

den Uyl, T. E., Gladwin, T. E., Rinck, M., Lindenmeyer, J., & Wiers, R. W. (2017). A clinical trial with combined transcranial direct current stimulation and alcohol approach bias retraining. *Addiction biology*, *22*(6), 1632-1640. https://doi.org/10.1111/adb.12463

Depue, B. E., Burgess, G. C., Willcutt, E. G., Ruzic, L., & Banich, M. T. (2010). Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: Evidence from deficits in individuals with ADHD. *Neuropsychologia, 48*(13), 3909–3917. https://doi.org/10.1016/j.neuropsychologia.2010.09.013

Depue, B. E., Curran, T., & Banich, M. T. (2007). Prefrontal Regions Orchestrate Suppression of Emotional Memories via a Two-Phase Process. *Science, 317*(5835), 215–219. https://doi.org/10.1126/science.1139560

Di Ciano, P., & Everitt, B. J. (2004). Conditioned reinforcing properties of stimuli paired with self-administered cocaine, heroin or sucrose: implications for the persistence of addictive behaviour. *Neuropharmacology, 47*(1), 202–213. https://doi.org/10.1016/j.neuropharm.2004.06.005

Diwadkar, V. A., Re, M., Cecchetto, F., Garzitto, M., Piccin, S., Bonivento, C., Maieron, M., D'Agostini, S., Balestrieri, M., & Brambilla, P. (2017). Attempts at memory control induce dysfunctional brain activation profiles in Generalized Anxiety Disorder: An exploratory fMRI study. Psychiatry Research: *Neuroimaging, 266*, 42–52. https://doi.org/10.1016/j.pscychresns.2017.05.010

Dubuson, M., Kornreich, C., Vanderhasselt, M. A., Baeken, C., Wyckmans, F., Dousset, C., et al. (2021). Transcranial direct current stimulation combined with alcohol cue inhibitory control training reduces the risk of early alcohol relapse: a randomized placebo-controlled clinical trial. *Brain Stimulation, 14*(6), 1531–1543. doi: 10.1016/j.brs.2021.10.386

Ekhtiari, H., Nasseri, P., Yavari, F., Mokri, A., & Monterosso, J. (2016). Neuroscience of drug craving for addiction medicine. *Neuroscience for Addiction Medicine: From Prevention to Rehabilitation - Constructs and Drugs*, *223*, 115–141. https://doi.org/10.1016/bs.pbr.2015.10.002

Everitt, B. J., Dickinson, A., & Robbins, T. W. (2001). The neuropsychological basis of addictive behaviour. *Brain Research Reviews, 36*(2–3), 129–138. https://doi.org/10.1016/s0165-0173(01)00088-1

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature Neuroscience, 8*(11), 1481–1489. https://doi.org/10.1038/nn1579

Everitt, B. J., & Robbins, T. W. (2016). Drug Addiction: Updating Actions to Habits to Compulsions Ten Years On. *Annual Review of Psychology, 67*(1), 23–50. https://doi.org/10.1146/annurev-psych-122414-033457

Franken, I. H. A. (2003). Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27*(4), 563–579. https://doi.org/10.1016/s0278-5846(03)00081-2

Gagnepain, P., Hulbert, J., & Anderson, M. C. (2017). Parallel Regulation of Memory and Emotion Supports the Suppression of Intrusive Memories. *The Journal of Neuroscience, 37*(27), 6423–6441. https://doi.org/10.1523/jneurosci.2732-16.2017

Garrison, K. A., & Potenza, M. N. (2014). Neuroimaging and Biomarkers in Addiction Treatment. *Current Psychiatry Reports, 16*(12). https://doi.org/10.1007/s11920-014-0513-5

Goldstein, R. Z., & Volkow, N. D. (2002). Drug Addiction and Its Underlying Neurobiological Basis: Neuroimaging Evidence for the Involvement of the Frontal Cortex. *American Journal of Psychiatry, 159*(10), 1642–1652. https://doi.org/10.1176/appi.ajp.159.10.1642

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*(11), 652–669. https://doi.org/10.1038/nrn3119

Harlé, K. M., Shenoy, P., Stewart, J. L., Tapert, S. F., Yu, A. J., & Paulus, M. P. (2014). Altered Neural Processing of the Need to Stop in Young Adults at Risk for Stimulant Dependence. *The Journal of Neuroscience, 34*(13), 4567–4580. https://doi.org/10.1523/jneurosci.2297-13.2014

Hogarth, L. (2020). Addiction is driven by excessive goal-directed drug choice under negative affect: translational critique of habit and compulsion theory. *Neuropsychopharmacology*, *45*(5), 720-735. https://doi.org/10.1038/s41386-020-0600-8

Houben, K., Havermans, R. C., Nederkoorn, C., & Jansen, A. (2012). Beer à No-Go: Learning to stop responding to alcohol cues reduces alcohol intake via reduced affective associations rather than increased response inhibition. *Addiction, 107*(7), 1280-1287. https://doi.org/10.1111/j.1360-0443.2012.03827.x

Hu, S., Ide, J. S., Zhang, S., Sinha, R., & Li, C. R. (2015). Conflict anticipation in alcohol dependence — A model-based fMRI study of stop signal task. *NeuroImage: Clinical, 8*, 39–50. https://doi.org/10.1016/j.nicl.2015.03.008

Huster, R. J., Enriquez-Geppert, S., Lavallee, C. F., Falkenstein, M., & Herrmann, C. S. (2013). Electroencephalography of response inhibition tasks: Functional networks and cognitive contributions. International *Journal of Psychophysiology, 87*(3), 217–233. https://doi.org/10.1016/j.ijpsycho.2012.08.001

Jones, A., & Field, M. (2013). The effects of cue-specific inhibition training on alcohol consumption in heavy social drinkers. *Experimental and Clinical Psychopharmacology, 21*(1), 8–16. https://doi.org/10.1037/a0030683

Joormann, J., Hertel, P. T., LeMoult, J., & Gotlib, I. H. (2009). Training forgetting of negative material in depression. *Journal of Abnormal Psychology, 118*(1), 34–43. https://doi.org/10.1037/a0013794

Kober, H., DeVito, E. E., DeLeone, C. M., Carroll, K. M., & Potenza, M. N. (2014). Cannabis Abstinence During Treatment and One-Year Follow-Up: Relationship to Neural Activity in Men. *Neuropsychopharmacology, 39*(10), 2288–2298. https://doi.org/10.1038/npp.2014.82

Koob, G. F., & Moal, M. L. (1997). Drug Abuse: Hedonic Homeostatic Dysregulation. *Science, 278*(5335), 52–58. https://doi.org/10.1126/science.278.5335.52

Koob, G. F., & Le Moal, M. (2005). Plasticity of reward neurocircuitry and the "dark side" of drug addiction. *Nature Neuroscience, 8*(11), 1442–1444. https://doi.org/10.1038/nn1105-1442

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of Addiction. *Neuropsychopharmacology, 35*(1), 217–238. https://doi.org/10.1038/npp.2009.110

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. The Lancet *Psychiatry, 3*(8), 760–773. https://doi.org/10.1016/s2215-0366(16)00104-8

Kutlu, M. G., & Gould, T. J. (2016). Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction. *Learning & memory*, *23*(10), 515-533. http://www.learnmem.org/cgi/doi/10.1101/lm.042192.116.

Langleben, D. D., Ruparel, K., Elman, I., Busch-Winokur, S., Pratiwadi, R., Loughead, J., O'Brien, C. P., & Childress, A. R. (2008). Acute Effect of Methadone Maintenance Dose on Brain fMRI Response to Heroin-Related Cues. *American Journal of Psychiatry, 165*(3), 390–394. https://doi.org/10.1176/appi.ajp.2007.07010070

Lee, J. L. C. (2008). Memory reconsolidation mediates the strengthening of memories by additional learning. *Nature Neuroscience, 11*(11), 1264–1266. https://doi.org/10.1038/nn.2205

Lee, J. L. C., Di Ciano, P., Thomas, K. L., & Everitt, B. J. (2005). Disrupting Reconsolidation of Drug Memories Reduces Cocaine-Seeking Behavior. *Neuron, 47*(6), 795–801. https://doi.org/10.1016/j.neuron.2005.08.007

Le Moal, M., & Koob, G. F. (2007). Drug addiction: Pathways to the disease and pathophysiological perspectives. *European Neuropsychopharmacology, 17*(6–7), 377–393. https://doi.org/10.1016/j.euroneuro.2006.10.006

Levy, B. J., & Anderson, M. C. (2012). Purging of Memories from Conscious Awareness Tracked in the Human Brain. *The Journal of Neuroscience, 32*(47), 16785–16794. https://doi.org/10.1523/jneurosci.2640-12.2012

Li, Q., Wang, Y., Zhang, Y., Li, W., Yang, W., Zhu, J., Wu, N., Chang, H., Zheng, Y., Qin, W., Zhao, L., Yuan, K., Liu, J., Wang, W., & Tian, J. (2012). Craving correlates with mesolimbic responses to heroin-related cues in short-term abstinence from heroin: An event-related fMRI study. *Brain Research, 1469*, 63–72. https://doi.org/10.1016/j.brainres.2012.06.024

Li, Q., Li, W., Wang, H., Wang, Y., Zhang, Y., Zhu, J., Zheng, Y., Zhang, D., Wang, L., Li, Y., Yan, X., Chang, H., Fan, M., Li, Z., Tian, J., Gold, M. S., Wang, W., & Liu, Y. (2014). Predicting subsequent relapse by drug-related cue-induced brain activation in heroin addiction: an event-related functional magnetic resonance imaging study. *Addiction Biology, 20*(5), 968–978. Portico. https://doi.org/10.1111/adb.12182

Lüscher, C., Robbins, T. W., & Everitt, B. J. (2020). The transition to compulsion in addiction. *Nature Reviews Neuroscience, 21*(5), 247–263. https://doi.org/10.1038/s41583-020-0289-z

Mamat, Z., & Anderson, M. (2023, February 14). Improving Mental Health by Training the Suppression of Unwanted Thoughts. https://doi.org/10.31234/osf.io/5cn7g

Marlatt, G. A., & Donovan, D. M. (Eds.). (2005). *Relapse prevention: Maintenance strategies in the treatment of addictive behaviors*. Guilford press.

Marsh, L. C., & Anderson, M. (2022). Inhibition as a cause of forgetting. https://doi.org/10.31234/osf.io/6bwc2

Mary, A., Dayan, J., Leone, G., Postel, C., Fraisse, F., Malle, C., Vallée, T., Klein-Peschanski, C., Viader, F., de la Sayette, V., Peschanski, D., Eustache, F., & Gagnepain, P. (2020). Resilience after trauma: The role of memory suppression. *Science, 367*(6479). https://doi.org/10.1126/science.aay8477

Marzi, T., Regina, A., & Righi, S. (2014). Emotions shape memory suppression in trait anxiety. *Frontiers in Psychology, 4*. https://doi.org/10.3389/fpsyg.2013.01001

Milton, A. L., & Everitt, B. J. (2012). The persistence of maladaptive memory: Addiction, drug memories and anti-relapse treatments. *Neuroscience & Biobehavioral Reviews, 36*(4), 1119–1139. https://doi.org/10.1016/j.neubiorev.2012.01.002

Moeller, S. J., Bederson, L., Alia-Klein, N., & Goldstein, R. Z. (2016). Neuroscience of inhibition for addiction medicine. *Neuroscience for Addiction Medicine: From Prevention to Rehabilitation - Constructs and Drugs*, 223, 165–188. https://doi.org/10.1016/bs.pbr.2015.07.007

Nardo, T., Batchelor, J., Berry, J., Francis, H., Jafar, D., & Borchard, T. (2022). Cognitive Remediation as an Adjunct Treatment for Substance Use Disorders: A Systematic Review. *Neuropsychology Review, 32*(1), 161–191. https://doi.org/10.1007/s11065-021-09506-3

Noël, X. (2023). A critical perspective on updating drug memories through the integration of memory editing and brain stimulation. *Frontiers in Psychiatry, 14*, 1161879. https://doi.org/10.3389/fpsyt.2023.1161879

Noël, X., Brevers, D., & Bechara, A. (2013). A neurocognitive approach to understanding the neurobiology of addiction. *Current Opinion in Neurobiology, 23*(4), 632–638. https://doi.org/10.1016/j.conb.2013.01.018

Noreen, S., & MacLeod, M. D. (2014). To think or not to think, that is the question: Individual differences in suppression and rebound effects in autobiographical memory. *Acta Psychologica, 145*, 84–97. https://doi.org/10.1016/j.actpsy.2013.10.011

O'Brien, C. P. (2005). Anticraving Medications for Relapse Prevention: A Possible New Class of Psychoactive Medications. *American Journal of Psychiatry, 162*(8), 1423–1431. https://doi.org/10.1176/appi.ajp.162.8.1423

O'Brien, C. P., & McLellan, A. T. (2013). Myths about the treatment of addiction. Applied ethics in mental health care: An interdisciplinary reader. Sisti, D.A., Caplan, A. L., & Rimon-Greenspan, H. *Applied Ethics in Mental Health Care: An Interdisciplinary Reader* (211-221). MIT Press.

Patel, V., Chisholm, D., Parikh, R., Charlson, F. J., Degenhardt, L., Dua, T., Ferrari, A. J., Hyman, S., Laxminarayan, R., Levin, C., Lund, C., Medina Mora, M. E., Petersen, I., Scott, J., Shidhaye, R., Vijayakumar, L., Thornicroft, G., & Whiteford, H. (2016). Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. *The Lancet*, *387*(10028), 1672–1685. https://doi.org/10.1016/s0140-6736(15)00390-6

Redish, A. D., Jensen, S., & Johnson, A. (2008). Addiction as vulnerabilities in the decision process. *Behavioral and Brain Sciences*, *31*(4), 461–487. https://doi.org/10.1017/s0140525x08004986

Robbins, T. W., Ersche, K. D., & Everitt, B. J. (2008). Drug Addiction and the Memory Systems of the Brain. *Annals of the New York Academy of Sciences, 1141*(1), 1–21. Portico. https://doi.org/10.1196/annals.1441.020

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain research reviews*, *18*(3), 247-291. https://doi.org/10.1016/0165-0173(93)90013-P

Robinson, T. E., & Berridge, K. C. (2001). Incentive-sensitization and addiction. *Addiction*, *96*(1), 103-114. https://doi.org/10.1046/j.1360-0443.2001.9611038.x

Schmidt, M., Anderson, M. C., & Tempel, T. (2023). Suppression-induced forgetting of motor sequences. *Cognition, 230*, 105292. https://doi.org/10.1016/j.cognition.2022.105292

Stephens, E., Braid, A., & Hertel, P. T. (2013). Suppression-Induced Reduction in the Specificity of Autobiographical Memories. *Clinical Psychological Science, 1*(2), 163–169. https://doi.org/10.1177/2167702612467773

Storm, B. C., & White, H. A. (2010). ADHD and retrieval-induced forgetting: Evidence for a deficit in the inhibitory control of memory. *Memory, 18*(3), 265–271. https://doi.org/10.1080/09658210903547884

Stramaccia, D. F., Meyer, A.-K., Rischer, K. M., Fawcett, J. M., & Benoit, R. G. (2021). Memory suppression and its deficiency in psychological disorders: A focused meta-analysis. *Journal of Experimental Psychology: General, 150*(5), 828–850. https://doi.org/10.1037/xge0000971

Verdejo-Garcia, A. (2016). Cognitive training for substance use disorders: Neuroscientific mechanisms. *Neuroscience & Biobehavioral Reviews, 68*, 270–281. https://doi.org/10.1016/j.neubiorev.2016.05.018

Volkow, N. D., Fowler, J. S., & Wang, G.-J. (2004). The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology, 47*(1), 3–13. https://doi.org/10.1016/j.neuropharm.2004.07.019

Zilverstand, A., & Goldstein, R. Z. (2020). Dual models of drug addiction. *Cognition and Addiction*, 17–23. https://doi.org/10.1016/b978-0-12-815298-0.00003-4

Zilverstand, A., Huang, A. S., Alia-Klein, N., & Goldstein, R. Z. (2018). Neuroimaging Impaired Response Inhibition and Salience Attribution in Human Drug Addiction: A Systematic Review. *Neuron, 98*(5), 886–903. https://doi.org/10.1016/j.neuron.2018.03.048

Waldhauser, G. T., Dahl, M. J., Ruf-Leuschner, M., Müller-Bamouh, V., Schauer, M., Axmacher, N., Elbert, T., & Hanslmayr, S. (2018). The neural dynamics of deficient memory control in heavily traumatized refugees. *Scientific Reports, 8*(1). https://doi.org/10.1038/s41598-018-31400-x

Wei, X., Li, W., Chen, J., Li, Y., Zhu, J., Shi, H., Liu, J., Xue, J., Liu, W., Wang, F., Liu, Y., Dang, S., Chen, J., Li, Q., & Wang, W. (2020). Assessing drug cue-induced brain response in heroin dependents treated by methadone maintenance and protracted abstinence measures. *Brain Imaging and Behavior, 14*(4), 1221–1229. https://doi.org/10.1007/s11682-019-00051-5

Wiers, R. W. (2018). Cognitive Training in Addiction: Does It Have Clinical Potential? Biological Psychiatry: *Cognitive Neuroscience and Neuroimaging, 3*(2), 101–102. https://doi.org/10.1016/j.bpsc.2017.12.008

Wise, R. A., & Koob, G. F. (2013). The Development and Maintenance of Drug Addiction. *Neuropsychopharmacology, 39*(2), 254–262. https://doi.org/10.1038/npp.2013.261

White, N. M. (1996). Addictive drugs as reinforcers: multiple partial actions on memory systems. *Addiction, 91*(7), 921–950. Portico. https://doi.org/10.1046/j.1360-0443.1996.9179212.x

PART II: METHOD

CHAPTER 4: Forgetting alcohol: a double-blind, randomized controlled trial investigating memory inhibition training in young binge drinkers

The work presented in Chapter 4 was published in Frontiers in Neuroscience

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

Reference:

Almeida-Antunes, N., Vasconcelos, M., Crego, A., Rodrigues, R., Sampaio, A., & López-Caneda, E. (2022). Forgetting Alcohol: A Double-Blind, Randomized Controlled Trial Investigating Memory Inhibition Training in Young Binge Drinkers. *Frontiers in Neuroscience, 16*, 914213. https://doi.org/10.3389/fnins.2022.914213

Journal indexed in JCR. Impact Factor (2022): 4.3

Neuroscience (Miscellaneous): Q2

Citations number: Google Scholar: 1; ISI Web of Knowledge: 1

This protocol was registered in the National Institute of Health (NIH) Clinical Trials Database (ClinicalTrials.gov; identifier: NCT05237414) with the title "*Combining Cognitive Training With tDCS to Enhance memory Inhibition in Young Binge Drinkers*"

Unique Protocol ID: PTDC/PSI-ESP/28672/2017

In addition, this work was also presented at a scientific event, the XV Encontro Nacional da APPE, in May 2021.

Poster Presentation Reference:

Almeida-Antunes, N., Vasconcelos, M., Rodrigues, R., Crego, A., Lopéz-Caneda, E. (2021, April 9, 10). *Forgetting alcohol: A Double-blind, Randomized Controlled Trial Investigating Memory Inhibition Training in Binge Drinkers* [Poster Presentation]. XV Encontro Nacional da APPE.

4.1. Abstract

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

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

Discussion: This study protocol will provide the first behavioral and neurofunctional MI assessment in BDs. Along with poor MI abilities, BDs are expected to show alterations in event-related potentials and functional connectivity patterns associated with MI. Results should also demonstrate the effectiveness of the protocol, with BDs exhibiting an improved capacity to suppress alcohol-related memories after both combined and cognitive training, along with a reduction in alcohol use and craving in the short/mediumterm. Collectively, these findings might have major implications for the understanding and treatment of alcohol misuse.

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

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

4.2. Introduction

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

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

DLPFC has been frequently involved in addictive behaviors, namely in the top-down control processes aiming at regulating motivational reactions to drug cues (Hayashi et al., 2013; Volkow and Morales, 2015). Diminished DLPFC function has been related to reduced cognitive control and higher susceptibility to cue-induced relapse in alcohol abuse (Goldstein and Volkow, 2011). In addition, recent evidence has suggested that the DLPFC plays an important role in memory inhibition (MI), the ability to

suppress unwanted or contextually relevant thoughts/memories (Anderson and Hulbert, 2021). MI is commonly studied through the Think/No-Think (TNT) paradigm, an adaptation of the classical Go/NoGo task typically used to evaluate suppression of motor responses (Huster et al., 2013). Briefly, this paradigm is usually divided into three phases (i.e., learning, TNT, and memory-test phases). In the first phase, participants are instructed to learn cue-target pairs, which can be composed of different types of material (i.e., words, pictures, or even autobiographical). During the TNT task, on each trial, a cue from a pair appears in green (Think trials) or red (No-Think trials). For Think trials, participants must remember the paired item and retain it in awareness; for No-Think trials, participants are asked to prevent the paired item from entering awareness. Lastly, the memory-test phase assesses memory for all pairs, with recall measured on Think, No-Think, and Baseline items (i.e., items that were studied during the learning phase but that did not appear in the TNT phase). Studies using this paradigm report consistently two main findings, supporting the assumption that people can voluntarily suppress retrieval (Anderson and Hanslmayr, 2014). Specifically, final recall for No-Think items is significantly reduced than final recall for Think items, suggesting that retrieval suppression reduces the benefits of reminders on memory. Most importantly, suppressing retrieval frequently decreases the memory for No-Think items below that exhibited for Baseline ones, resulting in the suppression-induced forgetting effect or MI (Anderson and Hulbert, 2021).

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

Despite little is known about the MI processes in cases of substance abuse, some studies have demonstrated that alcohol-dependent individuals display anomalies in the ability to intentionally inhibit specific information in comparison with healthy subjects (Noël et al., 2009; Nemeth et al., 2014). Likewise, recent studies have proposed that MI seems to be impaired in several psychiatric disorders, namely in posttraumatic stress disorder (Catarino et al., 2015), attention deficit hyperactivity disorder (Depue et al., 2010) and depressive disorders (Joormann et al., 2009). In the same line, MI training

revealed to be effective in enhancing the ability to selectively forget unpleasant memories in both healthy subjects and psychiatric patients (Jacobus and Tapert, 2013; Küpper et al., 2014).

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

contribute to the reduction –although limited to the short term- of alcohol consumption (Houben et al., 2011), we will develop a coupled tDCS and MI training protocol to investigate whether this training is able (1) to enhance MI capabilities and reduce alcohol cue reactivity (both assessed during the post-training EEG assessment), and (2) to decrease craving and/or alcohol use—monitoring up to 3 months after protocol implementation- in trained BD participants.

4.3. Materials and Methods

4.3.1. Management and Ethics

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

4.3.2. Study Design and Setting

The authors confirm that all ongoing and related trials of this intervention are registered in the National Institutes of Health (NIH) Clinical Trials Database (ClinicalTrials.gov; identifier: NCT05237414). The CONSORT checklist is available as S1 CONSORT Checklist in Supplementary Material. Participant recruitment started at February 5, 2019 and the anticipated date for follow-up completion is May 15, 2022 (see Figure 11). This study is composed of three different phases: (1) behavioral and electrophysiological analyses of MI abilities in young BDs as compared to age-matched non/low-drinkers; (2) a double-blind, randomized controlled trial aiming at assessing the effects of a MI training protocol at the behavioral and electrophysiological level; and (3) monitoring of self-reported alcohol consumption and alcohol craving 10 days and 3 months after the MI training (see Figure 12). Therefore, this experimental procedure aims to answer four main research questions and test specific hypotheses:

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

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

2. What is the effect of a MI training on behavioral TNTA task performance? Specifically, will the BDs show a reduced recollection of no-think images—mainly for alcoholic no-think—after training? The results should demonstrate the effectiveness of the training protocol, with BDs exhibiting an improved capacity to suppress alcohol-related memories after both combined and cognitive MI training.

3. Are the electrophysiological correlates underlying MI mechanisms and alcohol cue reactivity changed by MI training? The MI training protocol should lead to significant modifications in the ERP and FC patterns, reflecting stronger MI capabilities and reduced alcohol cue reactivity in trained BD participants.

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

Figure 11

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

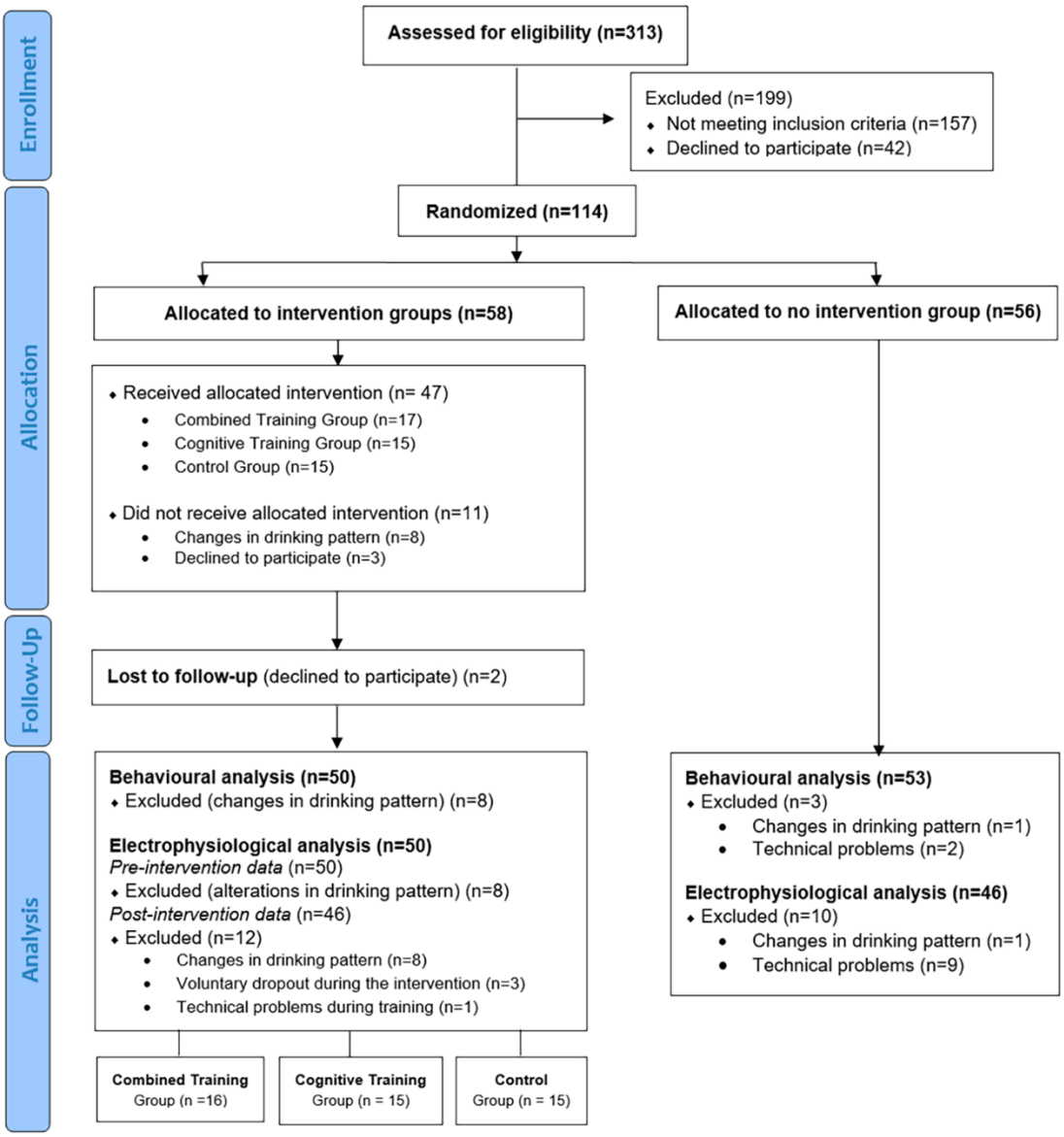
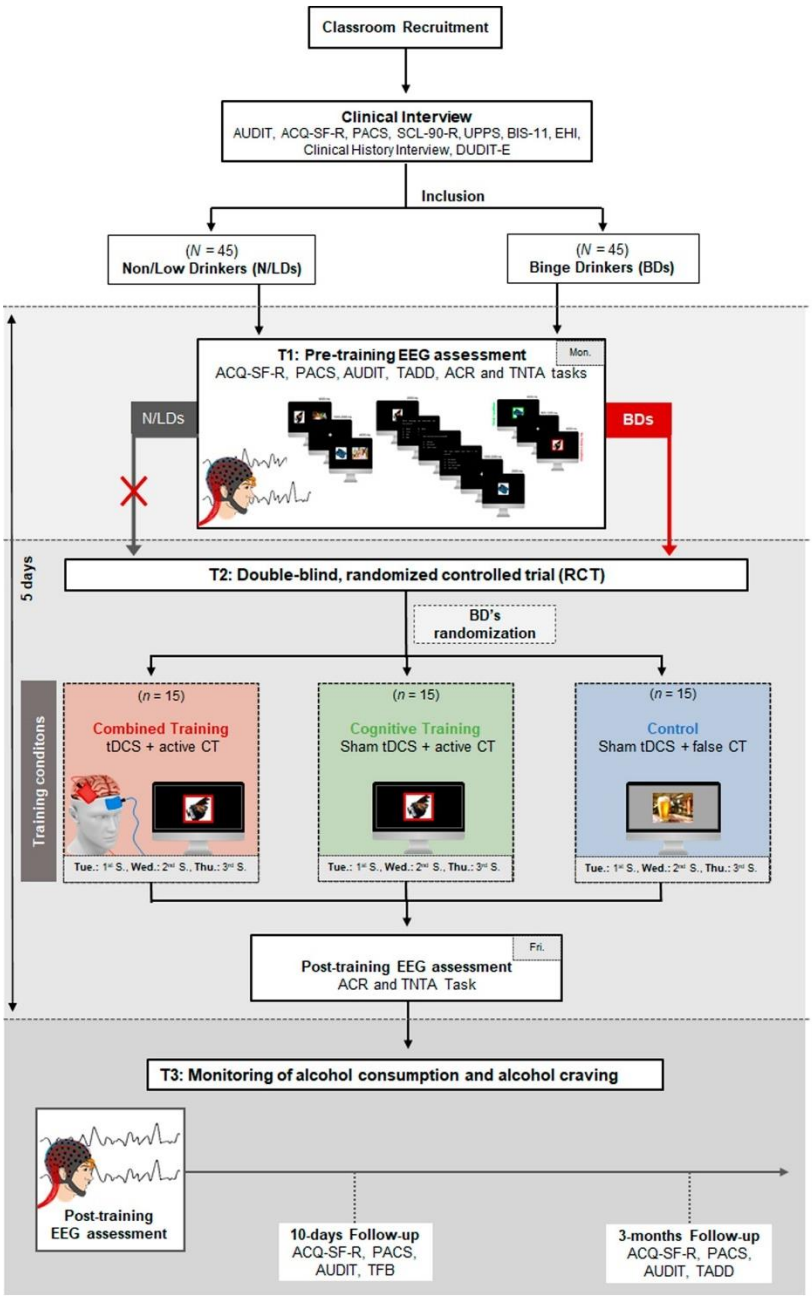


Figure 12

Graphic representation of the procedure.



Note. Participants will perform a clinical interview (T1) to guarantee they fulfill the inclusion criteria and to assess baseline measures (e.g., psychological symptoms and impulsivity). Forty-five college students with a BD pattern will enter the study. To compare BDs with non/low-drinkers, the study will also include a group of 45 aged-matched non/low-drinkers, which will only perform the pre-training EEG assessment. During the pre-training EEG assessment (T2; Monday), alcohol craving and consumption levels will be measured, and participants will perform the TNTA task to assess the behavioral and electrophysiological MI mechanisms. Then (T3), BDs will be randomly distributed for one of three training conditions: Combined Training (i.e., verum tDCS and cognitive training [CT]), Cognitive Training (i.e., sham tDCS and verum CT), and Control (i.e., sham tDCS and sham CT). They will perform three sessions over three consecutive days (i.e., Tuesday, Wednesday, and Thursday). After the training sessions, BDs will perform a post-training EEG assessment (T4; Friday) with a procedure similar

to T2. The monitoring of alcohol consumption and alcohol craving (T5) will be conducted 10 days and 3 months after T4. ACQ-SF-R, Alcohol Craving Questionnaire-Short Form Revised; ACR, Alcohol Cue Reactivity task; AUDIT, Alcohol Use Disorder Identification Test; BDs, Binge Drinkers; BIS-11, Barratt Impulsivity Scale-11; CT, cognitive training; DUDIT-E, Drug Use Disorders Identification Test-Extended; EEG, electroencephalogram; Fri, Friday; GSI, Global Severity Index; Mon, Monday; N/LDs, Non/low-drinkers; PACS, Penn Alcohol Craving Scale; SCL-90-R, Symptom Checklist-90-Revised questionnaire; TADD, Typical and Atypical Drinking Diary; TLFB, Alcohol Timeline Followback; Tue, Tuesday; Thu, Thursday; UPPS-P, Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency; Wed, Wednesday.

4.3.3. Target Population

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

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

substance abuse; (f) occurrence of one or more episodes of loss of consciousness for more than 20 min; (g) non-corrected sensory deficits; (h) Global Severity Index (GSI) > 90 [Symptom Checklist-90-Revised questionnaire (SCL90-R), Derogatis, 1983] or a score above 90 in at least two of the symptomatic dimensions.

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

4.3.4. Experimental Tasks

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

4.3.4.2. Think/No-Think Alcohol Task. The TNTA task is a version of the classical Think/No-Think paradigm (Anderson and Green, 2001), which was specially developed to examine MI mechanisms in alcohol-related contexts (López-Caneda et al., 2019b; see Figure 13). This task includes thirty-six pictures (18 related to alcohol and 18 non-related to alcohol) from the Galician Beverage Picture Set (GBPS; LópezCaneda and Carbia, 2018) and 36 images of neutral objects obtained from the POPORO database (Kovalenko et al., 2012). The GBPS is a database of alcohol and non-alcohol pictures embedded in real-life scenarios which comprises 6 types of beverages: beer, wine, and liquor (alcoholic drinks), and water, juice, and milk (non-alcoholic drinks). The TNTA task includes 6 images from each of the 6

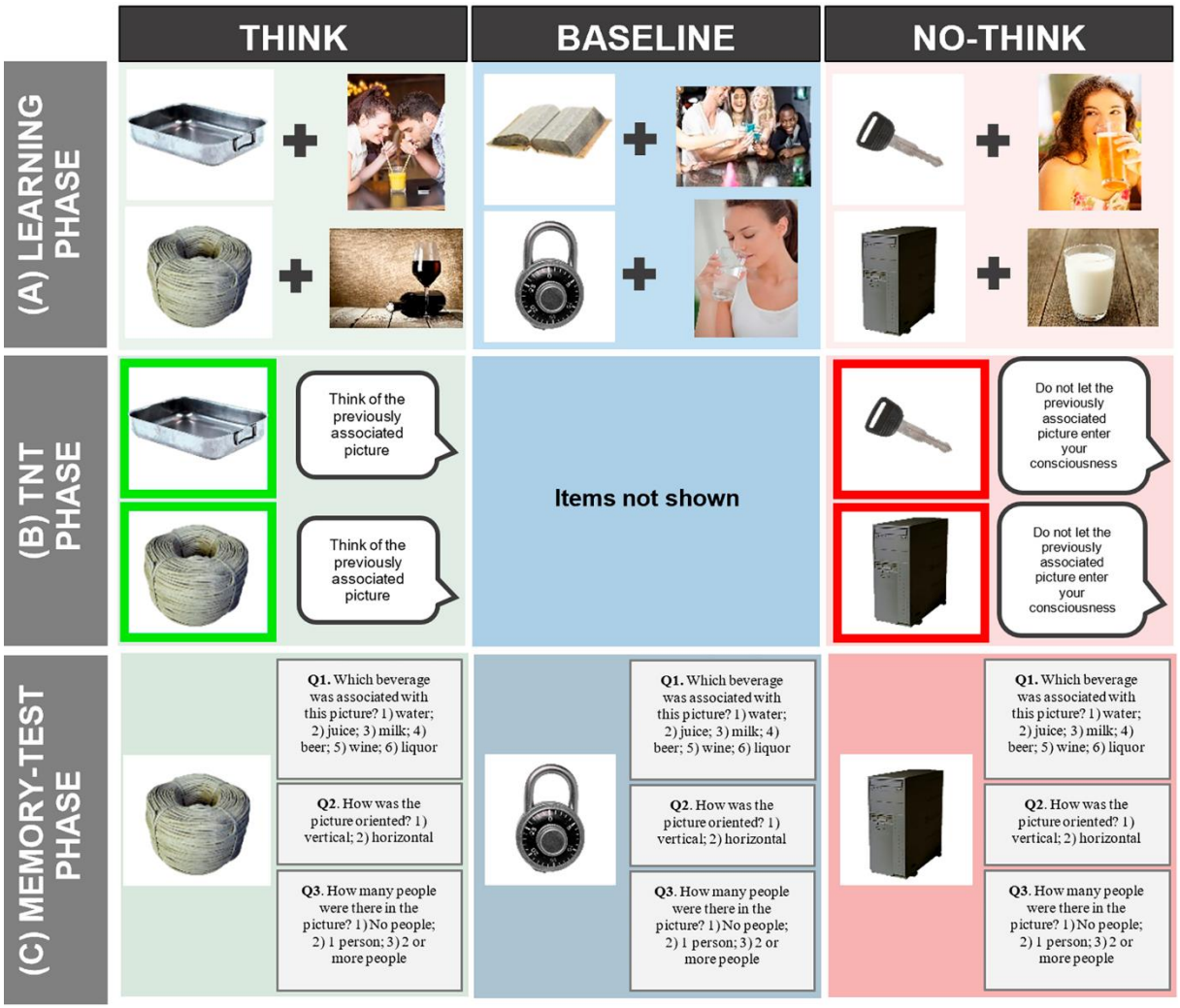
beverages. The pictures also differ in terms of orientation (vertical or horizontal) and number of people (no people, 1 person, 2 or more people). As such, within each type of beverage, 3 are vertical (each one with a different number of people: 0 people, 1 person, 2 or more people) and the other 3 are horizontal (also with 0 people, 1 person, 2 or more people). The task is divided into three phases, i.e., (1) the Learning phase, (2) the Think/No-Think (TNT) phase and (3) the Memory-Test phase, which are carefully described below.

4.3.4.2.1. Learning Phase. During the Learning phase (Figure 13A), participants are asked to memorize 36 image-pairs (i.e., a neutral image paired with an image including alcoholic or non-alcoholic drinks) divided into three blocks of 12 pairs. Each block starts with the presentation of the 12 image-pairs at the center of the screen, each for 4,000 ms, in a randomized order, and with an inter-stimuli interval (ISI) ranging from 1,100 to 1,300 ms (with a 4,000 ms rest every 4 pairs). Subsequently, each of the neutral images is presented for 2,000 ms, and participants must try to remember the image that was associated with the neutral object through three questions: Q1. "Which beverage was associated with this picture?"; Q2. "How was the picture oriented?"; Q3. "How many people were there in the picture?" In each block, the 12 pairs and the questions are repeated three times. At the end of each block, feedback with the number of correct responses will be provided. Correct recall will only be considered when participants provide the right answer to the three questions. Thus, the combination of the potential answers to the three questions ($6 \times 2 \times 3 = 36$) ensured that each target image displayed a unique combination.

4.3.4.2.2. Think/No-Think Phase. In this phase (Figure 13B), there are two possible actions: to Think or to No-Think on the alcoholic/non-alcoholic image paired with the neutral object previously. Specifically, in the Think condition—determined by a green frame that circumvents the neutral image -, participants will be asked to focus on the neutral image and think of the alcoholic/non-alcoholic image that was associated with it. In the No-Think condition—neutral image circumvented by a red frame—participants are instructed to focus on the image and not let the previously associated alcoholic/non-alcoholic picture enter their consciousness. Images will randomly repeated 15 times and presented for 3,000 ms (offset-onset ISI = 1,100–1,300 ms). From the initial set of 36 neutral images shown in the learning phase only 24 will be depicted during the TNT phase, 12 in each condition (i.e., Think and No-Think). The remaining 12 neutral images not depicted in this phase will be used as a baseline condition for the following Memory Test phase.

Figure 13

Overall depiction of the Think/No-Think Alcohol (TNTA) task.



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

4.3.4.2.3. Memory Test Phase. During this phase (Figure 13C), the 36 neutral images from each pair are again presented, including the 12 images of the baseline condition. Participants are asked to remember the image (alcoholic or non-alcoholic) that was initially associated with the neutral object using the same three questions of the Learning phase. Three different versions of the task (where all the pictures were part of the three conditions: Think, No-Think and baseline) will be created and counterbalanced across participants.

4.3.4.3. Think/No-Think Alcohol Task Variations for Active and False Cognitive Training. Two variations of the TNTA task were developed for the active CT and for the false CT. The stimuli employed in these variations of the TNTA task were also obtained from the GBPS and POPORO databases; however, these stimuli differ from those used in the original TNTA task. The structure of the task for the MI active CT is the same as the original TNTA task. However, in this variation, the Learning phase is only composed of two blocks of 12-image pairs, and in the TNT phase, all the stimuli to be inhibited are alcohol-related images.

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

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

4.5. Procedure

4.5.1. T1: Clinical Interview

All the stages of the procedure are detailed in Figure 12. During the clinical interview (T1), we will verify the fulfillment of the exclusion/inclusion criteria and assess the baseline levels of some constructs (e.g., craving levels, impulsivity). Consequently, the following instruments will be used (see Supplementary Figure B.1): (1) the AUDIT along with five additional alcohol use questions (i.e., speed of drinking [number of drinks consumed per hour], number and type of drinks consumed in a standard week, percentage of times getting drunk when going out, age of onset of regular alcohol use and BD); (2) the DUDIT-E to examine other drugs use; (3) the Penn Alcohol Craving Scale (PACS; Pombo et al., 2008) and the Alcohol Craving Questionnaire-Short Form Revised (ACQ-SF-R; Rodrigues et al., 2021); (4) the Barratt Impulsivity Scale-11 (BIS-11; Cruz and Barbosa, 2012) and the short form of the Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency (UPPS-P; Cyders et al., 2014) impulsive

behavior scale; (5) the Symptom Checklist90-Revised questionnaire (SCL-90-R) to evaluate the presence of psychopathological traits; (6) a clinical history interview to explore the personal/family history of psychopathological and neurological disorders as well as the overall medical history of the participants; and (7) the Edinburgh Handedness Inventory (EHI; Espírito-Santo et al., 2017) to evaluate the participants' handedness.

4.5.2. T2: Pre-training Electroencephalographic Assessment

During the pre-training EEG assessment (see Figure 12), psychological (i.e., craving levels), behavioral (i.e., alcohol consumption levels and task performance) and neurofunctional (e.g., ERPs, brain FC) outcomes will be assessed (for more details on the instruments used see Supplementary Figure B.1). EEG data will be collected while participants perform the ACR and the TNTA task. Before the EEG recording, participants will be asked to perform a breathalyzer test to ensure that blood alcohol concentration is 0.0% (Alcoscan ALC-1). Along with the AUDIT, we will administer the Alcohol Timeline Followback (TLFB) and the Typical and Atypical Drinking Diary (TADD) in order to determine alcohol consumption levels during the previous week and the previous 3 months, respectively. After filling in the questionnaires, participants will perform the ACR task, which lasts from 5 to 10 min. Then, participants' resting brain activity will be recorded for 3 min during eyes-closed prior to the TNTA task. Finally, they will perform the TNTA task with a duration of 1 h and 10 min. Accordingly, the total duration of the pre-training EEG assessment will be approximately two and a half hours.

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

4.5.3. T3: MI Training Sessions

BDs will be randomly assigned to one of the three training subgroups: (a) *Combined training*; (b) *Cognitive training*; or (c) *Control* (see Figure 12). The participants' allocation to the training group will be done by an independent researcher who will be responsible to program the tDCS parameters. Thus, both participants and research team will be blind to the randomization procedure.

During T3, subjects will perform the variation of the TNTA task corresponding to the group to which they will be assigned. After the first phase of the task (i.e., Learning Phase), neuromodulation (sham or active) will be performed using tDCS. Twenty minutes of 2 mA direct current will be applied to the scalp using a saline-soaked pair of 35 cm2 surface sponge electrodes, through an Eldith DC Stimulator Plus (Neuroconn, Germany). To stimulate the right DLPFC, the anodal electrode will be placed over F4 according to the 10–20 international system for EEG electrode placement. The cathode electrode will be placed over the contralateral supraorbital area. During the active simulation, the current will fade in for 15 s, will be constant at 2 mA for 20 min, and then will fade out for 15 s. During the sham stimulation, the electric current will fade in for 15 s, then will be constant at 2 mA for 15 s and will fade out for 15 s. This procedure makes both active and sham stimulation indistinguishable for the participants. Before and after the stimulation, participants will answer to a continuous Visual Analog Scale that allows checking for possible secondary effects of the electrical stimulation.

4.5.4. T4: Post-training Electroencephalographic Assessment

During T4 (see Figure 12), participants will perform the ACR and TNTA tasks under the same procedure to the one undertaken during the T2.

4.5.5. T5: Monitoring of Alcohol Consumption and Alcohol Craving

Ten days after the T4, the primary craving and alcohol consumption outcomes will be assessed (see Figure 12). For this purpose, we will administer the PACS, the ACQ-SF-R and the AUDIT. Additionally, 3 months post-intervention, BDs will answer the same questionnaires and also the TADD aiming at assessing potential medium-term effects of the MI training.

4.6. Data Collection and Analysis

4.6.1. Data Collection

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

4.6.2. Electroencephalographic Data Processing

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

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

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

4.6.3. Statistics

The first step of the statistical analyses will be to examine the behavioral and EEG correlates of MI among college BDs and non/low-drinkers. For that purpose, the outcomes of the TNTA task collected during the pre-training assessment (T2) in BDs and non/low-drinkers will be compared and correlated with alcohol consumption (AUDIT) and alcohol craving measures (i.e., the PACS' and ACQ-SF-R's scores, and the ERPs and valence/arousal ratings recorded during the ACR task). Secondly, with the purpose of verifying the impact of the combined, cognitive and control training procedures applied to BDs on psychological, behavioral, and neurofunctional measures, the pre-training data (T2) from the 45 BDs will be compared with data from T4 (post-training) and T5 (monitoring of alcohol consumption and alcohol craving). In addition, the three training groups will be compared with each other in order to determine potential differences between the training procedures at T4 and T5 stages.

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

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

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

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

For the TNTA task, we will analyze the ERPs, specifically the mean amplitudes of N2, LPP, and FSW. A mixed-model ANOVA with one between-subject factor Group (non/lowdrinkers, BDs) and four within-subject factors: Condition (Think, No-Think), Content (Alcohol, Non-Alcohol), Region (Left, Midline,

Right), and Electrode (2 electrodes) will be conducted on the mean amplitude of each component to explore the MI neural mechanisms during T2. A repeated-measures ANOVA with five within-subject factors: Moment (T2 and T4), Condition (Think, No-Think), Content (Alcohol, Non-Alcohol), Region (Left, Midline, Right) and Electrode (two electrodes) will be conducted on the mean amplitude of each component separately, to explore the effects of MI training on the neural activity.

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

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

4.7. Discussion

At the present, the literature is still scarce regarding both the core functional anomalies in BDs and the neurobiological factors that underlie the evolution from pre-clinical (e.g., hazardous alcohol use, BD) to clinical conditions related to alcohol (i.e., AUD) (Witkiewitz et al., 2019). This study protocol constitutes an important step to fill in the existing gap and an opportunity to shed new light on a broad and more comprehensive understanding of the memory suppression mechanisms and their potential implication on heavy alcohol use. To the best of our knowledge, this protocol will be the first to describe the design and implementation of a randomized controlled trial that examines MI in BDs and tests the effectiveness of different types of MI training using both CT and neuromodulation by tDCS with the aim of reducing alcohol use and craving. Examining the extent to which BDs may have difficulties to inhibit alcoholrelated

information, what its behavioral and neurophysiological underpinnings are and how they can be potentially modified by training, will extend previous research on inhibition training in social and problem drinkers (Petit et al., 2012; Jones et al., 2014; Di Lemma and Field, 2017; Smith et al., 2017; Kilwein et al., 2018). Moreover, findings resulting from this research could hold important clinical implications for alcohol misuse treatment, particularly for that focused on the training of response inhibition to alcohol cues (Houben et al., 2011, 2012; Tschuemperlin et al., 2019).

Besides its innovative character granted by the use of a neuromodulation technique and the collection of behavioral and electrophysiological data, the protocol involves the longitudinal assessment of important psychological variables and measurements of alcohol craving/consumption registered at follow-up periods of up to 3 months. This monitoring will allow a comprehensive proximal and distal characterization of potential changes in BD behavior resulting from the MI training. Ultimately, the present study may be particularly important as it can provide a new and useful tool for the clinical community and, consequently, contribute to improving the quality of life of individuals suffering from problems related to alcohol and/or other substances. Moreover, our findings might encourage other researchers to conduct new studies on this topic and, thus, lead to a build-up of a strong and more comprehensive body of knowledge involving MI in substance misuse that can be translated into measurable societal impact.

4.8. References

Almeida-Antunes, N., Antón-Toro, L., Crego, A., Rodrigues, R., Sampaio, A., & López-Caneda, E. (2022). "It's a beer!": Brain functional hyperconnectivity during processing of alcohol-related images in young binge drinkers. *Addiction Biology*, 27, e13152.

Anderson, M. C., & Green, C. (2001). Suppressing unwanted memories by executive control. *Nature, 410*, 366-369. https://doi.org/10.1038/35066572

Anderson, M. C., & Hanslmayr, S. (2014). Neural mechanisms of motivated forgetting. *Trends in Cognitive Sciences, 18*, 279-292. https://doi.org/10.1016/j.tics.2014.03.002

Anderson, M. C., & Hulbert, J. C. (2021). Active forgetting: Adaptation of memory by prefrontal control. *Annual Review of Psychology, 72*, 1-36. https://doi.org/10.1146/annurev-psych-072720-094140

Anderson, M. C., Ochsner, K. N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S. W., ... & Gabrieli, J. D. (2004). Neural systems underlying the suppression of unwanted memories. *Science, 303*, 232-235. https://doi.org/10.1126/science.1089504

Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B., & Monteiro, M. G. (2001). AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. Department of Mental Health and Substance Dependence, World Health Organization, Geneva, Switzerland.

Balsa, C., Vital, C., Urbano, C. (2014). *III Inquérito Nacional ao Consumo de Substâncias Psicoativas na População Geral Portugal 2012*. Lisboa: SICAD - Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências.

Berman, A. H., Palmstierna, T., Källmén, H., & Bergman, H. (2007). The self-report drug use disorders identification test—extended (DUDIT-E): reliability, validity, and motivational index. *Journal of Substance Abuse Treatment*, 32, 357-369. https://doi.org/10.1016/j.jsat.2006.10.001

Boggio, P. S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., ... & Fregni, F. (2008). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind, sham-controlled study. *Drug and Alcohol Dependence, 92*, 55-60. https://doi.org/10.1016/j.drugalcdep.2007.06.011.

Bradley, M. M., & Lang, P. J. (1994). Measuring Emofion-the Self-Assessment Mannequin and the Semanfic Differenfial. *Journal of Behaviour Therapy and Experimental Psychiatry, 25,* 49, 59. https://doi.org/10.1016/0005-7916(94)90063-9

Brumback, T., Squeglia, L. M., Jacobus, J., Pulido, C., Tapert, S. F., & Brown, S. A. (2015). Adolescent heavy drinkers' amplified brain responses to alcohol cues decrease over one month of abstinence. *Addictive Behaviors, 46*, 45-52. https://doi.org/10.1016/j.addbeh.2015.03.001

Bruña, R., Maestú, F., & Pereda, E. (2018). Phase locking value revisited: teaching new tricks to an old dog. *Journal of Neural Engineering, 15*, 056011. https://doi.org/10.1088/1741-2552/aacfe4

Campanella, S., Peigneux, P., Petit, G., Lallemand, F., Saeremans, M., Noël, X., ... & Verbanck, P. (2013). Increased cortical activity in binge drinkers during working memory task: a preliminary assessment through a functional magnetic resonance imaging study. *PloS One, 8*, e62260. https://doi.org/10.1371/journal.pone.0062260

Carbia, C., López-Caneda, E., Corral, M., & Cadaveira, F. (2018). A systematic review of neuropsychological studies involving young binge drinkers. *Neuroscience & Biobehavioral Reviews, 90*, 332-349. https://doi.org/10.1016/j.neubiorev.2018.04.013.

Catarino, A., Küpper, C. S., Werner-Seidler, A., Dalgleish, T., & Anderson, M. C. (2015). Failing to forget: Inhibitory-control deficits compromise memory suppression in posttraumatic stress disorder. *Psychological Science, 26*, 604-616. https://doi.org/10.1177/0956797615569889

Cohen, J. (2013). *Statistical power analysis for the behavioral sciences*. Routledge. https://doi.org/10.4324/9780203771587

Crego Barreiro, M. A., Cadaveira Mahía, F., Parada Iglesias, M., Corral Varela, M. M., Caamaño Isorna, F., & Rodríguez Holguín, S. Increased amplitude of P3 event-related potential in young binge drinkers. *Alcohol, 46*, 415–425. https://doi.org/10.1016/j.alcohol.2011.10.002

Czapla, M., Simon, J. J., Friederich, H. C., Herpertz, S. C., Zimmermann, P., & Loeber, S. (2015). Is binge drinking in young adults associated with an alcohol-specific impairment of response inhibition? *European Addiction Research, 21*, 105-113. https://doi.org/10.1159/000367939

da Silva, M. C., Conti, C. L., Klauss, J., Alves, L. G., do Nascimento Cavalcante, H. M., Fregni, F., ... & Nakamura-Palacios, E. M. (2013). Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. *Journal of Physiology-Paris, 107*, 493-502. https://doi.org/10.1016/j.jphysparis.2013.07.003

den Uyl, T. E., Gladwin, T. E., Lindenmeyer, J., & Wiers, R. W. (2018). A clinical trial with combined transcranial direct current stimulation and attentional bias modification in alcohol-dependent patients. *Alcoholism: Clinical and Experimental Research*, *42*, 1961-1969. https://doi.org/10.1111/acer.13841

den Uyl, T. E., Gladwin, T. E., Rinck, M., Lindenmeyer, J., & Wiers, R. W. (2017). A clinical trial with combined transcranial direct current stimulation and alcohol approach bias retraining. *Addiction Biology, 22*, 1632-1640. https://doi.org/10.1111/adb.12463

den Uyl, T. E., Gladwin, T. E., & Wiers, R. W. (2015). Transcranial direct current stimulation, implicit alcohol associations and craving. *Biological Psychology, 105*, 37-42. https://doi.org/10.1016/j.biopsycho.2014.12.004

den Uyl, T. E., Gladwin, T. E., & Wiers, R. W. (2016). Electrophysiological and behavioral effects of combined transcranial direct current stimulation and alcohol approach bias retraining in hazardous drinkers. *Alcoholism: Clinical and Experimental Research*, 40, 2124-2133. https://doi.org/10.1111/acer.13171

Depue, B. E., Burgess, G. C., Willcutt, E. G., Ruzic, L., & Banich, M. (2010). Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: evidence from deficits in individuals with ADHD. *Neuropsychologia, 48*, 3909-3917. https://doi.org/10.1016/j.neuropsychologia.2010.09.013

Derogatis, L. R. (1983). SCL-90-R revised manual. Baltimore: Johns Hopkins University School of Medicine.

Di Lemma, L. C., & Field, M. (2017). Cue avoidance training and inhibitory control training for the reduction of alcohol consumption: a comparison of effectiveness and investigation of their mechanisms of action. *Psychopharmacology, 234*, 2489-2498. https://doi.org/10.1007/s00213-017-4639-0

Ditye, T., Jacobson, L., Walsh, V., & Lavidor, M. (2012). Modulating behavioral inhibition by tDCS combined with cognitive training. *Experimental Brain Research, 219*, 363-368. https://doi.org/10.1007/s00221-012-3098-4

Dormal, V., Lannoy, S., Bollen, Z., D'Hondt, F., & Maurage, P. (2020). Can we boost attention and inhibition in binge drinking? Electrophysiological impact of neurocognitive stimulation. *Psychopharmacology, 237*, 1493-1505. https://doi.org/10.1007/s00213-020-05475-2

Dubuson, M., Kornreich, C., Vanderhasselt, M. A., Baeken, C., Wyckmans, F., Dousset, C., ... & Noël, X. (2021). Transcranial direct current stimulation combined with alcohol cue inhibitory control training reduces the risk of early alcohol relapse: A randomized placebo-controlled clinical trial. *Brain Stimulation, 14*, 1531-1543. https://doi.org/10.1016/j.brs.2021.10.386

Ekhtiari, H., Tavakoli, H., Addolorato, G., Baeken, C., Bonci, A., Campanella, S., ... & Hanlon, C. A. (2019). Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: a consensus paper on the present state of the science and the road ahead. *Neuroscience & Biobehavioral Reviews, 104*, 118-140. https://doi.org/10.1016/j.neubiorev.2019.06.007

Espírito-Santo, H., Pires, C. F., Garcia, I. Q., Daniel, F., Silva, A. G. D., & Fazio, R. L. (2017). Preliminary validation of the Portuguese Edinburgh Handedness Inventory in an adult sample. *Applied Neuropsychology: Adult*, *24*, 275-287. https://doi.org/10.1080/23279095.2017.1290636

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41*, 1149-1160. https://doi.org/10.3758/BRM.41.4.1149

Fregni, F., Nitsche, M. A., Loo, C. K., Brunoni, A. R., Marangolo, P., Leite, J., ... & Bikson, M. (2015). Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): review and recommendations from an expert panel. *Clinical Research and Regulatory Affairs, 32*, 22-35. https://doi.org/10.3109/10601333.2015.980944

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*, *12*, 652-669. https://doi.org/10.1038/nrn3119

Hayashi, T., Ko, J. H., Strafella, A. P., & Dagher, A. (2013). Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proceedings of the National Academy of Sciences, 110*, 4422-4427. https://doi.org/10.1073/pnas.1212185110

Holcomb, L. A., Huang, S., Cruz, S. M., & Marinkovic, K. (2019). Neural oscillatory dynamics of inhibitory control in young adult binge drinkers. *Biological Psychology, 146*, 107732. https://doi.org/10.1016/j.biopsycho.2019.107732

Houben, K., Havermans, R. C., Nederkoorn, C., & Jansen, A. (2012). Beer à No-Go: Learning to stop responding to alcohol cues reduces alcohol intake via reduced affective associations rather than increased response inhibition. *Addiction, 107*, 1280-1287. https://doi.org/10.1111/j.1360-0443.2012.03827.x

Houben, K., Nederkoorn, C., Wiers, R. W., & Jansen, A. (2011). Resisting temptation: decreasing alcohol-

related affect and drinking behavior by training response inhibition. *Drug and Alcohol Dependence, 116*, 132-136. https://doi.org/10.1016/j.drugalcdep.2010.12.011

Huster, R. J., Enriquez-Geppert, S., Lavallee, C. F., Falkenstein, M., & Herrmann, C. S. (2013). Electroencephalography of response inhibition tasks: functional networks and cognitive contributions. *International Journal of Psychophysiology, 87*, 217-233. https://doi.org/10.1016/j.ijpsycho.2012.08.001

Jacobus, J., & Tapert, S. F. (2013). Neurotoxic effects of alcohol in adolescence. *Annual Review of Clinical Psychology, 9*, 703-721. https://doi.org/10.1146/annurev-clinpsy-050212-185610

Jansen, J. M., Daams, J. G., Koeter, M. W., Veltman, D. J., Van Den Brink, W., & Goudriaan, A. E. (2013). Effects of non-invasive neurostimulation on craving: a meta-analysis. *Neuroscience & Biobehavioral Reviews, 37*, 2472-2480. https://doi.org/10.1016/j.neubiorev.2013.07.009

Joormann, J., Hertel, P. T., LeMoult, J., & Gotlib, I. H. (2009). Training forgetting of negative material in depression. *Journal of Abnormal Psychology, 118*, 34. https://doi.org/10.1037/a0013794

Jones, A., McGrath, E., Houben, K., Nederkoorn, C., Robinson, E., & Field, M. (2014). A comparison of three types of web-based inhibition training for the reduction of alcohol consumption in problem drinkers: study protocol. *BMC Public Health, 14*, 1-10. https://doi.org/10.1186/1471-2458-14-796

Jones, S. A., Lueras, J. M., & Nagel, B. J. (2018). Effects of binge drinking on the developing brain: studies in humans. *Alcohol research: current reviews*, *39*, 87.

Kekic, M., Boysen, E., Campbell, I. C., & Schmidt, U. (2016). A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. *Journal of Psychiatric Research, 74*, 70-86. https://doi.org/10.1016/j.jpsychires.2015.12.018

Kilwein, T. M., Bernhardt, K. A., Stryker, M. L., & Looby, A. (2018). Decreased alcohol consumption after pairing alcohol-related cues with an inhibitory response. *Journal of Substance Use, 23*, 154-161.https://doi.org/10.1080/14659891.2017.1378736

Klauss, J., Penido Pinheiro, L. C., Silva Merlo, B. L., Correia Santos, G. D. A., Fregni, F., Nitsche, M. A., & Miyuki Nakamura-Palacios, E. (2014). A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *International Journal of Neuropsychopharmacology, 17*, 1793-1803. https://doi.org/10.1017/S1461145714000984

Klauss, J., Anders, Q. S., Felippe, L. V., Nitsche, M. A., & Nakamura-Palacios, E. M. (2018). Multiple sessions of transcranial direct current stimulation (tDCS) reduced craving and relapses for alcohol use: a randomized placebo-controlled trial in alcohol use disorder. *Frontiers in Pharmacology, 9*, 716. https://doi.org/10.3389/fphar.2018.00716

Kovalenko, L. Y., Chaumon, M., & Busch, N. A. (2012). A pool of pairs of related objects (POPORO) for investigating visual semantic integration: behavioral and electrophysiological validation. *Brain Topography, 25*, 272-284. https://doi.org/10.1007/s10548-011-0216-8

Kraus, L., Guttormsson, U., Leifman, H., Arpa, S., Molinaro, S., Monshouwer, K., ..., Hibell, B. (2016). ESPAD Report 2015. Results from the European School Survey Project on Alcohol and Other Drugs. Lisbon: European Monitoring Centre for Drugs and Drug Addiction and the European School Survey Project on Alcohol and Other Drugs. Available online at: http://www.espad.org/sites/espad.org/files/ESPAD_report_2015.pdf

Küpper, C. S., Benoit, R. G., Dalgleish, T., & Anderson, M. C. (2014). Direct suppression as a mechanism for controlling unpleasant memories in daily life. *Journal of Experimental Psychology: General, 143*, 1443. https://doi.org/10.1037/a0036518

Lannoy, S., D'hondt, F., Dormal, V., Billieux, J., & Maurage, P. (2017). Electrophysiological correlates of performance monitoring in binge drinking: Impaired error-related but preserved feedback processing. *Clinical Neurophysiology, 128*, 2110-2121. https://doi.org/10.1016/j.clinph.2017.08.005

Lannoy, S., Dormal, V., Billieux, J., Brion, M., D'Hondt, F., & Maurage, P. (2019). A dual-process exploration of binge drinking: evidence through behavioral and electrophysiological findings. *French Journal of Psychiatry, 1*, S92. https://doi.org/10.1111/ adb.12685

Lees, B., Meredith, L. R., Kirkland, A. E., Bryant, B. E., & Squeglia, L. M. (2020). Effect of alcohol use on the adolescent brain and behavior. *Pharmacology Biochemistry and Behavior*, 192, 172906. https://doi.org/10.1016/j.pbb.2020.172906

López-Caneda, E., Cadaveira, F., & Campanella, S. (2019a). Binge drinking in the adolescent and young brain. *Frontiers in Psychology*, 2724. https://doi.org/10.3389/ fpsyg.2018.02724.

López-Caneda, E., Cadaveira, F., Crego, A., Doallo, S., Corral, M., Gómez-Suárez, A., & Rodríguez Holguín, S. (2013). Effects of a persistent binge drinking pattern of alcohol consumption in young people: a follow-up study using event-related potentials. *Alcohol and Alcoholism, 48*, 464-471. https://doi.org/10.1093/alcalc/agt046

López-Caneda, E., & Carbia, C. (2018). The Galician Beverage Picture Set (GBPS): A standardized database of alcohol and non-alcohol images. *Drug and Alcohol Dependence, 184*, 42-47. https://doi.org/10.1016/j.drugalcdep.2017.11.022

López-Caneda, E., Crego, A., Campos, A. D., González-Villar, A., & Sampaio, A. (2019b). The Think/No-Think Alcohol Task: A New Paradigm for Assessing Memory Suppression in Alcohol-Related Contexts. *Alcoholism: Clinical and Experimental Research, 43*, 36-47. https://doi.org/10.1111/acer.13916

López-Caneda, E., Rodríguez Holguín, S., Cadaveira, F., Corral, M., & Doallo, S. (2014). Impact of alcohol use on inhibitory control (and vice versa) during adolescence and young adulthood: a review. *Alcohol and Alcoholism, 49*, 173-181. https://doi.org/10.1093/alcalc/agt168

Maurage, P., Lannoy, S., Mange, J., Grynberg, D., Beaunieux, H., Banovic, I., ... & Naassila, M. (2020). What we talk about when we talk about binge drinking: Towards an integrated conceptualization and evaluation. *Alcohol and Alcoholism, 55*, 468-479. 1. https://doi.org/10.1093/alcalc/agaa041

Martin, D. M., Liu, R., Alonzo, A., Green, M., Player, M. J., Sachdev, P., & Loo, C. K. (2013). Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. *International Journal of Neuropsychopharmacology, 16*, 1927-1936. https://doi.org/10.1017/S1461145713000539

National Institute of Alcohol Abuse and Alcoholism. (2004). NIAAA council approves definition of binge drinking. NIAAA Newsletter, 3, p. 3. Available at: http://pubs.niaaa.nih.gov/publications/Newsletter/winter2004/Newsletter_Number3.pdf

Nemeth, V. L., Kurgyis, E., Csifcsak, G., Maraz, A., Almasi, D. A., Drotos, G., ... & Must, A. (2014). The impact of intermediate-term alcohol abstinence on memory retrieval and suppression. *Frontiers in Psychology, 5*, 1396. https://doi.org/10.3389/fpsyg.2014.01396

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., ... & Pascual-Leone, A. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain Stimulation, 1*, 206-223. https://doi.org/10.1016/j.brs.2008.06.004

Noël, X., Billieux, J., Van der Linden, M., Dan, B., Hanak, C., De Bournonville, S., ... & Verbanck, P. (2009). Impaired inhibition of proactive interference in abstinent individuals with alcoholism. *Journal of Clinical and Experimental Neuropsychology, 31*, 57-64. https://doi.org/10.1080/13803390801982726

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational intelligence and neuroscience*, *2011*. https://doi.org/10.1155/2011/156869

Peeters, M., Wiers, R. W., Monshouwer, K., van de Schoot, R., Janssen, T., & Vollebergh, W. A. (2012). Automatic processes in at-risk adolescents: the role of alcohol-approach tendencies and response

inhibition in drinking behavior. *Addiction, 107*, 1939-1946. https://doi.org/10.1111/j.1360-0443.2012.03948.x.

Peirce, J. W. (2007). PsychoPy—psychophysics software in Python. *Journal of neuroscience methods, 162*, 8-13. https://doi.org/10.1016/j.jneumeth.2006.11.017

Petit, G., Kornreich, C., Verbanck, P., & Campanella, S. (2013). Gender differences in reactivity to alcohol cues in binge drinkers: A preliminary assessment of event-related potentials. *Psychiatry Research, 209*, 494-503. https://doi.org/10.1016/j.psychres.2013.04.005

Petit, G., Kornreich, C., Dan, B., Verbanck, P., & Campanella, S. (2014). Electrophysiological correlates of alcohol-and non-alcohol-related stimuli processing in binge drinkers: A follow-up study. *Journal of Psychopharmacology, 28*, 1041-1052. https://doi.org/10.1177/0269881114545663.

Pombo, S., Ismail, F., & Cardoso, J. N. (2008). "CRAVERS" PELO ÁLCOOL. *Psicologia, Saúde e Doenças, 9*, 349-365.

Pronk, T., van Deursen, D. S., Beraha, E. M., Larsen, H., & Wiers, R. W. (2015). Validation of the Amsterdam Beverage Picture Set: A controlled picture set for cognitive bias measurement and modification paradigms. *Alcoholism: Clinical and Experimental Research, 39*, 2047-2055. https://doi.org/10.1111/acer.12853

Rodrigues, R., López-Caneda, E., Almeida-Antunes, N., Sampaio, A., & Crego, A. (2021). Portuguese validation of the Alcohol Craving Questionnaire–Short Form–Revised. *PloS One, 16*, e0251733. https://doi.org/10.1371/journal.pone.0251733

Ryerson, N. C., Neal, L. B., & Gable, P. A. (2017). Attenuating the alcohol allure: attentional broadening reduces rapid motivational response to alcohol pictures. *Psychopharmacology, 234*, 1247-1254. https://doi.org/10.1007/s00213-017-4557-1.

Smith, J. L., Dash, N. J., Johnstone, S. J., Houben, K., & Field, M. (2017). Current forms of inhibitory training produce no greater reduction in drinking than simple assessment: A preliminary study. *Drug and Alcohol Dependence, 173*, 47-58. https://doi.org/10.1016/j.drugalcdep.2016.12.018

Townshend, J. M., & Duka, T. (2005). Binge drinking, cognitive performance and mood in a population of young social drinkers. *Alcoholism: Clinical and Experimental Research*, *29*, 317-325. https://doi.org/10.1097/01.ALC.0000156453.05028.F5

Tschuemperlin, R. M., Stein, M., Batschelet, H. M., Moggi, F., & Soravia, L. M. (2019). Learning to resist the urge: a double-blind, randomized controlled trial investigating alcohol-specific inhibition training in abstinent patients with alcohol use disorder. *Trials, 20*, 1-16. https://doi.org/10.1186/s13063-019-3505-2

Vanderhasselt, M. A., Allaert, J., De Raedt, R., Baeken, C., Krebs, R. M., & Herremans, S. (2020). Bifrontal tDCS applied to the dorsolateral prefrontal cortex in heavy drinkers: influence on reward-triggered approach bias and alcohol consumption. *Brain and Cognition*, 138, 105512. https://doi.org/10.1016/j.bandc.2019.105512

Van Veen, B. D., Van Drongelen, W., Yuchtman, M., & Suzuki, A. (1997). Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on biomedical engineering*, *44*, 867-880. https://doi.org/10.1109/10.623056

Volkow, N. D., & Morales, M. (2015). The brain on drugs: from reward to addiction. *Cell, 162*, 712-725. https://doi.org/10.1016/j.cell.2015.07.046

Witkiewitz, K., Litten, R. Z., & Leggio, L. (2019). Advances in the science and treatment of alcohol use disorder. *Science Advances, 5*. https://doi.org/10.1126/sciadv.aax4043

World Health Organization. (2019). Status report on alcohol consumption, harm and policy responses in 30 European countries 2019 (No. WHO/EURO: 2019-3545-43304-60696). World Health Organization. Regional Office for Europe.

World Health Organization. (2011). Global status report on alcohol and health. Geneva. World Health Organization.

PART III: EMPIRICAL STUDIES

CHAPTER 5: "It's a beer!": Brain functional hyperconnectivity during processing of alcohol-related images in young binge drinkers

The work presented in Chapter 5 was published in Addiction Biology

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

Reference:

Almeida-Antunes, N., Antón-Toro, L., Crego, A., Rodrigues, R., Sampaio, A., & López-Caneda, E. (2022). " It's a beer!": Brain functional hyperconnectivity during processing of alcohol-related images in young binge drinkers. *Addiction Biology*, *27*, e13152. https://doi.org/10.1111/adb.13152

Journal indexed in JCR. Impact Factor (2022): 4.46

Medicine (Miscellaneous): Q1; Pharmacology: Q1; Psychiatry and Mental Health: Q2

Citations number: Google Scholar: 5; ISI Web of Knowledge: 5

In addition, results from this empirical work were fully presented as a poster presentation at the 18th European Society for Biomedical Research on Alcoholism (ESBRA) Conference (Timisoara, Romania), one of the most prestigious congresses at the European level concerned with alcoholism research. This work received the ESBRA Poster Award Winner 2021.

Poster Presentation Reference:

Almeida-Antunes, N., Antón-Toro, L., Crego, R., Rodrigues, R., Sampaio, A., López-Caneda, E. (2021, October 7-9). *Brain Functional Hyperconnectivity During Processing of Alcohol-Related Images in Young Binge Drinkers* [Poster Presentation]. 18th European Society for Biomedical Research on Alcoholism Conference. Timisoara, Romania.

5.1. Abstract

Alcohol attentional bias has been pointed as a major marker of alcohol misuse. Recent evidence has revealed that brain functional connectivity (FC) may be a valuable index of the brain networks' integrity in young binge drinkers (BDs). However, there is no study to date examining the FC networks linked to the processing of alcohol-related images in this population. The present study aimed to explore the FC signatures underlying alcohol attention bias in young BDs. Thus, electroencephalographic (EEG) activity was recorded in 54 college students (55.5% females; 27 non/low-drinkers and 27 BDs) while performing a visual alcohol cue-reactivity task. We evaluated whole-brain FC profiles during the processing of alcoholic and non-alcoholic cues, as well as their potential relationship with craving and severity of alcohol use. Results showed that, at the behavioral level, BDs rated alcohol-related images as more pleasant/attractive than non/low-drinkers. Furthermore, at the electrophysiological level, BDs exhibited increased beta-band FC –particularly in the fronto-parieto-occipital network- when processing alcoholic cues. Conversely, they displayed reduced theta-band FC relatively to non/low-drinkers for non-alcoholic images. These hyper-/hypo-connectivity patterns were associated with higher alcohol craving levels. Findings are congruent with previous neurofunctional studies reporting an attentional bias towards alcohol-related information in BDs. These results may have important clinical implications as this neural reactivity to alcoholic cues may contribute to the maintenance and/or escalation of the drinking pattern. Finally, the present study constitutes the first evidence showing that FC networks may be a sensitive indicator to alcohol attentional bias in BDs.

Keywords: binge drinking, attentional bias, alcoholic images, alcohol cue reactivity, electroencephalography, functional connectivity.

5.2. Introduction

Binge Drinking (BD) consists of excessive alcohol drinking episodes alternated by periods of low consumption or abstinence. In the last decade, a growing interest in this form of alcohol misuse has been observed, mainly due to its high prevalence among youngsters and the adverse consequences resulting from this pattern.[1] Evidence has shown that adolescent and young adult binge drinkers (BDs) exhibit impaired cognitive functioning, altered brain structure, and neurofunctional abnormalities.[2-4] Importantly, research has also proposed that BD may constitute a first step towards alcohol dependence,[5] as similar impairments to those documented in alcohol-dependent individuals have been observed in young BDs.[6, 7] Among the similarities observed between BDs and people with alcoholism, the reactivity to alcohol-related cues deserves particular attention, since it has been strongly associated with craving[8, 9] and may consequently contribute to the maintenance and/or escalation of the drinking pattern[10, 11]

Attentional bias has been pointed as a critical phenomenon presented in alcohol use disorders (AUDs)[12] and sub-clinical conditions, including BD.[2, 8, 13] This bias is usually characterized by a tendency to preferentially allocate attentional resources to alcohol-related cues when they are presented together with other type of stimuli.[8] This heightened attention resulting from an increase in the incentive motivational properties of alcohol-related stimuli, may lead to higher alcohol consumption and craving levels,[10, 11] contributing to the emergence and persistence of AUD.[14]

Although studies examining attentional bias in young BDs are limited, the electroencephalographic (EEG) and functional magnetic resonance imaging (fMRI) studies conducted so far seem to point to an increased reactivity to alcoholic cues in this population. Specifically, BDs exhibit increased brain activity in regions involved in reward processing[13] as well as larger N1, P1 and P3 amplitudes of the event-related potentials (ERPs), during the processing of alcohol-related stimuli.[2]

Recently, analysis of brain functional connectivity (FC) –i.e., the temporal dependency of neuronal activation patterns of anatomically separated brain regions[15] - has provided important information regarding the functional networks' integrity in a variety of psychopathological conditions, including AUDs.[16] Research in this field has revealed changes in multiple brain networks in patients with alcoholism, indicating reduced FC during task-performance[17] and resting state conditions.[18] Similarly, several neuroimaging studies have reported FC disruptions in BDs during resting state.[19, 20]

In addition, FC has showed to be an efficient approach to explore alcohol cue reactivity in AUDs, as fMRI studies have reported increased FC between subcortical and prefrontal regions for alcohol-related stimuli in abstinent alcohol-dependent individuals.[21] However, given that attentional bias to drug cues may operate in early orienting and automatic processes rather than maintained attention[22], the study of these

short and rapid mechanisms would greatly benefit from the use of techniques with higher time resolution, which is not the case for fMRI.[23] In contrast, EEG is a non-invasive technique with an excellent temporal resolution, providing the millisecond-by-millisecond time-course of neural processing and thus may shed new light on the early brain processes underlying alcohol cue reactivity.

As we mentioned above, several BD studies have examined the electrophysiological activity associated with alcohol attentional bias through ERPs; nevertheless, the evidence about the underlying neuronal network interactions is still scarce. As cognitive and perceptual processing involves the interaction between neuronal ensembles from specialized but widely distributed brain regions[24, 25], exploring how transient neuronal associations form and interact is important to understand the neuronal basis of alcohol attentional bias. Accordingly, the present study aims to fill the existing gap assessing the FC networks linked to the processing of alcohol-related images in young BDs.

FC is a method used to study the dynamic connections between neuronal populations which, over the last two decades, has emerged as a key technique in the exploration of the neuronal interactions between both neighboring and distant regions that occurs during resting-state brain activity as well as during different cognitive/perceptual tasks[26]. The neural information transmitted from one region to another occurs by action potentials temporally organized in bursts that may occur during oscillations, contributing to the establishment of long-range synchronization.[24, 27] Thus, EEG -with its powerful time-resolution- appears to be a suitable approach to investigate the brain's functional connections. In this vein, this neuroimaging technique combined with FC may offer an optimal strategy to understand how alcohol attentional bias are comprehended in the brain.

Bearing this in mind, in the present study, we used the EEG signal to explore the brain FC signatures linked to a visual alcohol cue-reactivity task in young BDs. To the best of our knowledge, this is the first EEG study assessing FC networks underlying the processing of alcohol-related images in this population. We hypothesized that BDs would exhibit increased FC for alcohol-related stimuli when compared to non/low-drinkers (N/LDs), particularly in the visual attention networks (e.g., fronto-parietal and fronto-occipital networks), suggesting increased attentional processing of alcoholic cues. Contrarily, BDs will show reduced FC relatively to N/LDs during the processing of non-alcoholic images, reflecting lower attentional capture for such stimuli.

5.3. Material and Methods

5.3.1. Participants

Participants were recruited through a screening questionnaire administered in the classroom of several courses at the University of Minho (UM). The screening included the Alcohol Use Disorder Identification Test (AUDIT) along with other questions concerning alcohol and other drugs use. Two groups were formed based on their AUDIT scores. Students who reported (i) drinking 5 or more drinks on one occasion at least once a month, and (ii) drinking at a speed of consumption of at least two drinks per hour during these episodes, were classified as BDs. Those who reported (i) never drink 5 or more drinks on each occasion and (ii) an AUDIT score ≤ 4, were considered N/LDs.

All participants provided written informed consent prior to the clinical interview, which was performed to assess the following exclusion criteria: use of illegal drugs except for cannabis (i.e., at most once a month) as determined by the Drug Use Disorders Identification Test-Extended (DUDIT-E); alcohol abuse (i.e., score ≥ 20 in the AUDIT); consumption of medical drugs with psychoactive effects (e.g., sedatives or anxiolytics) during the two weeks before the experiment; personal history of psychopathological disorders (according to DSM-V criteria); history of traumatic brain injury or neurological disorder; family history of psychopathological disorders (including alcoholism); occurrence of an episode of loss of consciousness for more than 20 minutes; non-corrected sensory deficits; score > 90 in the Global Severity Index (GSI) of the Symptom Checklist-90 revised questionnaire (SCL-90-R) or in at least two of the symptomatic dimensions.

Sixty-one participants who met the criteria were selected to perform the experiment; however, seven of them were excluded from the analysis due to insufficient quality in the EEG signal. Accordingly, a total of 54 participants (27 BDs and 27 N/LDs), aged between 18 and 23 (M = 19.37; SD = 1.36), were included in this study. The demographic, drinking characteristics and craving levels of the two groups are summarized in Table 5.

5.3.2. Procedure

The experimental procedure was conducted in accordance with the Declaration of Helsinki, meeting the requirements for exemption and anonymity, and received approval by the Institutional Ethics Committee for Social Sciences and Humanities of the University of Minho, Braga, Portugal (CECSH 078/2018). Participants were asked to refrain from consuming alcohol in the last 24 hours and not having BD episodes in the 3 days before the EEG session. Additionally, they were instructed not to smoke, drink tea or coffee for at least 3 hours before the assessment. Before the EEG session, we used the

Breathalyzer test (Alcoscan ALC-1) to verify that the blood alcohol concentration value was 0.0%. Moreover, we administrated the Portuguese version of the Alcohol Craving Questionnaire-Short Form-Revised (ACQ-SF-R) to evaluate alcohol craving and the AUDIT. Then, each subject was seated in a comfortable armchair located in a light- and sound-attenuated electrically shielded room and the EEG experiment was carried out.

Table 5

Demographic, drinking characteristics and craving measures of the BD and Control groups (mean (SD))

	BD (*n* = 27)	N/LDs (*n*=27)
Demographic measures		
Gender ratio (male/female)	13/14	11/16
Age	19.33(1.14)	19.41 (1.58)
Drinking Characteristics		
Total AUDIT score***	6.63(2.24)	.81(.83)
Age of onset of regular drinking[a]	16.63(1.01)	16.80(.94)
Age of onset of BD	17.74(.94)	-
Number of drinks in a standard week***	12.19(7.02)	.88(1.30)
Percentage of drunkenness***	44.63(29.55)	2.58(9.91)
Tobacco users	8	3
Cannabis users (at most once a month)	3	0
Alcohol Craving Measures		
PACS score***	3.07(2.67)	.35(.98)
Total ACQ-SF-R Score***	2.06(.75)	1.32(.42)
Compulsivity Factor***	1.40(.49)	1.02(.07)
Purposefulness Factor**	2.84(1.50)	1.73(1.15)
Emotionality Factor**	2.11(.94)	1.32(.70)

Notr. AUDIT: Alcohol Use Disorders Identification Test; PACS: Penn Alcohol Craving Scale; ACQ-SF-R: Alcohol Craving Questionnaire-Short Form-Revised.

[a]18 years old is the legal drinking age in Portugal for spirit drinks, and 16 years old is the legal drinking age for wine and beer

*p < 0.05 significant group differences, **p < .01 significant group differences, ***p < .001 significant group differences,

5.3.3. Alcohol Cue Reactivity (ACR) Task

Images of alcoholic and non-alcoholic drinks taken from the Amsterdam Beverage Picture Set[28] were used as visual stimuli. Each trial started with a white fixation cross in a grey background for a variable duration ranging from 1000 to 1500 ms. Subsequently, an alcoholic or non-alcoholic image was presented centrally for 3000 ms. The full task included a total of 80 trials (40 alcoholic and 40 non-alcoholic). Participants were asked to look at each picture and to remain focused on the fixation cross. After the ACR task, which lasted approximately five minutes, participants had to rate their emotional responses (valence and arousal) for each of the 80 pictures using the Self-Assessment Mannequin[29].

5.3.4. EEG Acquisition

EEG signal was recorded by the ActiveTwo Biosemi electrode system (Biosemi, Inc., Amsterdam, the Netherlands) from 64 electrodes organized according the 10/10 system using a Common Mode Sense (CMS) recording montage. Vertical and horizontal electro-oculogram activity was recorded to control for eye movements and blinks. The impedances of all electrodes were kept below 20 kΩ and the EEG signal was amplified and digitized at 512 Hz rate and filtered on-line with a 0.01–100 Hz bandpass filter.

In order to eliminate ocular and motor movements, we used a semi-automatic detection method. For each subject, the normal distribution of raw signal (restricting its frequency range using band-pass filter for each type of artifact) was calculated. Signals ≥ 2 standard deviations from mean score were automatically marked as artifacts. In a posterior step, the correct artifacts removal was visually inspected by an expert signal analyst. Thus, every trial affected by movement or other kind of artifacts were discarded from subsequent analysis. Finally, we performed a statistical analysis to discard potential between-groups differences in the number of motor artifacts and number of discarded trials (26,44% for BD group, and 23,73% for N/LD group). We extracted the number artifacts for each subject and performed a between-groups t-test. We did not find significant differences neither for the number of motor artifacts ($t = 1.227$; $p = 0.225$) nor for the number of discarded trials ($t = 0.891$; $p = 0.377$).

5.3.5. EEG data analysis and source reconstruction

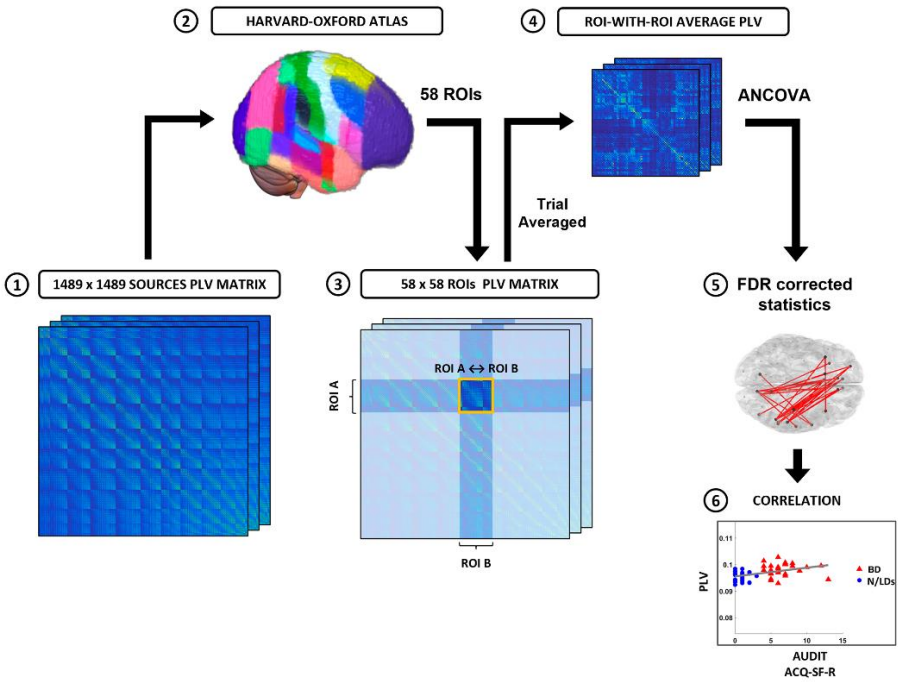
EEG data were transformed into source space employing a realistic *Boundary elements model* (BEM)[30] as forward model and a Linearly Constrain, Minimum Variance (LCMV) beamformer[31] as inverse model. Cortical sources were reconstructed in four classical bands: theta (4 – 8 Hz), alpha (8 – 12 Hz), beta (12 – 30 Hz), and low gamma (30 – 45 Hz), using the Montreal Neurological Institute (MNI) template-

based T1 images (ICBM 152).[32] In order to assess the quality of estimated signal, we calculated the well-known P100 visual component in source space, as the mean power spectrum in the time window from 100 ms to 150 ms. These assessments are depicted in Supplementary Figure C.1.

The final source model consisted of 1489 cortical sources positions (subcortical sources were discarded), labelled according to the Harvard-Oxford probabilistic atlas as described in Desikan et al. (2006).[33] FC analysis was calculated under the hypothesis of phase synchronization by means of the Phase Locking Value (PLV)[34] in an early time window from 0 to 400 ms (Figure 14). In order to study the brain processing of alcoholic and non-alcoholic stimuli independently, each condition was analyzed separately. In a first step, PLV was calculated separately for each pair of source positions, generating a 1489 x 1489 FC matrix. Secondly, we averaged the PLV values of all the links connecting each pair of 58 cortical regions of interest (ROI) according to the Harvard-Oxford atlas,[33] obtaining a 58 x 58 whole-brain FC matrix. Additionally, a number of quality-check analyses were performed in order to enhance the robustness of the results and minimize or remove potential artefact-driven outcomes.[35]

Figure 14

Pipeline method for FC calculation.



Note. (1) PLV values of each pair of cortical source positions (1489 × 1489) form the global connectivity matrix. (2) Whole brain data from 58 cortical regions of interest (ROIs) drawn from the Harvard-Oxford probabilistic atlas33 were extracted. (3) PLV values of all the links connecting each pair of 58 cortical regions of interest (ROI) were averaged, (4) obtaining a 58 × 58 whole-brain FC matrix. The connectivity values in (4) were compared between- and within-groups with ANCOVA test and corrected using a False Discovery Rate (FDR) in order to (5) analyse potential statistically significant hypo- or hyper-connected

ROI pairs. Finally, (6) PLV values of significant inter-ROIs links were correlated with self-reported measures of craving for alcohol (ACQ-SF-R)

5.3.6. Correction of source leakage bias

Many phase synchronization metrics such PLV are known to suffer from source leakage effects, traditionally overcame using zero-lag insensitive metrics. However, such metrics have showed low test-retest reliability in MEG and EEG data,[36] and ignores bidirectional and indirect true connections.[37] We addressed this problem correcting our results by the direct estimation of source leakage, using a Beamformer filter correlation (BFc) as covariate in our statistical analysis.[35, 38] Concretely, once the matrix of significant links is generated, we performed over them a second ANCOVA comparison between groups, using BFc as covariate. This approach successfully removes the leakage differences between groups, remaining the significant links free of source leakage bias (35% for beta and 100% for theta bands).

5.3.7. Experimental Design and Statistical Analysis

Demographic, drinking variables and craving measures were analyzed by independent samples t-test. The self-reported emotional responses –i.e., valence and arousal ratings- to alcoholic and non-alcoholic pictures were analyzed by a mixed-model ANOVA with one between-subject factor (Group: N/LD and BD) and one within-subject factor (Stimuli: alcoholic and non-alcoholic).

For the whole-brain analysis, the PLV value between each pair of ROIs was compared between groups by an ANCOVA test using BFc as covariate and gender as factor. The resulting *p*-values were corrected for multiple comparisons (number of pair comparisons and number of frequency bands) with a False Discovery Rate (FDR) of 0.1.[39] The resulting FDR-corrected alpha threshold was 0.002 for alcoholic condition in beta-band and 0.0008 for non-alcoholic condition in theta band, and only *p*-values below that threshold were reported as significant. Once the significant links for each condition were determined, Spearman correlations were conducted between the PLV values and the ACQ-SF-R scores. Results were corrected for multiple comparisons (number of links and number of tests) using FDR approach of 0.1. Only links which survived this correction were reported as significant. Additionally, we performed a similar ANCOVA test within-groups between conditions, with an FDR-corrected alpha threshold of 0.0009.

5.4. Results

5.4.1. Behavioral Results

Behavioral results are summarized in Table 6.

5.4.1.1. Valence. The analysis of valence ratings showed significant effects for the Stimuli factor [$F(1,52)= 24.20$, $p< .001$, $\eta_p^2 = .318$], with higher scores for non-alcoholic than alcoholic stimuli. Also, there was a significant Stimuli x Group interaction [$F(1,52)= 5.42$, $p= .024$, $\eta_p^2 = .094$]. The post hoc analysis revealed that BDs had scores significantly higher for alcoholic stimuli than their N/LD peers [$F(1,52)= 6.26$, $p= .016$, $\eta_p^2 = .107$], while no significant differences between groups were found for non-alcoholic stimuli. Additionally, the N/LD group exhibited higher scores for non-alcoholic than for alcoholic stimuli [$F(1,52)= 26.24$, $p< .001$, $\eta_p^2 = .335$].

5.4.1.2. Arousal. The analysis of arousal ratings revealed neither a significant Stimuli effect nor a significant Group x Stimuli interaction. However, post-hoc comparisons revealed a non-significant trend for different arousal rates between alcoholic and non-alcoholic stimuli in BDs [$F(1,52)=3.73$, $p= .059$, $\eta p^2 = .067$]). Planned comparisons in the form of paired-samples t-test were used to explore these differences. Results showed that BDs rated alcoholic (M= 5.09, SD= 1.07) as more arousing than non-alcoholic (M= 4.23, SD= 1.46) stimuli [t(26)= 2.39, p= .024].

Table 6

Arousal and valence ratings for alcoholic and non-alcoholic stimuli, mean(SD)

Ratings	BDs	N/LDs
Arousal		
Alcoholic stimuli	5.09(1.07)	4.67(1.05)
Non-alcoholic stimuli	4.23(1.46)	4.58(2.17)
Valence		
Alcoholic stimuli	5.08(1.09)	4.21(1.43)
Non-alcoholic stimuli	5.93(1.62)	6.59(1.63)

5.4.2. Functional Connectivity Results

5.4.2.1. Whole-brain synchronization analysis. We calculated ANCOVA statistical differences in terms of PLV FC for each pair of 58 cortical ROIs, between the N/LD and BD group for the 4 classical frequency bands, independently for alcoholic and non-alcoholic stimuli.

Regard to alcoholic condition, the BD group showed a pattern of hypersynchronization -i.e., enhanced synchronization between ROIs- in 32 connectivity links for the beta-band ($p < 0.002$) when compared with the N/LD group. These links mainly exhibited significant hypersynchronization of prefrontal areas with parietal, temporal and occipital regions, namely among the bilateral medial

prefrontal cortex (mPFC) -including anterior cingulate (ACC)-, the right occipital cortex -including cuneus-, right medial parietal regions, such as precuneus, and right posterior temporal cortex. Figure 15 shows the spatial distribution of significant connectivity links in the beta-band.

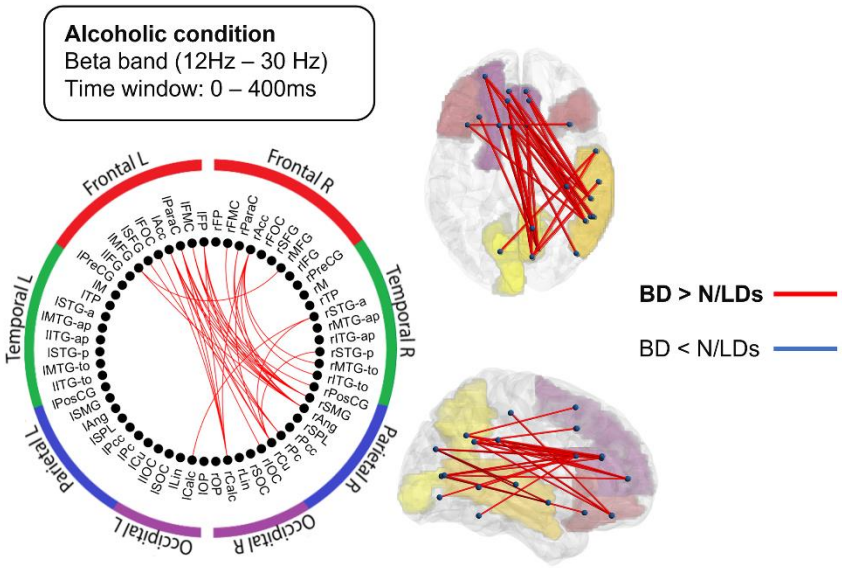
Concerning non-alcoholic condition, BD group displayed a pattern of hyposynchronization relatively to N/LD participants in 12 connectivity links for the theta-band ($p < 0.0008$). These links showed significant hyposynchronization mainly between the mPFC, left inferior frontal gyrus (lIFG), frontal orbital cortex (lFOC), and the occipital cortex –including primary visual areas (i.e., the calcarine cortex and right cuneus). Figure 16 depicts the spatial distribution of significant connectivity links in the theta-band. All significant results were corrected for source leakage bias by BFc.

Additionally, within-groups comparisons were also conducted for both N/LD and BD participants. These analyses showed that the BD group displayed higher FC in the theta band to alcoholic relatively to non-alcoholic stimuli in 14 links between fronto-occipital and left fronto-temporal regions, and lower FC in one connectivity link among inter-hemispheric parietal regions (see Supplementary Figure C.2). The beta-band FC did not show significant differences for BD group. Within-group analyses for the N/LD group did not show significant effects in any frequency band. Boxplots of PLV values for each group and condition are depicted in Supplementary Figures C.3 (beta band) and C.4 (theta band).

Finally, in order to verify that our significant results were not driven by differences in tobacco and cannabis consumption, we conducted a between-group ANCOVA for each significant link, using cannabis and tobacco as covariates, separately. Results showed that cannabis (Figure C.5) and tobacco (Figure C.6) consumption did not influence the differences in the FC, remaining all links as significant.

Figure 15

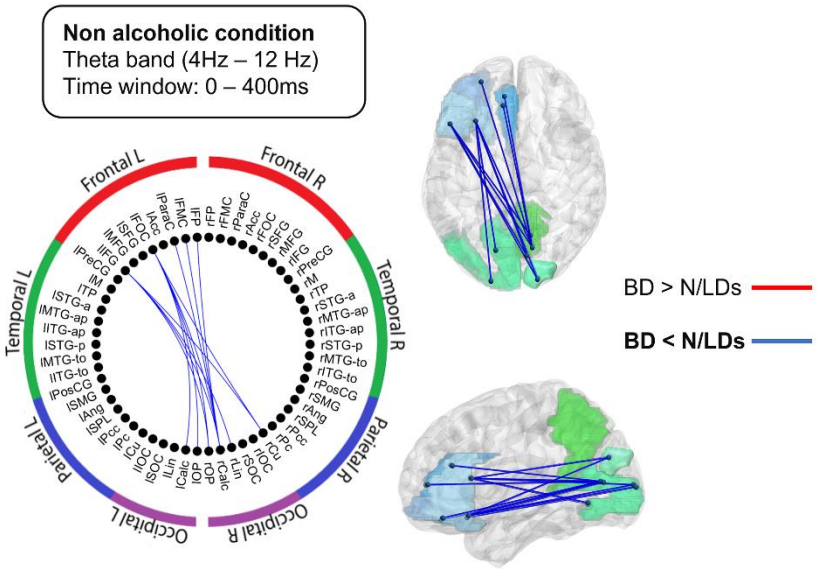
Distribution of significant FC links in beta band (12–30 Hz) for alcoholic condition at 0–400 ms time window.



Note. Red links represent higher connectivity between pairs of cortical regions (coloured areas) for BD group. All links were corrected for multiple comparisons by FDR method and for source leakage effects

Figure 16

Distribution of significant FC links in theta band (4–12 Hz) for non-alcoholic condition at 0–400 ms time window.



Note. Blue links represent lower connectivity between pairs of cortical regions (coloured areas) for BD group. All links were corrected for multiple comparisons by FDR method and for source leakage effects

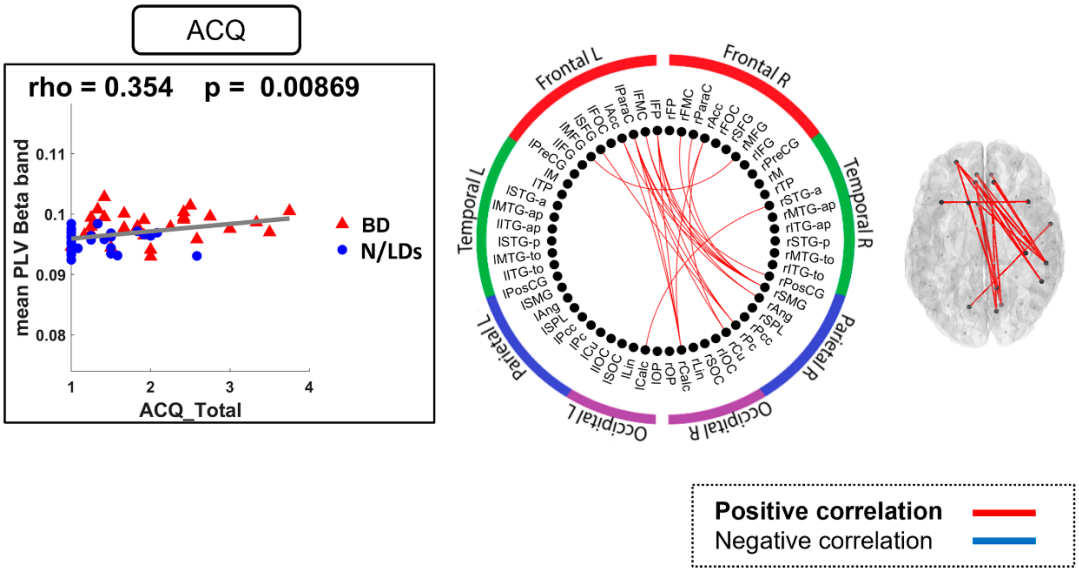
5.4.2.2. Whole-brain synchronization correlations

Correlation analysis was performed for PLV values with ACQ-SF-R scores in order to explore the relationship between electrophysiological connectivity and craving levels. Only significant connectivity links were used for these correlations, corrected by FDR.

PLV values for alcoholic stimuli in the beta band revealed that 22 of the 32 connectivity links presented a significant and positive correlation with ACQ-SF-R scores. Figure 17 shows the distribution of links with significant correlations and the parameters *p* and *rho* for the mean of correlated links. With regard to the PLV values for non-alcoholic stimuli in the theta band, correlation analysis revealed significant and negative correlations between ACQ-SF-R scores and 5 of 12 connectivity links. Figure 18 shows the distribution of links with significant correlations and the parameters *p* and *rho* for the mean of correlated links.

Figure 17

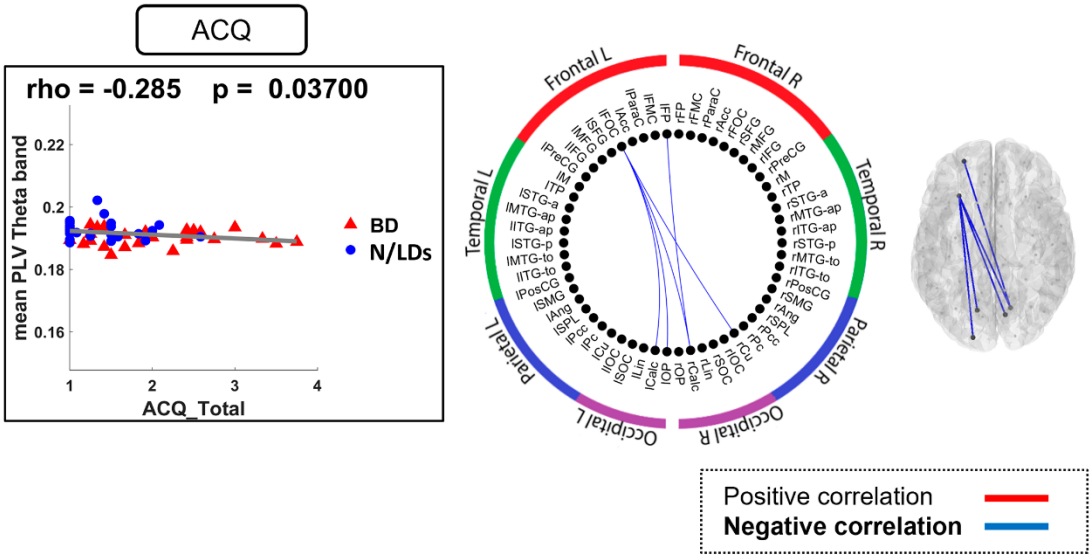
Representation of beta band FC links with significant correlations with ACQ-SF-R score in the alcoholic condition (right).



Note. Red links represent significant positive correlations. Correlation analyses were corrected for multiple comparisons by FDR (number of regions and number of tests). The left part shows the scatter plots and statistical parameters of correlation analysis between the mean FC value of significant links and the ACQ-SF-R score

Figure 18

Representation of theta band FC links with significant correlations with ACQ-SF-R score in the non-alcoholic condition (right).



Note. Blue links represent significant negative correlations. Correlation analyses were corrected for multiple comparisons by FDR (number of regions and number of tests). The left part shows the scatter plots and statistical parameters of correlation analysis between the mean FC value of significant links and ACQ-SF-R score.

5.5. Discussion

The present study is the first to examine the brain connectivity patterns underlying the processing of alcohol-related images in young BDs, using a neuroimaging approach with high temporal resolution – i.e., the EEG technique- combined with FC analysis. This method allowed us to capture the readiness of brain responses to alcoholic cues in this population. Overall, the results showed a beta-band hyperconnectivity in BDs, relative to N/LDs, during the processing of alcohol-related images. This increased connectivity for alcoholic cues was mainly observed over the right fronto-parietal, fronto-occipital and fronto-temporal regions. Conversely, during the processing of non-alcoholic stimuli, BDs exhibited a theta-band hypoconnectivity pattern –over a similar, left-lateralized fronto-occipital network- when compared to N/LDs. Furthermore, correlational analyses showed that these patterns of hyper-/hypo-connectivity were in turn associated with increased alcohol craving levels (i.e., higher ACQ-SF-R scores). These findings are consistent with an attentional bias for alcohol-related cues in BDs,[2, 13] revealing that young people with binge alcohol consumption display increased neural processing when faced with alcohol-related information.

Considering that beta-band has been associated with sensory alertness, anticipatory attentional processing, and early visual cue-reactivity,[40, 41] our results of increased beta FC for alcoholic pictures

observed in BDs may reveal an attentional prioritization over alcohol-related information in this population. Likewise, augmented beta has been also observed in response to substance-related cues in studies addressing other substance abuse[42, 43] and during the exposure to food-related cues in overweight women,[44] suggesting that increased beta may reflect a processing bias for highly desired and salient stimuli. Indeed, it is known that beta-band is involved in the activation of cortical representations of relevant stimuli, facilitating network level communication, namely top-down attentional interactions.[45] Research has shown that top-down beta originated from higher cognitive brain areas and delivered to earlier sensory ones can support selective attention.[41] In the present study, BDs displayed a beta-band hyperconnectivity in response to alcoholic cues over brain networks involving frontal regions and sensory areas, including the fronto-parietal network, which is thought to be involved in top-down attention[41]. Furthermore, the increased FC to alcoholic cues was also observed over a fronto-occipital network. The connection between these brain regions seems to mediate expectancy-related attentional mechanisms for specific stimulus during visual processing and discrimination[46] and has also been associated with visual selective attention.[47] Thus, our findings suggest that BDs, during the exposure to alcoholic cues, may exhibit an overactivation of brain networks responsible for attentional mechanisms involved in the processing of relevant/desired stimuli, which leads to increased processing of alcohol-related information.

The increased beta FC for alcoholic cues in BDs may also be associated with a dopaminergic activity elicited by a reward anticipation caused by the exposure to such cues. In this line, a recent study by Elton et al. (2021) also showed a significant role of dopamine for both alcohol and non-drug reward attentional bias. Specifically, they found that dopamine depletion decreases FC between prefrontal and subcortical brain areas involved in reward processing and motivation, and these decreases were, in turn, predicted by altered attentional bias.[48] Similarly, evidence has revealed that beta oscillations are linked to dopaminergic neuromodulation, suggesting that dopamine may mediate beta power generation.[49]

As stated by the incentive-sensitization theory of addiction, the repeated exposure to substance produces progressively larger dopaminergic responses, increasing its salient and motivational properties.[50] Thus, substance-related cues would produce conditioned hyper-reactive dopaminergic responses,[51] enhancing attentional bias and subjective craving towards them.[52] In the same vein, the concept of cue-reactivity proposes that the repeated exposure to substance stimulus changes the reward value from actual to anticipated consumption, leading the conditioned stimulus that predicts the reward to elicit a higher dopaminergic activity than the substance consumption by itself.[53] Accordingly, an EEG study reported increased beta oscillatory power for reward-predicting cues, which was described as dopaminergic effects of neural reward anticipation.[54] Considering this evidence, perhaps with the

successive BD episodes over time, young BDs may start to process alcohol-related stimuli as an anticipatory reward. In this way, the exposure to such stimuli may elicit augmented dopaminergic activity and, subsequently, increased beta-band synchronization.

On the other hand, this study also showed significant FC differences between BDs and N/LDs in the theta-band. Although theta synchronization has been associated with distinct cognitive processes, several studies have addressed its role in attentional processing.[55] Thus, the reduced theta FC exhibited by BDs for non-alcoholic stimuli may reflect a diminished attentional processing of such stimuli. Alterations in fronto-occipital theta-band power have also been observed following rewarding cues.[56] Thus, the reduced fronto-occipital theta synchronization exhibited by the BD group for non-alcoholic images in comparison to the N/LDs may also be associated with the BDs' perception of a lower reward of the non-alcoholic stimuli. Accordingly, this decreased fronto-occipital synchronization was negatively correlated with craving levels, suggesting a potential relationship between attention to non-alcoholic images and craving for alcohol. Similarly, decreased theta has been observed in alcohol-dependent individuals[57] and BDs[7] during the performance of cognitive tasks, mainly reflecting deficient inhibitory and attentional processing. Therefore, the reduced theta FC suggests that BDs process non-alcoholic information in lesser extent than N/LDs

In addition, when we compared theta synchronization values between alcoholic and non-alcoholic stimuli in the BD group, we found higher theta FC patterns over fronto-occipital and left fronto-temporal regions for alcoholic relatively to non-alcoholic cues. Evidence has suggested that frontal midline theta emerges from medial prefrontal activity elicited as response to a variety of situations which require enhanced attentional control.[58] Also, several studies have revealed that theta may play a role in allocating neural resources in order to attend to an external stimulus[59] and in integrating task-relevant representations with top-down effects across a broad neural covering.[60] Thus, our results may suggest that BDs employ additional cortical resources to attend highly salient stimuli, such as alcohol-related cues, when compared to lesser salient non-alcoholic ones. The medial prefrontal cortex would play a privileged role integrating rewarding features of alcoholic cues through top-down attentional processing,[19] driving the attention towards stimuli with higher motivational values, in this case, the alcoholic cues. This evidence is in line with our beta FC results revealing that BDs exhibit predominant increase of attentional networks synchronization toward alcohol-related stimuli.

According to the addiction theories, in individuals with AUD or recurrent BD episodes, alcoholic stimuli would gain increasing incentive-motivational properties, such as high saliency and attractiveness, prioritizing the perception of alcohol-related cues and leading to an attentional bias towards them.[12]

Consistent with this assumption, our behavioral results showed that BDs rated the alcoholic images as more pleasant and attractive than their N/LD peers. This increased subjective valence for alcohol-related cues experienced by BDs, possibly confirms the greater saliency and rewarding value of this type of stimuli, which in turn induce a state of attentional bias towards them.

5.5.1. Conclusions

In summary, the present study provides the first body of knowledge regarding the brain connectivity underlying alcohol-cue reactivity in young BDs, revealing that this sub-clinical population exhibit increased neural processing when faced with alcohol-related information. Specifically, this study showed that BDs exhibit increased beta-band FC during the processing of alcoholic pictures, particularly in the fronto-parietal, fronto-temporal and fronto-occipital networks. Contrarily, during the processing of non-alcoholic cues, BDs displayed reduced theta-band FC in the fronto-occipital network. These findings are in line with previous EEG and fMRI studies conducted in BDs,[2, 13] supporting the presence of an attentional bias towards alcohol-related information in this population. Altogether, our results suggest that BDs exhibit a hyperconnectivity pattern in the attentional networks when exposed to alcoholic cues, which leads to an increased processing of such stimuli. In contrast, the reduced theta FC for non-alcoholic cues might reflect diminished processing of non-alcoholic information in young BDs, probably reflecting a low rewarding value of such stimuli in this population. This evidence might have important implications in the alcohol abuse research as these neural mechanisms of alcohol cue reactivity may be contributing to the maintenance of alcohol consumption or even to the development of AUD. Additionally, our results are especially valuable since they are the first evidence showing that FC networks may be a sensitive indicator for alcohol attentional bias in young BDs.

5.6. References

1. López-Caneda E, Cadaveira F, Campanella S. Binge drinking in the adolescent and young brain. *Front. Psychol.* 2019; 9, 2724. https://doi.org/10.3389/ fpsyg.2018.02724.
2. Almeida-Antunes N, Crego A, Carbia C, Sousa SS, Rodrigues R, Sampaio A, López-Caneda E. Electroencephalographic signatures of the binge drinking pattern during adolescence and young adulthood: a PRISMA-driven systematic review. *NeuroImage: Clinical*. 2021; 102537. https://doi.org/10.1016/j.nicl.2020.102537
3. Carbia C, López-Caneda E, Corral M, Cadaveira F. A systematic review of neuropsychological studies involving young binge drinkers. *Neurosci. Biobehav. Rev.* 2018; 90, 332–349. https://doi.org/10.1016/j.neubiorev.2018.04.013
4. Lees B, Mewton L, Stapinski LA, Squeglia LM, Rae CD, Teesson M. Neurobiological and cognitive profile of young binge drinkers: a systematic review and meta-analysis. *Neuropsychol. Rev.* 2019; 1–29. https://doi.org/10.1007/s11065-019-09411-w.

5. Enoch MA. Genetic and environmental influences on the development of alcoholism: resilience vs. risk. *Ann. N. Y. Acad. Sci*. 2006; 1094, 193–201. https://doi.org/10.1196/annals.1376.019.
6. Lannoy S, Billieux J, Dormal V, Maurage P. Behavioral and cerebral impairments associated with binge drinking in youth: A critical review. *Psychol. Belg.* 2019; 59, 116. https://doi.org/10.5334/pb.476.
7. López-Caneda E, Holguín SR, Correas Á, Carbia C, González-Villar A, Maestú F, Cadaveira F. Binge drinking affects brain oscillations linked to motor inhibition and execution. *J. Psychopharmacol.* 2017; 31, 873-882. https://doi.org/10.1177/0269881116689258
8. Bollen Z, Masson N, Salvaggio S, D'Hondt F, Maurage P. Craving is everything: An eye-tracking exploration of attentional bias in binge drinking. *J. Psychopharmacol.* 2020; 34, 636–647. https://doi.org/10.1177/0269881120913131.
9. Flaudias V, Heeren A, Brousse G, Maurage P. Toward a triadic approach to craving in addictive disorders: the metacognitive Hub Model. *Harvard Rev. Psychiatry*. 2019; 27, 326–331. https://doi.org/10.1097/HRP.0000000000000225.
10. Field M, Eastwood B. Experimental manipulation of attentional bias increases the motivation to drink alcohol. *Psychopharmacology*. 2005; 183, 350-357. https://doi.org/10.1007/s00213-005-0202-5
11. Manchery L, Yarmush DE, Luehring-Jones P, Erblich J. Attentional bias to alcohol stimuli predicts elevated cue-induced craving in young adult social drinkers. *Addict. Behav.* 2017; 70, 14–17. https://doi.org/10.1016/j.addbeh.2017.01.035
12. Field M, Cox WM. Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug Alcohol Depend.* 2008; 97, 1-20. https://doi.org/10.1016/j.drugalcdep.2008.03.030
13. Brumback T, Squeglia LM, Jacobus J, Pulido C, Tapert SF, Brown SA. Adolescent heavy drinkers' amplified brain responses to alcohol cues decrease over one month of abstinence. *Addict. Behav.* 2015; 46, 45–52. https://doi.org/10.1016/j. addbeh.2015.03.001.
14. Field M, Marhe R, Franken I. The clinical relevance of attentional bias in substance use disorders. *CNS Spectr*. 2014; 19, 225-230. https://doi.org/10.1017/S1092852913000321
15. Van Den Heuvel, M. P., Pol, H. E. H., 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur. Neuropsychopharmacol.* 20, 519-534. https://doi.org/10.1016/j.euroneuro.2010.03.008
16. Martínez-Maldonado A, Jurado-Barba R, Sion A, Domínguez-Centeno I, Castillo-Parra G, Prieto-Montalvo J, Rubio G. Brain functional connectivity after cognitive-bias modification and behavioral changes in abstinent alcohol-use disorder patients. *Int. J. Psychophysiol.* 2020; 154, 46-58. https://doi.org/10.1016/j.ijpsycho.2019.10.004
17. Courtney KE, Ghahremani DG, Ray LA. Fronto-striatal functional connectivity during response inhibition in alcohol dependence. *Addict. Biol.* 2013; 18, 593-604. https://doi.org/10.1111/adb.12013
18. Wang Y, Zhao Y, Nie H, Liu C, Chen J. Disrupted brain network efficiency and decreased functional connectivity in multi-sensory modality regions in male patients with alcohol use disorder. *Front. Hum. Neurosci.* 2018; 12, 513. https://doi.org/10.3389/fnhum.2018.00513
19. Arienzo D, Happer JP, Molnar SM, Alderson-Myers A, Marinkovic K. Binge drinking is associated with altered resting state functional connectivity of reward-salience and top-down control networks. *Brain Imaging Behav.* 2020; 14, 1731-1746. https://doi.org/10.1007/s11682-019-00107-6

20. Sousa SS, Sampaio A, Marques P, López-Caneda E, Gonçalves ÓF, Crego A. Functional and structural connectivity of the executive control network in college binge drinkers. *Addict. Behav.* 2019; 99, 106009. https://doi.org/10.1016/j.addbeh.2019.05.033
21. Strosche A, Zhang X, Kirsch M, Hermann D, Ende G, Kiefer F, Vollstädt-Klein S. Investigation of brain functional connectivity to assess cognitive control over cue-processing in Alcohol Use Disorder. *Addict. Biol.* 2020; 26, e12863. https://doi.org/10.1111/adb.12863
22. Frankland, L., Bradley, B. P., & Mogg, K. Time course of attentional bias to drug cues in opioid dependence. *Psychol. Addict. Behav*. 2016; 30, 601–606. https://doi.org/10.1037/adb0000169
23. Mheich, A., Hassan, M., Khalil, M., Berrou, C., & Wendling, F. A new algorithm for spatiotemporal analysis of brain functional connectivity. *J. Neurosci. Methods*. 2015; 242, 77-81. https://doi.org/10.1016/j.jneumeth.2015.01.002
24. Bastos, A. M., & Schoffelen, J. M. A tutorial review of functional connectivity analysis methods and their interpretational pitfalls. *Front. Syst. Neurosci.* 2016, 9, 175. https://doi.org/10.3389/fnsys.2015.00175
25. Siegel, M., Donner, T. H., & Engel, A. K. Spectral fingerprints of large-scale neuronal interactions. Nat. Rev. Neurosci. 2012, 13, 121-134. https://doi.org/10.1038/nrn3137
26. Buzsáki, G., and Wang, X.-J. Mechanisms of gamma oscillations. *Annu. Rev. Neurosci.* 2012, 35, 203–225. https://doi.org/10.1146/annurev-neuro-062111-150444
27. Wang, X. J. Neurophysiological and computational principles of cortical rhythms in cognition. *Physiol. Rev.* 2010, 90, 1195-1268.
28. Pronk T, van Deursen DS, Beraha EM, Larsen H, Wiers RW. Validation of the Amsterdam Beverage Picture Set: A controlled picture set for cognitive bias measurement and modification paradigms. *Alcohol. Clin. Exp. Res.* 2015; 39, 2047-2055. https://doi.org/10.1111/acer.12853
29. Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. *J. Behav. Ther. Exp. Psychiatry.* 1994; 25, 49-59. https://doi.org/10.1016/0005-7916(94)90063-9
30. Fuchs M, Wagner M, Kastner J. Boundary element method volume conductor models for EEG source reconstruction. *Clin. Neurophysiol*. 2001; 112, 1400-1407. https://doi.org/10.1016/S1388-2457(01)00589-2
31. Van Veen BD, Van Drongelen W, Yuchtman M, Suzuki A. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Trans. Biomed. Eng.* 1997; 44, 867-880. https://doi.org/10.1109/10.623056
32. Mazziotta J et al. A four-dimensional probabilistic atlas of the human brain. J. *Am. Med. Inform. Assoc.* 2001; 8, 401-430. https://doi.org/10.1136/jamia.2001.0080401
33. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner, RL, Dale AM, Maguire RP, Hyman BT, Alber MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006; 31, 968-980. https://doi.org/10.1016/j.neuroimage.2006.01.021
34. Bruña R, Maestú F, Pereda E. Phase locking value revisited: teaching new tricks to an old dog. *J. Neural Eng.* 2018; 15, 056011. doi: 10.1088/1741-2552/aacfe4
35. Antón-Toro LF, Bruña R, Suárez-Méndez I, Correas Á, García-Moreno LM, Maestú F. Abnormal organization of inhibitory control functional networks in future binge drinkers. *Drug Alcohol Depend.* 2020; 218, 108401. https://doi.org/10.1016/j.drugalcdep.2020.108401
36. Garcés P, Martín-Buro MC, Maestú F. Quantifying the test-retest reliability of magnetoencephalography resting-state functional connectivity. *Brain connectivity*. 2016; 6, 448-460. https://doi.org/10.1016/j.ijpsycho.2011.09.001

37. Petkoski S, Palva JM, Jirsa VK. Phase-lags in large scale brain synchronization: Methodological considerations and in-silico analysis. *PLOS Computat. Biol.* 2018; 14, e1006160. https://doi.org/10.1371/journal.pcbi.1006160
38. López-Sanz D, Bruña R, Garcés P, Martín-Buro MC, Walter S, Delgado ML, Montenegro M, Higes RL, Marcos A, Maestú F. Functional connectivity disruption in subjective cognitive decline and mild cognitive impairment: a common pattern of alterations*. Front. Aging Neurosci.* 2017; 9, 109. https://doi.org/10.3389/fnagi.2017.00109
39. Benjamini Y, Hochberg Y. Multiple hypotheses testing with weights. *Scand. Stat. Theory Appl*. 1997; 24, 407-418. https://doi.org/10.1111/1467-9469.00072
40. Gola M, Kamiński J, Brzezicka A, Wróbel A. Beta band oscillations as a correlate of alertness—changes in aging. *Int. J. Psychophysiol.* 2012; 85, 62-67. https://doi.org/10.1016/j.ijpsycho.2011.09.001
41. Kamiński J, Brzezicka A, Gola M, Wróbel A. Beta band oscillations engagement in human alertness process. *Int. J. Psychophysiol.* 2012; 85, 125-128. https://doi.org/10.1016/j.ijpsycho.2011.11.006
42. Knott V, Cosgrove M, Villeneuve C, Fisher D, Millar A, McIntosh J. EEG correlates of imagery-induced cigarette craving in male and female smokers. *Addict. Behav.* 2008; 33, 616-621. https://doi.org/10.1016/j.addbeh.2007.11.006
43. Littel M, Franken IH, Van Strien JW. Changes in the electroencephalographic spectrum in response to smoking cues in smokers and ex-smokers. *Neuropsychobiology.* 2009; 59, 43-50. https://doi.org/10.1159/000205517
44. . Hume DJ, Howells FM, Rauch HL, Kroff J, Lambert EV. Electrophysiological indices of visual food cue-reactivity. Differences in obese, overweight and normal weight women. *Appetite.* 2015; 85, 126-137. https://doi.org/10.1016/j.appet.2014.11.012
45. Spitzer B, Haegens S. Beyond the status quo: a role for beta oscillations in endogenous content (re) activation. *eNeuro*. 2017; 4, e0170-17.2017 1–15. https://doi.org/10.1523/ENEURO.0170-17.2017
46. Pantazatos, S. P., Yanagihara, T. K., Zhang, X., Meitzler, T., & Hirsch, J. Frontal–occipital connectivity during visual search. 2012; *Brain Connectivity*, 2, 164-175. https://doi.org/10.1089/brain.2012.0072
47. Rangel-Pacheco, A., Lew, B. J., Schantell, M. D., Frenzel, M. R., Eastman, J. A., Wiesman, A. I., & Wilson, T. W. Altered fronto-occipital connectivity during visual selective attention in regular cannabis users. 2021; *Psychopharmacology*, 238, 1351-1361. https://doi.org/10.1007/s00213-020-05717-3
48. Elton, A., Faulkner, M. L., Robinson, D. L., & Boettiger, C. A. Acute depletion of dopamine precursors in the human brain: effects on functional connectivity and alcohol attentional bias. *Neuropsychopharmacology.* 2021; 46, 1421-1431. https://doi.org/10.1038/s41386-021-00993-9
49. Marco-Pallarés J, Cucurell D, Cunillera T, Krämer UM, Càmara E, Nager W, Bauer P, Schüle R, Schöls L, Münte TF, Rodriguez-Fornells A. Genetic variability in the dopamine system (dopamine receptor D4, catechol-O-methyltransferase) modulates neurophysiological responses to gains and losses. *Biol. Psychiatry.* 2009; 66, 154-161. https://doi.org/10.1016/j.biopsych.2009.01.006
50. Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. *Am. Psychol.* 2016; 71, 670–679. https://doi.org/10.1037/amp0000059
51. Ostlund SB, LeBlanc KH, Kosheleff AR, Wassum KM, Maidment NT. Phasic mesolimbic dopamine signaling encodes the facilitation of incentive motivation produced by repeated cocaine exposure. *Neuropsychopharmacol.* 2014; 39, 2441-2449. https://doi.org/10.1038/npp.2014.96

52. Franken IH. Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. 2003; 27, 563-579. https://doi.org/10.1016/S0278-5846(03)00081-2
53. Agarwal K, Manza P, Leggio L, Livinski AA, Volkow ND, Joseph PV. Sensory Cue Reactivity: Sensitization in Alcohol Use Disorder and Obesity. *Neurosci. Biobehav. Rev.* 2021; 124, 326-357. https://doi.org/10.1016/j.neubiorev.2021.02.014
54. Bunzeck N, Guitart-Masip M, Dolan RJ, Düzel E. Contextual novelty modulates the neural dynamics of reward anticipation. *J. Neurosci.* 2011; 31, 12816-12822. https://doi.org/10.1523/JNEUROSCI.0461-11.2011
55. Womelsdorf T, Vinck M, Leung SL., Everling S. Selective theta-synchronization of choice-relevant information subserves goal-directed behavior. *Front. Hum. Neurosci.* 2010; 4, 210. https://doi.org/10.3389/fnhum.2010.00210
56. van Wingerden, M., Vinck, M., Lankelma, J., & Pennartz, C. M. Theta-band phase locking of orbitofrontal neurons during reward expectancy. J. Neurosci. 2010, 30, 7078-7087. https://doi.org/10.1523/JNEUROSCI.3860-09.2010
57. Kamarajan C, Porjesz B, Jones KA, Choi K, Chorlian DB, Padmanabhapillai A, Rangaswamy M, Stimus AT, Begleiter H. The role of brain oscillations as functional correlates of cognitive systems: a study of frontal inhibitory control in alcoholism. *Int. J. Psychophysiol.* 2004; 51, 155-180. https://doi.org/10.1016/j.ijpsycho.2003.09.004
58. Cavanagh JF, Frank MJ. Frontal theta as a mechanism for cognitive control. *Trends Cogn. Sci.* 2014; 18, 414-421. https://doi.org/10.1016/j.tics.2014.04.012
59. Arnal LH, Wyart V, Giraud AL. Transitions in neural oscillations reflect prediction errors generated in audiovisual speech. *Nat. Neurosci.* 2011; 14, 797. https://doi.org/10.1038/nn.2810
60. Halgren E, Kaestner E, Marinkovic K, Cash SS, Wang C, Schomer DL, Madsen JR, Ulbert I. Laminar profile of spontaneous and evoked theta: Rhythmic modulation of cortical processing during word integration. *Neuropsychologia.* 2015; 76, 108-124. https://doi.org/10.1016/j.neuropsychologia.2015.03.021

CHAPTER 6: Trying to Forget Alcohol: Brain mechanisms underlying memory suppression in young binge drinkers

The work presented in Chapter 6 is under review

The referencing style used in this Chapter is in accordance with the journal.

Results from this empirical work were also presented at four scientific international events. In June 2022, preliminary results were presented as an oral presentation at the *Congreso Internacional de Magnetoencefalografía* (Sória, Spain). In September 2022, updated results were presented as part of a symposium at the 2nd World Congress on Alcohol and Alcoholism - Joint Meeting of International Society of Biomedical Research on Alcoholism (ISBRA) and ESBRA 2022 (Cracow, Poland). Moreover, the abstract of this presentation was published in the journal Alcoholism – Clinical and Experimental Research. In March 2023, the findings of this empirical study were submitted to the ECNP Workshop for Early Career Scientists in Europe 2023 (Nice, France), where I was honored with an Accommodation Award and invited to present this work as both poster and an oral presentation. The abstracts of this event were published in the Neuroscience Applied. In July 2023, supplementary ERP results of this work were presented as a poster presentation at the XIII Congreso de la Sociedad Española de Psicofisiología y Neurociencia Cognitiva y Afectiva (SEPNECA).

Conference Session References:

Almeida-Antunes, N., Antón-Toro, L., Crego, R., Rodrigues, R., Sampaio, A., López-Caneda, E. (2022, June, 24-26). *Suppressing alcohol memories: Functional connectivity patterns in young binge drinkers* [Conference Session]. Congreso Internacional de Magnetoencefalografía (CIMEG-V). Sória, Spain.

Almeida-Antunes, N., Anton-Toro, L., Crego, A., Rodrigues, R., Vasconcelos, M., Sampaio, A., & Lopez-Caneda, E. (2022, September). Suppressing alcohol memories: Functional connectivity patterns in young binge drinkers. *Alcoholism-Clinical and Experimental Research* (Vol. 46, pp. 35-36).

Antunes, N. A., Antón-Toro, L., Crego, A., Rodrigues, R., Sampaio, A., & López-Caneda, E. (2023). Alcohol, to think or not to think? Brain hyperconnectivity during alcohol memory suppression in young binge drinkers. *Neuroscience Applied*, *2*, 101052. https://doi.org/10.1016/j.nsa.2023.101052

Poster Presentation Reference:

Almeida-Antunes, N., Antón-Toro, L., Crego, A., Rodrigues, R., Sampaio, A., & López-Caneda, E. (2023, March, 16-19). Alcohol, to think or not to think? Brain hyperconnectivity during alcohol memory suppression in young binge drinkers [Poster Presentation]. ECNP Workshop for Early Career Scientists in Europe 2023. Nice, France.

Almeida-Antunes, N., Crego, A., Rodrigues, R., Sampaio, A., & López-Caneda, E. (2023, July, 19-21). Understanding the Neurocognitive Processes of Memory Inhibition in Binge Drinkers: Insights from Event-Related Potentials [Poster Presentation]. XIII Congreso de la Sociedad Española de Psicofisiología y Neurociencia Cognitiva y Afectiva. Santiago de Compostela, Spain.

6.1. Abstract

People are able to voluntarily suppress unwanted thoughts or memories, a phenomenon known as suppression-induced forgetting or memory suppression. Despite harmful alcohol use, such as binge drinking, has been linked to impaired inhibitory control (IC) and augmented alcohol-cue reactivity, no study to date has assessed memory inhibition abilities towards alcohol-related cues in binge drinkers (BDs). Thus, the present preregistered study aimed to evaluate the behavioral and neurofunctional mechanisms associated with memory inhibition, specifically those related to the suppression of alcohol-related memories, in young BDs. For this purpose, electroencephalographic activity was recorded in eighty-two college students aged between 18 and 24 years old from the University of Minho (50% females; 40 non/low-drinkers [N/LDS] and 42 BDs) while they performed the Think/No-Think Alcohol task. Brain functional connectivity (FC) was calculated using the phase locking value and, subsequently, a dynamic seed-based analysis was conducted to explore the FC patterns between IC and memory networks. Comparatively to N/LDs, BDs exhibited decreased alpha-band FC between the anterior cingulate cortex and the left fusiform gyrus during attempts to suppress non-alcohol memories, accompanied by unsuccessful forgetting of those memories. Conversely, BDs displayed augmented gamma-band FC between the IC network and memory regions –i.e., hippocampus, parahippocampus and fusiform gyrus- during suppression of alcohol-related memories. Inhibitory abnormalities in BDs may lead to hypoconnectivity between IC and memory networks and deficient suppression of non-alcohol-related memories. However, while suppressing highly salient and reward-predicting stimuli, such as alcohol-related memories, BDs display a hyperconnectivity pattern between IC and memory networks, likely due to their augmented attention towards intrusive alcoholic memories and the attempts to compensate for potential underlying IC deficits. These findings hold important implications for alcohol research and treatment, as they open up new avenues for reducing alcohol use by shifting the focus to empowering suppression/control over alcohol-related memories.

Keywords: Binge Drinking, Functional Connectivity, Memory Suppression, Alcohol-Related Memories, Inhibitory Control Network, Memory Network.

6.2. Introduction

Sometimes we are faced with unpleasant or distracting memories we would like not to think about, and we often strive to exclude them from awareness. Evidence has demonstrated that people can control intruding memories by stopping memory retrieval, leading to forgetting, a phenomenon known as memory suppression.[1-3] Suppression mechanisms have been commonly studied through the Think/No-Think (TNT) paradigm,[4,5] where participants must remember and retain (Think) or prevent from entering awareness (No-Think) a paired item from cue-target pairs previously learned.[1,6] Studies have reported that suppressing retrieval frequently decreases memory for No-Think items below that exhibited for Think and, most importantly, for Baseline items, resulting in the so-called memory suppression.[7]

Research has shown that memory suppression recruits brain regions that resemble areas involved in inhibitory control (IC). Specifically, forgetting has been associated with increased activation of prefrontal regions, particularly the dorsolateral prefrontal cortex (DLPFC) and the inferior frontal gyrus (IFG), and deactivations of brain areas supporting episodic recollection, including the hippocampus and medial temporal cortex.[5,6,8-11] Additionally, studies exploring effective connectivity showed a causal influence of the right DLPFC on the activity of the hippocampus, supporting a top-down regulation of memory.[8, 12-16]

Noteworthy, deficits in IC, coupled with the persistence of intrusive and undesirable thoughts, are common characteristics of several psychiatric disorders, including posttraumatic stress disorder, anxiety disorders and obsessive-compulsive disorder.[17-19] Although scarce, several studies in these clinical conditions suggested impaired capacity to prevent efficiently unwanted thoughts/memories.[20-24] Surprisingly, memory inhibition mechanisms in addiction -a clinical condition characterized by recurrent substance-related thoughts that frequently lead to compulsive consumption- have received little attention so far. To our knowledge, only two behavioral studies were conducted in detoxified alcohol dependent individuals[25] and healthy hazardous drinkers[26]. Collectively, the findings of these studies indicated disrupted memory suppression abilities - including in the presence of alcohol-related cues[26] - among individuals with alcohol-related problems, which might entail difficulties to maintain long-term abstinence in detoxified patients.[25]

Interestingly, evidence revealed that dysregulation of the prefrontal cortex (PFC) underlies compulsive drug-taking, being its diminished activation associated with reduced top-down control.[27] Additionally, studies reported increased DLPFC activation during drug-related cues exposure, which correlated with craving for alcohol and other substances[27-31] and was associated with higher susceptibility to cue-induced relapse in alcohol abuse.[32] Despite DLPFC and hippocampus being classical targets for the neurotoxic effects of alcohol[33,34], and the fact that the control over intrusive (alcohol-related) memories

may influence alcohol craving and intake, as far as we know, no study explored the neurofunctional mechanisms underlying memory suppression in individuals with alcohol-related problems.

Binge Drinking (BD), a pattern characterized by alternations between excessive alcohol drinking episodes and periods of low consumption or abstinence, is a problematic form of alcohol misuse highly prevalent in young people.[35-37] Over the last decade, several studies have shown augmented reactivity to alcoholic stimuli[38-42] and reduced IC[43-47] in binge drinkers (BDs), which may result in difficulties controlling alcohol intake and augmented risk for developing alcohol dependence.[48,49]

In this study, the Think/No-Think Alcohol task (TNTA) - a TNT paradigm version developed to assess memory inhibition in drinking contexts[50]- was used to evaluate for the first time the potential behavioral and neurofunctional anomalies associated with memory inhibition, particularly those related to alcohol-related memories suppression, in BD college students. We hypothesized that BDs would show poor suppression of No-Think images-mainly alcoholic ones-, and abnormal functional connectivity (FC) patterns –as assessed by electroencephalography (EEG)- between regions associated with memory inhibition, namely the IC network (DLPFC and IFG) and the memory network (hippocampal and parahippocampal regions) relative to non/low drinkers (N/LDs).

6.3. Methods and Materials

The present study constitutes the first phase of a double-blind, randomized controlled trial registered in the clinicaltrials.gov registry (Identifier: NCT05237414).[51]

6.3.1. Participants

A screening questionnaire including the Alcohol Use Disorder Identification Test (AUDIT[52]) along with other questions concerning alcohol and other drugs use was administered to 2335 students from the University of Minho. Then, two groups were formed based on their AUDIT scores. Students who reported (i) drinking 5 or more drinks on one occasion at least once a month, and (ii) drinking at a rate of at least two drinks per hour during these episodes, were classified as BDs. Those who reported (i) never drink 5 or more drinks on each occasion and (ii) an AUDIT score ≤ 4, were considered N/LDs. Three hundred and fifteen participants provided written informed consent prior to the clinical interview, which was performed to assess the following exclusion criteria: use of illegal drugs except cannabis (i.e., at most once a month); alcohol abuse (i.e., score ≥20 in the AUDIT); consumption of medical drugs with psychoactive effects (e.g., sedatives or anxiolytics) during the two weeks before the experiment; personal history of psychopathological disorders (according to DSM-V criteria); history of traumatic brain injury or

neurological disorder; family history of substance abuse (including alcoholism); occurrence of an episode of loss of consciousness for more than 20 minutes; non-corrected sensory deficits; score ≥90 in the Global Severity Index of the Symptom Checklist-90 revised questionnaire[53] or in at least two of the symptomatic dimensions.

A total of 114 participants who met the criteria were selected to perform the experiment. However, thirty-two participants were excluded from posterior behavioral/EEG analysis: nine of them no longer met the inclusion criteria, nine had technical problems during the EEG recording, and 14 due to insufficient quality in the EEG signal. Therefore, a total of 82 participants (42 BDs and 40 N/LDs), aged between 18 and 24 (M = 20.01; SD = 1.71), were included in this study. The demographic and drinking characteristics are summarized in Table 7.

6.3.2. TNTA task

The TNTA task -fully described elsewhere[50,51]- has three phases: Learning, Think/No-Think (TNT) and Memory-Test phases. During the Learning phase (Figure 19A), participants are asked to memorize 36 pairs of neutral objects + alcoholic/non-alcoholic pictures. Then, only the neutral images are presented, and participants must try to remember the image that was associated with the neutral object through three questions about the picture orientation, the number of people and the beverage presented in the picture. In the TNT phase (Figure 19B), participants are asked to Think (green square)-i.e., to focus on the picture and to think about the alcoholic/non-alcoholic image that was associated with it - or to No-Think (red square)-i.e., focus on the image and not let the previously associated picture enter their consciousness. Only 24 neutral images were depicted during this phase, because the remaining 12 served as a baseline condition for the following phase. Finally, during the memory-test phase (Figure 19C), the 36 neutral images from each pair were again presented and participants must remember the image that was initially associated with the neutral object through the same questions of the Learning phase.

Table 7

Demographic, drinking characteristics and craving measures of the Binge Drinking (BD) and Non/Low-Drinking (N/LD) groups (mean (SD))

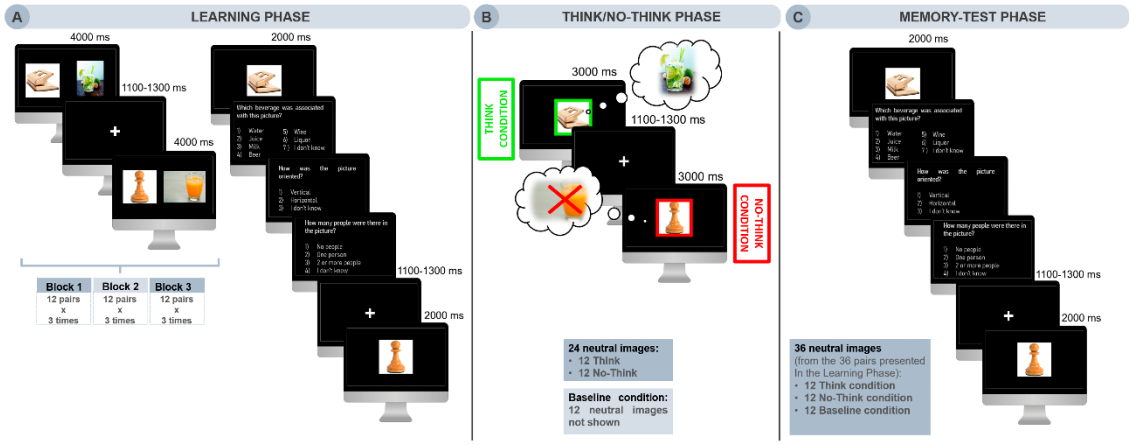
	BD (*n* = 42)	N/LDs (*n*=40)
Demographic measures		
Gender ratio (male/female)	21/21	20/20
Age	20.10(1.72)	19.90(1.7)
Drinking Characteristics		
Total AUDIT score**	7.36(2.76)	.73(.75)
Age of onset of binge drinking	18.02(1.10)	-
Number of drinks in the last week**	5.06(5.20)	.23(.62)
Max number of drinks/drinking episode (Typical week[a])**	5.71(4.40)	.20(.72)
Max number of drinks/drinking episode (Atypical week[a])**	9.19(5.05)	.83(1.01)
BD episodes/month	2.25(1.24)	-
Percentage of drunkenness**	44.51(26.99)	2.03(8.34)
Tobacco users**	16	2
Cannabis users (at most once a month)*	8	2
Alcohol Craving Measures		
PACS score**	3.57(3.16)	.88(2.26)
Total ACQ-SF-R Score**	2.20(.73)	1.35(.53)
Compulsivity Factor**	1.42(.52)	1.04(.12)
Purposefulness Factor**	3.21(1.41)	1.64(1.00)
Emotionality Factor**	2.22(1.02)	1.43(.92)

Note. [a]According to the Typical and Atypical Drinking Diary (TADD),[53] a typical week refers to a week characterized by usual alcohol consumption and an atypical week refers to a week characterized by increased alcohol consumption (e.g., during holidays, academic parties); AUDIT: Alcohol Use Disorders Identification Test; PACS: Penn Alcohol Craving Scale;[54] ACQ-SF-R: Alcohol Craving Questionnaire-Short Form-Revised.[55]

*p < .05; **p < .001 significant group differences;

Figure 19

Overall depiction of the Think/No-Think Alcohol (TNTA) task



6.3.3. EEG Acquisition and Analysis

EEG signal was recorded by the ActiveTwo Biosemi electrode system (Biosemi, Inc., Amsterdam, the Netherlands) from 64 electrodes organized according to the 10/10 system using a Common Mode Sense (CMS) recording montage. Vertical and horizontal electro-oculogram activity was recorded to control for eye movements and blinks. All electrodes were adjusted to maintain their offset lower than 30 mV. EEG signal was amplified and digitized at 512 Hz and bandpass filtered at 0.01–100 Hz.

6.3.3.1. ERP Analysis

Prior to the FC analysis, and to determine whether the TNTA task was able to replicate the same patterns of neural activity observed in previous EEG studies concerning memory suppression[50,57-59], we conducted an event-related potentials analysis (see Supplementary Material for the procedure detailed description).

6.3.3.2. FC data analysis and source reconstruction

After verifying elicitation and recording of the ERPs associated with memory suppression processes (see ERPs Results in Supplementary Material), we conducted the FC analysis. The FieldTrip package[60] was used for automatic detection of ocular, cardiac and muscle artifacts. The correct artifacts removal was visually inspected by an expert signal analyst. Finally, an independent component analysis based on SOBI[61] was applied to remove eye-blink and cardiac activity. The data was segmented into epochs of 2500ms (from −500 to 2000ms after stimulus onset) and trials marked as containing artifacts were discarded from the analysis (19.85%). Only trials corresponding to originally learned items during the learning phase were considered (75.78% of the number of trials after artefact removal). These epochs

were averaged separately according to the type of picture to be recalled or suppressed: Think Alcohol, Think No-Alcohol, No-Think Alcohol, and No-Think No-Alcohol.

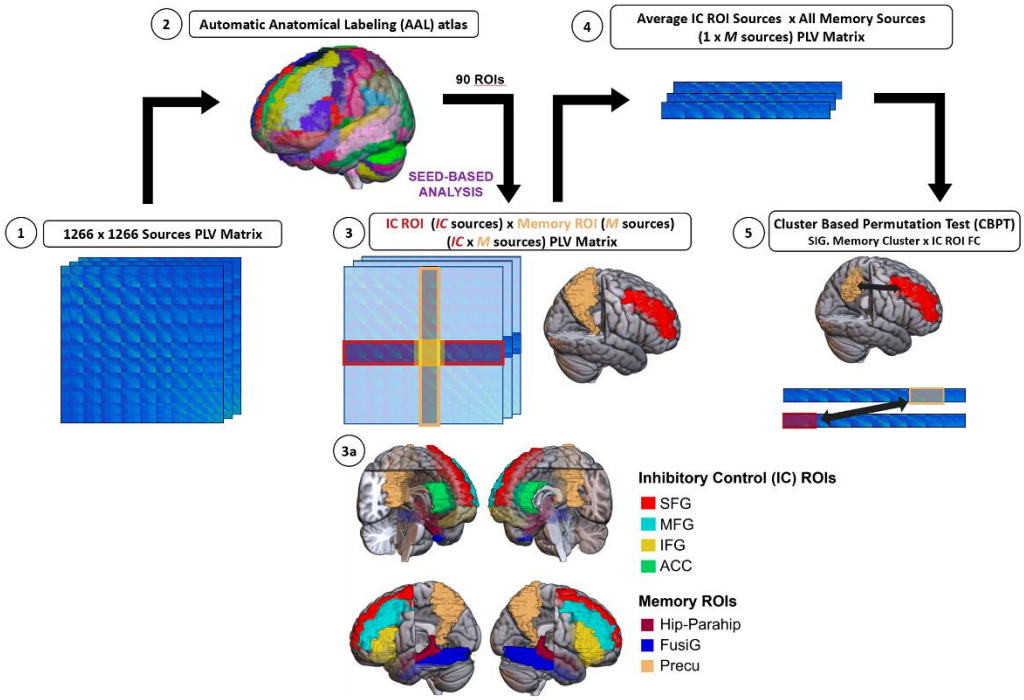
EEG data were transformed into source space employing a realistic *Boundary elements model* (BEM)[62] as forward model and a Linearly Constrain Minimum Variance (LCMV) beamformer[63] as inverse model. Cortical sources were reconstructed in five classical bands: theta (4-8 Hz), alpha (8-12 Hz), low-beta (12-20 Hz), high-beta (20-30 Hz) and low gamma (30-45 Hz), using the Montreal Neurological Institute (MNI) template-based T1 images (ICBM 152).[64] To assess the quality of the estimated signal, we calculated the well-known P100 visual component in source space, as the mean power spectrum in the 100-150ms time-window (see Figure D.1).

The final source model consisted of 1266 cortical source positions, labelled according to the Automatic Anatomical Labeling (AAL) atlas.[65] FC analysis was calculated under the hypothesis of phase synchronization by means of the Phase Locking Value (PLV)[66] in six time-windows with a 50% overlapping: 0-600ms; 300-900ms; 600-1200ms; 900-1500ms; 1200-1800ms; 1400-2000ms. To study the brain processing of Think and No-Think items with alcoholic and non-alcoholic content independently, the four conditions were analyzed separately. Firstly, PLV was calculated separately for each pair of source positions, generating a 1266 x 1266 FC matrix (Figure 20). From this whole-brain FC matrix we conducted a seed-based analysis.

We focused on regions of interest (ROIs) of the PFC commonly activated during attempts to suppress unwanted memories (i.e., IC network) and memory regions consistently reported as deactivated during memory suppression (i.e., memory network).[1,7-11,14,16] Specifically, and according with Mary and cols. (2020)[16], for the IC network we selected the following ROIs: left (lSFG; 27 source positions) and right superior frontal gyrus (rSFG; 31 source positions); left (lMFG; 34 source positions) and right middle frontal gyrus (rMFG; 40 source positions); left (lIFG; 40 source positions) and right inferior frontal gyrus (rIFG; 44 source positions); and the bilateral anterior cingulate cortex (ACC; 24 sources positions). The memory network consisted of left (lHip-lParahip; 13 source positions) and right hippocampus and parahippocampus (rHip-rParahip; 17 source positions); left (lFusiG, 19 source positions) and right fusiform gyrus (rFusiG; 15 sources positions); and bilateral precuneus (Precu; 49 source positions). The level of connectivity of each IC ROI (i.e., seed) with each memory region (i.e., target) was calculated. Thus, we estimated the average of the PLV values from the sources in the seed with each source of the target memory region.

Figure 20.

Pipeline method for FC calculation



Note. **(1)** For each experimental condition, PLV values of each pair of cortical source positions (1266 x 1266) form the global connectivity matrix. **(2)** From this whole-brain FC matrix a seed-based analysis was conducted, using pairs of ROIs drawn from AAL atlas. **(3)** The level of connectivity of each Inhibitory Control (IC) ROI with each memory region was calculated (*IC x M*) **(3a)**. **(4)** The PLV values from the sources in the IC ROI with each source of the memory region were averaged, obtaining a vector of as many entries as the number of sources in the memory region (1 x *M*) – describing the average FC between each source and the IC ROI. **(5)** The connectivity values in **(4)** were compared between and within groups using cluster-based permutation test.

6.3.4. Experimental Design and Statistical Analysis

Demographic and drinking measures were analyzed by independent-samples t-test. Regarding behavioral data, items learned during the learning phase and correctly recalled during the memory test phase were considered correct responses. The percentage of correct responses (for Think, No-Think and Baseline items) were computed according to the following formula:

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

As the distribution of the data was found to be non-normal, the Kruskal-Wallis test was used to analyze differences between groups in the percentage of correct responses. To explore the differences between conditions and within groups, a Wilcoxon test was used.

For the seed-based analysis, data consisted of a single value (PLV) per source of each memory region, reflecting the average FC between the IC ROI and each source of the memory ROI. These values were obtained for each condition per time-window and frequency-band and compared between groups using a cluster-based permutation test (CBPT). Specifically, we compared the difference between the FC values of the No-Think Alcohol and No-Think No-Alcohol conditions between groups. In addition, we compared the difference between the FC values of the two conditions (Think, No-Think) between groups, separately for each content type (Alcohol and No-Alcohol). The results of these analysis are detailed in the Supplementary Material. All results were corrected by Bonferroni stepwise method, and only those clusters that survived this correction were reported as significant.

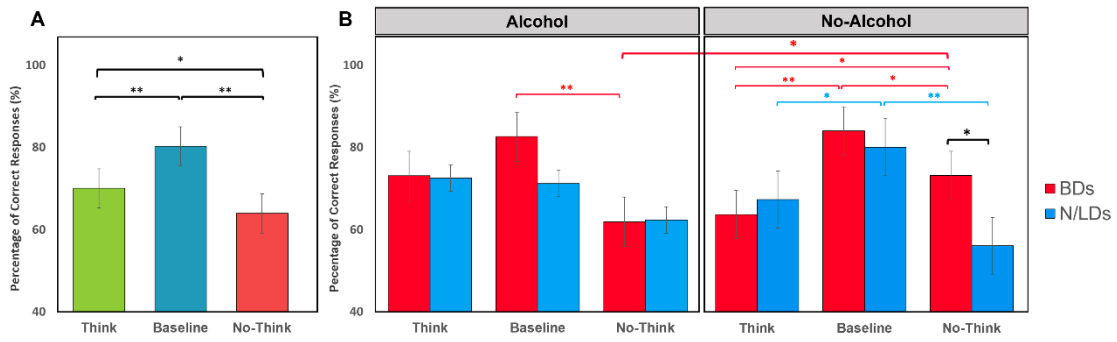
6.4. Results

6.4.1. Behavioral Results

Behavioral results are plotted in Figure 21. The Wilcoxon results showed that the recollection of No-Think ($Z = -4.89$, $p < 0.001$) and Think ($Z = -3.64$, $p < 0.001$) items was significantly reduced relative to Baseline items. In addition, the recollection of No-Think items was significantly reduced when compared with Think items ($Z = -3{,}64$, $p < .001$). The Kruskal-Wallis results revealed that BDs recollected more (i.e., suppressed less) No-Think No-Alcohol items when compared to N/LDs ($H = 6.60$, $p = 0.010$). Regarding the within-group differences, BDs showed reduced recollection of No-Think in comparison with Baseline Alcohol items ($Z = -3.20$, $p < 0.001$). Furthermore, BDs exhibited reduced recollection of Think ($Z = -3.67$, $p < 0.001$) and No-Think ($Z = -2.05$, $p = 0.041$) when compared to Baseline No-Alcohol items. However, BDs showed increased recollection of No-Think relatively to Think No-Alcohol items ($Z = -2{,}06$, $p = 0.40$). N/LDs also showed reduced recollection of Think ($Z = -2.06$, $p = 0.039$) and No-Think ($Z = -3.50$, $p < 0.001$) relatively to Baseline No-Alcohol items. Finally, BDs recollected more No-Think No-Alcohol when compared to No-Think Alcohol items ($Z = -2.30$, $p = 0.022$).

Figure 21

Barplots showing the percentage of correct responses



Note. **(A)** Think, Baseline and No-Think conditions and for **(B)** Think Alcohol, Think No-Alcohol, Baseline Alcohol, Baseline No-Alcohol, No-Think Alcohol, and No-Think No-Alcohol conditions, for binge drinkers (BDs) and non/low drinkers (N/LDs). *p≤0.05, **p<0.001

6.4.2. FC Results

6.4.2.1. *No-Think Alcohol – No-Think No-Alcohol*

Results revealed a significant Content by Group interaction in the No-Think condition. Specifically, when comparing the difference between the FC level (i.e., FC between the IC seeds and the target memory regions) of the No-Think Alcohol and No-Think No-Alcohol conditions between groups, seven significant clusters from four regions of the memory network were observed over two different time-windows (900-1500ms and 1400-2000ms). The spatial distribution of these clusters is depicted in Figure 22.

Within the 900-1500ms time-window, the lFusiG was significantly connected with the ACC (p=0.0104) in alpha band. Also, in this time-window, the rFusiG was significantly connected with the rMFG (p=0.0022) and the rSFG (p=0.0054) in gamma band. In addition, at the same time-window and frequency-band, the rHip-rParahip was significantly connected with the rIFG (p=0.0136), the rMFG (p=0.0026), and the rSFG (p=0.0032). Finally, in the last time-window (1400-2000ms), the Precu was significantly connected with the lMFG (p=0.0130) in beta band. All these clusters showed a lower difference between the level of FC of the two conditions (i.e., FC No-Think Alcohol – FC No-Think No Alcohol) in N/LDs when compared with BDs. The results for the seed-based analysis are summarized in Table 8.

Pairwise comparisons revealed that during No-Think condition BDs exhibited increased FC between all the IC seeds and the target memory regions for Alcohol compared with No-Alcohol content. Contrarily, N/LDs showed decreased FC between the IC and memory regions – excepting between the ACC and the lFusiG– for Alcohol relative to No-Alcohol content. Results also revealed that during the No-Think No-

Alcohol condition, BDs displayed decreased alpha-band FC between the ACC and the lFusiG relatively to N/LDs. In the No-Think Alcohol condition, BD exhibited increased FC between the rSFG and the memory network (i.e., rHiprParahip and rFusiG) in comparison with N/LDs.

Table 8

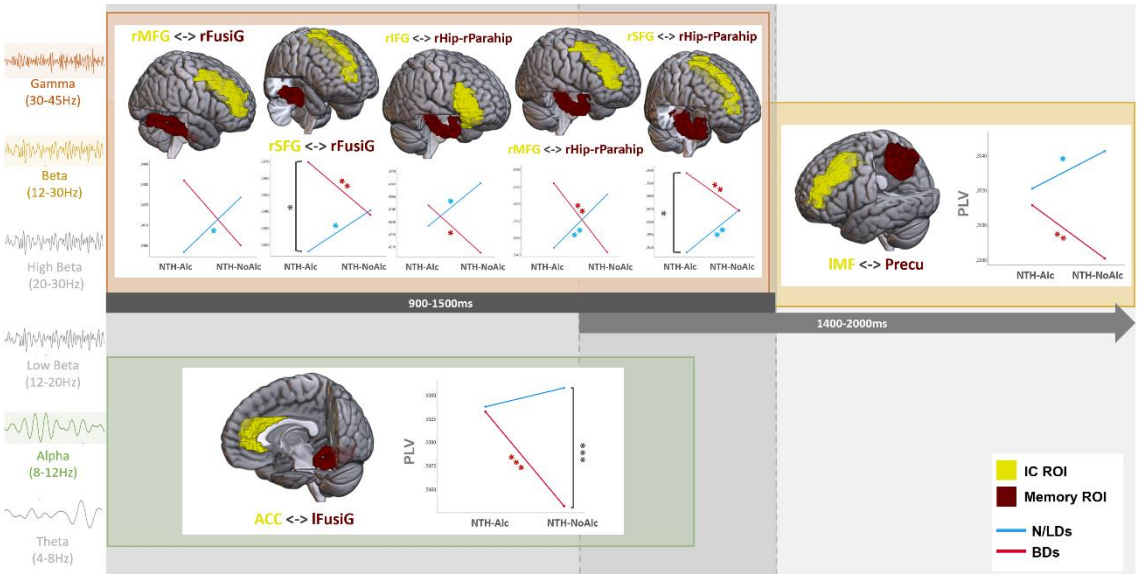
Seed-based FC results summary (No-Think condition – Content by Group interaction)

Time Window	Frequency band	IC Seed	Memory Region	% sources	p	Cluster α
900-1500ms	Alpha (8-12 Hz)	ACC	lFusiG	46.67%	0.0114	0.01
900-1500ms	Gamma (30-45 Hz)	rIFG	rHip-rParahip	76.47%	0.0094	0.01
900-1500ms	Gamma (30-45 Hz)	rMFG	rFusiG	63.16%	0.0038	0.01
			rHip-rParahip	88.24%	0.0036	0.01
900-1500ms	Gamma (30-45 Hz)	rSFG	rFusiG	42.11%	0.0126	0.01
			rHip-rParahip	94.12%	0.0038	0.01
1400-2000ms	Beta (12-30Hz)	lMFG	Precu	32.65%	0.0130	0.01

Note. The percentage of sources of the statistically significant clusters were calculated by dividing the number of sources that constituted the cluster by the total number of memory ROI sources.

Figure 22

No-Think Alcohol versus No-Think No-Alcohol seed-based FC results depiction



Note. **Left:** Six frequency-bands used in the FC analysis. Colored frequency-bands represent those where significant clusters were observed, in the gray ones there were no significant results. The brains contain the clusters from the memory network (dark red regions) significantly connected with the inhibitory control (IC) seeds (yellow regions) along the 900-1500ms time-window in gamma and alpha frequency-bands, and along the 1400-2000ms time-window in beta band. The graphics near the brains represent the FC level (i.e., Phase Locking Value [PLV]) between the corresponding IC seed and the target memory ROI per condition:No-Think Alcohol (NTH-Alc) and No-Think No-Alcohol (NTH-NoAlc) for both groups, BDs (red line) and N/LDs (blue line). rIFG: right inferior frontal gyrus; rMFG: right middle frontal gyrus; rSFG: right superior frontal gyrus; ACC: anterior cingulate cortex; rFusiG: right fusiform gyrus; lFusiG: left Fusiform gyrus; rHip-rParahip: right hippocampus and parahippocampus.

*p < .05; **p < .01; ***p<.001 significant differences.

6.5. Discussion

The current study examined the behavioral and neurofunctional mechanisms underlying memory inhibition, specifically those related to alcohol-related memories suppression, in young BDs. We explored the FC between IC and memory networks, using a dynamic seed-based analysis. BDs had greater difficulty suppressing non-alcohol memories than N/LDs, but similar performance during the suppression of alcoholic ones. Functionally, BDs displayed a hypoconnectivity pattern between the ACC and the lFusiG while suppressing no-alcohol memories relative to N/LDs, suggesting a reduced top-down control over visual representations from non-alcoholic images, which may be contributing for the unsuccessful forgetting of those memories. Contrarily, BDs showed a hyperconnectivity pattern between the right IC network and memory regions during attempts to suppress alcohol-related memories, indicating an

enhanced top-down control aiming at suppressing intruding alcohol memories from their awareness (Figure 23).

Results revealed that BDs exhibited decreased alpha-band FC between ACC and lFusiG 900-1500ms after No-Think No-Alcohol cues compared to N/LDs. The ACC is considered a critical region in IC, as it is responsible for conflict/error detecting and signaling the need to intensify cognitive control.[67,68] Likewise, recent findings revealed the ACC role in memory inhibition, signaling top-down IC processes for DLPFC and/or mediating the communication between the DLPFC and medial temporal regions during attempts of forgetting unwanted material.[69,70] Meanwhile, the fusiform gyrus has been implicated in the generation of visual mental images and the perception of objects and scenes,[71-73] suggesting that this region is activated during encoding and retrieval of visual information.[74] Therefore, the reduced communication between these regions observed in BDs may be indicative of reduced control over visual representations of non-alcohol memories, making them more difficult to suppress. Accordingly, recent evidence revealed that the PFC not only downregulates the hippocampus but also the fusiform cortex during suppression of visual object memories, which may hamper the subsequent *ecphoria* or restoration of sensory information, disrupting the perceptual traces of suppressed items.[10,16] This reduced level of control might be attributed to the diminished motivational and salience properties of non-alcohol stimuli.[6,75] Consequently, BDs may have not paid proper attention to this type of stimuli, potentially causing the ACC to fail in recognizing the importance of inhibiting them and thus signaling top-down control in a lesser extent. In line with this assumption, a recent study revealed that a reflexive orienting of attention and conscious detection of unwanted memories was crucial to their later forgetting, further emphasizing the idea that memories require attention and access to consciousness to be suppressed effectively.[76]

Aligned with this, the hypoconnectivity pattern between ACC and lFusiG was observed in the alpha band, a well-established electrophysiological signature of cortical inhibition.[77-79] Burgeoning studies have revealed that increased alpha phase synchronization reflects top-down control mechanisms.[80,81] Importantly, recent TNT studies also reported augmented alpha power in the lFusiG and occipital areas[82,83] and increased phase synchronization in this band[84] during memory suppression. Altogether, the decreased alpha-band between-network (ACC-lFusiG) connectivity supports the assumption that BDs displays reduced top-down control over perceptual representations of non-alcoholic images[71,80-85]– tentatively because the motivational aspects of non-alcohol stimuli are blunted[6,75]-, which may explain the unsuccessful forgetting of these memories.

Unexpectedly, BDs suppressed alcohol-related memories equally to N/LDs. However, they exhibited increased gamma-band FC between the rSFG and the memory network (rFusiG and rHip-

rParahip) relatively to N/LDs. This hyperconnectivity pattern may be interpreted as a *neurocompensatory* mechanism – i.e., recruitment of additional neural resources- that allowed BDs to perform the task at the same level as N/LDs. Research demonstrated that BDs have high motivational reactivity to alcohol-related cues, reflected as augmented brain activity and increased FC during processing of alcohol-related stimuli.[38-42] Consequently, the increased FC between IC and memory networks during suppression of alcohol-related memories may be related to the need to effectively suppress highly salient and reward-predicting stimuli (i.e., alcoholic drinks). These findings are congruent with other studies in individuals with alcohol-related problems, including BDs, showing brain overactivity during the inhibition of alcohol cues in Go/NoGo tasks.[86-90] Furthermore, several studies revealed that BDs display augmented brain activity to successfully inhibit their responses, reflecting a neural mechanism that allows them to compensate for an underlying deficit resulting from excessive alcohol use.[41,90-93] This hypothesis is further supported by the finding that BDs displayed increased FC while suppressing alcohol relative to non-alcohol memories, exhibiting increased suppression for alcoholic ones (see Figure 22). However, why this mechanism only occurs during the suppression of alcoholic stimuli remains elusive. The increased processing of alcohol-related information may lead BDs to experience higher memory intrusions than N/LDs during the suppression of alcohol items. Intrusions are memories that come to consciousness despite efforts to prevent their retrieval –e.g., in the TNT paradigm, intrusions occur during No-Think trials when an unwanted memory comes to participants' minds.[1,6,13,15,16] fMRI studies have reported increased right-side DLPFC activity,[13,16] decreased hippocampal activity,[6] and robust communication between right DLPFC and memory regions during attempts to counter intrusive memories, indicating enhanced top-down IC to suppress the intruding of unwanted content.[6,13,15,16] Thus, the augmented FC between the rSFG and the memory network during the suppression of alcoholic information may reveal an enhanced top-down control to countermand intruding alcohol-related memories that probably penetrate BDs' awareness more strongly. As such, the potential emergence of alcoholic memory intrusions in BDs' mind accompanied by the instruction to suppress them may explain the increased communication between regions involved in memory inhibition.

The fact that this hyperconnectivity has been found in the gamma frequency range endorses this explanation, since increased gamma power and/or phase synchronization has been associated with activation of existing memory traces, successful memory retrieval, and selective attention.[94-99] Thus, the enhanced gamma-band FC may reflect augmented attention towards alcoholic memories and increased activation of unwanted memory traces that emerge as intrusions, leading BDs to recruit additional top-down resources to suppress these intrusive memories and achieve similar performance to N/LDs.

The absence of an impaired suppression of alcohol-related memories in BDs at the behavioral level may be explained by this neurocompensatory mechanism but also by the possibility that these memories are not as intrusive as in more severe conditions (e.g., AUD) since they are not compulsive drinkers. Therefore, while the BD's increased attention towards alcohol-related information makes them still able to recruit additional neural resources and suppress these memories, individuals with severe and more compulsive drinking patterns may not effectively countermand the intrusiveness of memories/thoughts associated with alcohol, leading to difficulties in regulating drinking behavior. Supporting this hypothesis, the two studies showing impaired memory suppression in individuals with alcohol-related problems focused on populations with a more severe pattern (i.e., hazardous drinkers and individuals with AUD) than that of our BD's sample.[25,26] These studies revealed disrupted memory suppression abilities in the presence of alcohol-related cues[26] and that impairments in this ability may compromise long-term abstinence in detoxified patients.[25] Thus, further studies with this type of population are needed to gain a more comprehensive understanding of how memory suppression mechanisms may be affected and lead to compulsive alcohol consumption.

There are some limitations that should be considered when interpreting the results of the present study. Firstly, there was a lack of a quantitative or objective measure of memory intrusions, that is, participants did not indicate after each cue during the TNT phase whether the memory did come to mind or did not enter awareness at all. These critical trial-by-trial reports would allow us to identify if BDs had more intrusions during No-Think alcohol than no-alcohol items and if they had more alcohol-related memory intrusions relative to N/LDs. Accordingly, these data would allow us to verify if the hyperconnectivity pattern observed in BDs during the suppression of alcohol memories was, in fact, caused by the greater occurrence of intrusions during No-Think alcohol trials. Additionally, it should be relevant to collect more detailed data on drinking habits, particularly a measure of recent BD episodes since evidence has shown that heavier recent BD is associated with decreased activation of regions responsible for executive control, namely the DLPFC and ACC,[100] which play an important role in memory suppression mechanisms. Finally, the constrained sample size, although suitable for an EEG study, could limite the generalizability of results. Therefore, additional research is warranted to verify or refute the present findings.

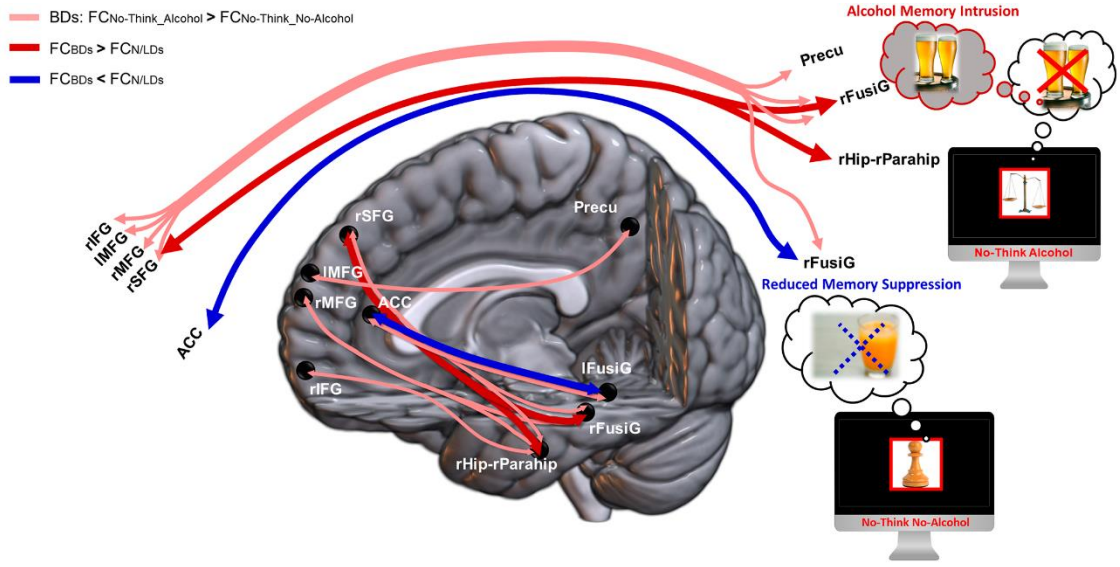
6.5.1. Conclusion

In conclusion, the present study provides the first evidence of disruptions in the neural and behavioral processes associated with memory suppression in young BDs. Results revealed that BDs

presented greater difficulty suppressing non-alcoholic memories, which was accompanied by reduced FC between IC and memory networks –suggesting weak IC ability and poor processing of these low-rewarding stimuli. Conversely, BDs displayed a hyperconnectivity pattern between these networks when tried to suppress alcohol-related memories, indicating enhanced attentional bias towards intrusive alcohol memories and/or a compensatory neurofunctional mechanism aiming at preserving similar task performance as N/LDs. Finally, although further research is needed -particularly in clinical populations such as individuals with AUD-, these findings may hold major implications for alcohol research and treatment, as they may provide insightful knowledge on the ability to exert control over intrusive (alcohol-related) memories and, thus, open up new avenues for reducing alcohol use and/or maintaining sustained long-term abstinence in individuals with alcohol-related problems.

Figure 23

Graphical representation showing the increased functional connectivity (FC) during the suppression of alcohol-related memories (red connections) and the reduced FC linked to the suppression of non-alcoholic memories (blue connections) in young binge drinkers (BDs) relative to non-/low-drinkers peers.



Note. Pink connections represent the hyperconnectivity pattern between the inhibitory control (IC) and memory networks during the suppression of alcoholic comparing with non-alcoholic memories in BDs. This increased FC suggest enhanced top-down control between IC and memory networks to countermand highly salient and reward-predicting stimuli, i.e., intruding alcohol-related memories. The hypoconnectivity pattern might indicate that BDs recruit, to a lesser extent, the IC network to suppress non-alcohol-related memories, as these stimuli have lower motivational value and therefore are less likely to cause intrusions. rIFG: right inferior frontal gyrus; rMFG: right middle frontal gyrus; lMFG: left middle frontal gyrus; rSFG: right superior frontal gyrus; ACC: anterior cingulate cortex; rFusiG: right fusiform gyrus; lFusiG: left fusiform gyrus; rHip-rParahip: right hippocampus and parahippocampus; Precu: precuneus.

6.6. References

1. Anderson MC, Hanslmayr S. Neural mechanisms of motivated forgetting. Trends *Cognitive Science*. 2014; 18: 279-292.
2. Anderson MC, Huddleston E. Towards a Cognitive and Neurobiological Model of Motivated Forgetting. In: Belli, R. (eds) True and False Recovered Memories. Nebraska Symposium on Motivation, vol 58. Springer; 2012.
3. Mars LC, Anderson MC. Oxford Handbook of human memory, Volume 1: Foundations. Kahana MJ, Wagner AD (Eds.), Oxford University Press; 2001.
4. Anderson MC, Green C. Suppressing unwanted memories by executive control. *Nature*. 2001; 410: 366-369.
5. Anderson MC, Ochsner KN, Kuhl B, Cooper J, Robertson E, Gabrieli SW, et al. Neural systems underlying the suppression of unwanted memories. *Science*. 2004; 303: 232-235.
6. Levy BJ, Anderson MC. Purging of memories from conscious awareness tracked in the human brain. *Journal of Neuroscience*. 2012, 32:16785-16794.
7. Anderson MC, Hulbert JC. Active forgetting: Adaptation of memory by prefrontal control. *Annual Review of Psychology*. 2021; 72: 1–36.
8. Benoit RG, Anderson MC. Opposing mechanisms support the voluntary forgetting of unwanted memories. *Neuron*. 2012; 76: 450-460.
9. Depue BE, Curran T, Banich MT. Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science*. 2007; 317: 215-219.
10. Gagnepain P, Henson RN, Anderson MC. Suppressing unwanted memories reduces their unconscious influence via targeted cortical inhibition. *Proceedings of the National Academy of Sciences*. 2014; 111: E1310-E1319.
11. Paz-Alonso PM, Bunge SA, Anderson MC, Ghetti S. Strength of coupling within a mnemonic control network differentiates those who can and cannot suppress memory retrieval. *Journal of Neuroscience*. 2013; 33: 5017-5026.
12. Apšvalka D, Ferreira CS, Schmitz TW, Rowe JB, Anderson MC. Dynamic targeting enables domain-general inhibitory control over action and thought by the prefrontal cortex. *Nature Communications*. 2022; 13: 1-21.
13. Benoit RG, Hulbert JC, Huddleston E, Anderson MC. Adaptive top–down suppression of hippocampal activity and the purging of intrusive memories from consciousness. *Journal of Cognitive Neuroscience*. 2015; 27: 96-111.
14. Benoit RG, Davies DJ, Anderson MC. Reducing future fears by suppressing the brain mechanisms underlying episodic simulation. *Proceedings of the National Academy of Sciences*. 2016; 113: E8492-E8501.
15. Gagnepain P, Hulbert J, Anderson MC. Parallel regulation of memory and emotion supports the suppression of intrusive memories. *Journal of Neuroscience*. 2017; 37: 6423-6441.
16. Mary A, Dayan J, Leone G, Postel C, Fraisse F, Malle C et al. Resilience after trauma: The role of memory suppression. *Science*. 2020; 367: 6479
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Publishing; 2013.
18. Goschke T. Dysfunctions of decision-making and cognitive control as transdiagnostic mechanisms of mental disorders: advances, gaps, and needs in current research. *International Journal of Methods in Psychiatric Research*. 2014; 23: 41-57.
19. Norman LJ, Taylor SF, Liu Y, Radua J, Chye Y, De Wit SJ et al. Error processing and inhibitory control in obsessive-compulsive disorder: A meta-analysis using statistical parametric maps. *Biological Psychiatry*. 2019; 85: 713-725.

20. Catarino A, Küpper CS, Werner-Seidler A, Dalgleish T, Anderson MC. Failing to forget: Inhibitory-control deficits compromise memory suppression in posttraumatic stress disorder. *Psychological Science*. 2015; 26: 604-616.
21. Depue BE, Burgess GC, Willcutt EG, Ruzic L, Banich M. Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: evidence from deficits in individuals with ADHD. *Neuropsychologia*. 2010; 48: 3909-3917.
22. Diwadkar VA, Re M, Cecchetto F, Garzitto M, Piccin S, Bonivento C, et al. Attempts at memory control induce dysfunctional brain activation profiles in generalized anxiety disorder: an exploratory fMRI study. *Psychiatry Research Neuroimaging.* 2017; 266: 42-52.
23. Marzi T, Regina A, Righi S. Emotions shape memory suppression in trait anxiety. Frontiers in Psychology. 2014; 4: 1001.
24. Storm BC, White HA. ADHD and retrieval-induced forgetting: Evidence for a deficit in the inhibitory control of memory. *Memory.* 2010; 18: 265-271.
25. Nemeth VL, Kurgyis E, Csifcsak G, Maraz A, Almasi DA, Drotos G, et al. The impact of intermediate-term alcohol abstinence on memory retrieval and suppression. *Frontiers in Psychology*. 2014; 5: 1396.
26. Simeonov L, Peniket M, & Das R. No-think, No drink? Assessing the ability of reconsolidation interference by intentional forgetting to suppress alcohol 49 memories in hazardous drinkers. *Behaviour Research and Therapy*. 2022; 152,
27. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*. 2011; 12: 652–669.
28. Heinz A, Wrase J, Kahnt T, Beck A, Bromand Z, Grüsser SM, et al. Brain activation elicited by affectively positive stimuli is associated with a lower risk of relapse in detoxified alcoholic subjects. *Alcoholism: Clinical and Experimental Research*. 2007; 31: 1138-1147.
29. George MS, Anton RF, Bloomer C, Teneback C, Drobes DJ, Lorberbaum JP, et al. Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. *Archives Of General Psychiatry*. 2001; 58: 345-352.
30. Myrick H, Anton RF, Li X, Henderson S, Drobes D, Voronin K, George MS. Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. *Neuropsychopharmacology*. 2004; 29: 393-402.
31. Olbrich HM, Valerius G, Paris C, Hagenbuch F, Ebert D, & Juengling FD. Brain activation during craving for alcohol measured by positron emission tomography. *Australian and New Zealand Journal of Psychiatry*. 2006; 40: 171-178.
32. Grüsser SM, Wrase J, Klein S, Hermann D, Smolka MN, Ruf M, et al. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology*. 2004; 175: 296-302.
33. Jacobus J, Tapert SF. Neurotoxic effects of alcohol in adolescence. *Annual Review of Clinical Psychology*. 2013; 9: 703–721.
34. White AM, Swartzwelder HS. Hippocampal function during adolescence: a unique target of ethanol effects. *Annals of the New York Academy of Sciences*. 2004; 1021: 206-220.
35. National Institute of Alcohol Abuse and Alcoholism. Understanding Binge Drinking. 2022.https://www.niaaa.nih.gov/sites/default/files/publications/NIAAA_Binge_Drinking_3.pdf. Accessed 2 February 2023.
36. Kraus L, Guttormsson U, Leifman H, Arpa S, Molinaro S, Monshouwer K, et al. ESPAD Report 2015. Results from the European School Survey Project on Alcohol and Other Drugs. Lisbon: European Monitoring Centre for Drugs and Drug Addiction. 2016.

37. Maurage P, Lannoy S, Mange J, Grynberg D, Beaunieux H, Banovic I, et al. What we talk about when we talk about binge drinking: Towards an integrated conceptualization and evaluation. *Alcohol Alcohol*. 2020; 55: 468–479.
38. Almeida-Antunes N, Antón-Toro L, Crego A, Rodrigues R, Sampaio A, López-Caneda E. "It's a beer!": Brain functional hyperconnectivity during processing of alcohol-related images in young binge drinkers. *Addiction Biology*. 2022; 27: e13152.
39. Brumback T, Squeglia LM, Jacobus J, Pulido C, Tapert S, Brown SA. Adolescent heavy drinkers' amplified brain responses to alcohol cues decrease over one month of abstinence. *Addictive Behaviors*. 2015; 46: 45–52.
40. Petit G, Kornreich C, Verbanck P, Campanella S. Gender differences in reactivity to alcohol cues in binge drinkers: a preliminary assessment of event-related potentials. *Psychiatry Research*. 2013; 209, 494–503.
41. Petit G, Kornreich C, Dan B, Verbanck P, Campanella S. Electrophysiological correlates of alcohol- and non-alcohol-related stimuli processing in binge drinkers: a follow-up study. *Journal of Psychopharmacology*. 2014; 28: 1041– 1052.
42. Ryerson NC, Neal LB, Gable PA. Attenuating the alcohol allure: attentional broadening reduces rapid motivational response to alcohol pictures. *Psychopharmacology*. 2017; 234: 1247–1254.
43. Carbia C, López-Caneda E, Corral M, Cadaveira F. A systematic review of neuropsychological studies involving young binge drinkers. *Neuroscience & Biobehavioral Reviews*. 2018; 90: 332–349.
44. Czapla M, Simon JJ, Friederich HC, Herpertz SC, Zimmermann P, Loeber S. Is binge drinking in young adults associated with an alcohol-specific impairment of response inhibition? *European Addiction Research*. 2015; 21: 105–113.
45. Henges AL, Marczinski CA. Impulsivity and alcohol consumption in young social drinkers. *Addictive Behaviors*. 2012; 37: 217-220.
46. López-Caneda E, Cadaveira F, Crego A, Gómez-Suárez A, Corral M, Parada M, et al. Hyperactivation of right inferior frontal cortex in young binge drinkers during response inhibition: a follow-up study. *Addiction*. 2012 107: 1796-1808.
47. López-Caneda E, Rodríguez Holguín S, Correas Á, Carbia C, González-Villar A, Maestú F, Cadaveira F. Binge drinking affects brain oscillations linked to motor inhibition and execution. *Journal of Clinical Psychopharmacology*, 2017; 31: 873-882.
48. Lannoy S, Dormal V, Billieux J, Brion M, D'Hondt F, Maurage P. A dual-process exploration of binge drinking: evidence through behavioral and electrophysiological findings. *Addiction Biology*. 2020; 25: e12685.
49. Peeters M, Wiers RW, Monshouwer K, van de Schoot R, Janssen T, Vollebergh WA. Automatic processes in at-risk adolescents: the role of alcohol-approach tendencies and response inhibition in drinking behavior. *Addiction*. 2012; 107: 1939–1946.
50. López-Caneda E, Crego A, Campos AD, González-Villar A, Sampaio A. The think/no-think alcohol task: a new paradigm for assessing memory suppression in alcohol-related contexts. *Alcoholism: Clinical and Experimental Research*. 2019; 43: 36–47.
51. Almeida-Antunes N, Vasconcelos M, Crego A, Rodrigues R, Sampaio A, López-Caneda E. Forgetting Alcohol: A Double-Blind, Randomized Controlled Trial Investigating Memory Inhibition Training in Young Binge Drinkers. *Frontiers in Neuroscience*. 2022; 16: 914213.
52. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test (AUDIT): guidelines for use in primary care. 2001.
53. Patterson C, Hogan L, Cox M. A comparison between two retrospective alcohol consumption measures and the daily drinking diary method with university students. The American Journal of Drug and Alcohol Abuse; 2019; 45(3), 248–253.

54. Derogatis LR. SCL-90-R revised manual. Baltimore: Johns Hopkins University School of Medicine. 1983.
55. Flannery BA, Volpicelli JR, Pettinati HM Psychometric properties of the Penn alcohol craving scale. *Alcoholism: Clinical and Experimental Research*. 1999; 23:1289–95.
56. Rodrigues R, López-Caneda E, Almeida-Antunes N, Sampaio A, Crego. Portuguese validation of the Alcohol Craving Questionnaire–Short Form–Revised. *PloS one*, 2021; 16: e0251733.
57. Bergström ZM, Velmans M, de Fockert, Richardson-Klavehn A. ERP evidence for successful voluntary avoidance of conscious recollection. *Brain Research*. 2007; 1151: 119-133.
58. Chen S, Mao X, Wu Y (2022) Can't stop thinking: The role of cognitive control in suppression-induced forgetting. *Neuropsychologia*. 2022; 172: 108274.
59. Waldhauser GT, Lindgren M, Johansson M. Intentional suppression can lead to a reduction of memory strength: behavioral and electrophysiological findings. *Frontiers in Psychology*. 2012; 3: 401.
60. Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*. 2011.
61. Belouchrani A, Abed-Meraim K, Cardoso JF, Moulines E. A blind source separation technique using second-order statistics. IEEE Transactions on Signal Processing. 1997; 45, 434–444.
62. Fuchs M, Wagner M, Kastner J. Boundary element method volume conductor models for EEG source reconstruction. *Clinical Neurophysiology*. 2001; 112, 1400-576 1407.
63. Van Veen BD, Van Drongelen W, Yuchtman M, Suzuki A. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical Engineering*, 1997; 44: 867-880.
64. Mazziotta J, et al. A four-dimensional probabilistic atlas of the human brain. *Journal of the American Medical Informatics Association*. 2001; 8: 401-430.
65. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002; 15: 273-289.
66. Bruña R, Maestú F, Pereda E. Phase locking value revisited: teaching new tricks to an old dog. *Journal of Neural Engineering*. 2018; 15: 056011.
67. Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciences.* 2004; 8: 539-546.
68. Lütcke H, Frahm J. Lateralized anterior cingulate function during error processing and conflict monitoring as revealed by high-resolution fMRI. *Cerebral Cortex*. 2008; 18: 508-515.
69. Butler AJ, James KH. The neural correlates of attempting to suppress negative versus neutral memories. *Cognitive, Affective, & Behavioral Neuroscience*. 2010; 10: 182-194.
70. Crespo-García M, Wang Y, Jiang M, Anderson MC, Lei X. Anterior cingulate cortex signals the need to control intrusive thoughts during motivated forgetting. *Journal of Neuroscience*. 2022; 42: 4342-4359.
71. Bar M, Kassam KS, Ghuman AS, Boshyan J, Schmid AM, Dale AM, et al. Top-down facilitation of visual recognition. *Proceedings of the National Academy of Sciences*. 2006; 103: 449-454.
72. Danker JF, & Anderson JR. The ghosts of brain states past: remembering reactivates the brain regions engaged during encoding. *Psychological Bulletin*. 2010; 136: 87.
73. Spagna A, Hajhajate D, Liu J, Bartolomeo P. Visual mental imagery engages the left fusiform gyrus, but not the early visual cortex: A meta-analysis of neuroimaging evidence. *Neuroscience & Biobehavioral Reviews*. 2021; 122: 201-217.
74. Dijkstra N, Bosch SE, & van Gerven MA. Shared neural mechanisms of visual perception and imagery. *Trends in Cognitive Sciences*. 2019; 23: 423-434.

75. Tolomeo S, Baldacchino A, Steele JD. Blunted Expected Reward Value Signals in Binge Alcohol Drinkers. *Journal of Neuroscience*. 2023.
76. Legrand N, Etard O, Viader F, Clochon P, Doidy F, Eustache F, Gagnepain P. Attentional capture mediates the emergence and suppression of intrusive memories. *Iscience*. 2022; 105516.
77. Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Frontiers in Human Neuroscience*. 2010; 4: 186.
78. Klimesch W. Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences*. 2012; 16: 606-617.
79. Zumer JM, Scheeringa R, Schoffelen JM, Norris DG, Jensen O. Occipital alpha activity during stimulus processing gates the information flow to object-selective cortex. *PLOS Biology*. 2014; 12: e1001965.
80. Sauseng P, Klimesch W, Doppelmayr M, Pecherstorfer T, Freunberger R, Hanslmayr S. EEG alpha synchronization and functional coupling during top-down processing in a working memory task. *Human Brain Mapping*. 2005; 26: 148-155.
81. Sadaghiani S, Scheeringa R, Lehongre K, Morillon B, Giraud AL, d'Esposito M, Kleinschmidt A. Alpha-band phase synchrony is related to activity in the fronto-parietal adaptive control network. *Journal of Neuroscience*. 2012; 32: 14305-14310.
82. Depue BE, Ketz N, Mollison MV, Nyhus E, Banich MT, Curran T. ERPs and neural oscillations during volitional suppression of memory retrieval. *Journal of Cognitive Neuroscience*. 2013; 25, 1–10.
83. Ketz N, O'Reilly RC, Curran T. Classification aided analysis of oscillatory signatures in controlled retrieval. *Neuroimage*. 2014; 85: 749-760.
84. Waldhauser GT, Bäuml KHT, Hanslmayr S (2015): Brain oscillations mediate successful suppression of unwanted memories. *Cerebral Cortex*. 2015; 25: 4180-4190.
85. Fellner MC, Waldhauser GT, Axmacher N. Tracking selective rehearsal and active inhibition of memory traces in directed forgetting. *Current Biology*. 2020; 30: 2638-2644.
86. Ames SL, Wong SW, Bechara A, Cappelli C, Dust M, Grenard JL, et al. Neural correlates of a go/nogo task with alcohol stimuli in light and heavy young drinkers. *Behavioural Brain Research*. 2014; 274: 382–9.
87. Czapla M, Baeuchl C, Simon JJ, Richter B, Kluge M, Friederich HC, et al. Do alcohol-dependent patients show different neural activation during response inhibition than healthy controls in an alcohol-related Fmri Go/No-Go-task? *Psychopharmacology*. 2017; 234:1001–15.
88. Stein M, Steiner L, Fey W, Conring F, Rieger K, Federspiel A, et al. Alcohol-related context modulates neural correlates of inhibitory control in alcohol dependent patients: preliminary data from an fmri study using an alcohol-related Go/Nogo-task. *Behavioural Brain Research*. 2021; 398:112973
89. Grieder M, Soravia LM, Tschuemperlin RM, Batschelet HM, Federspiel A, Schwab S, et al. Right Inferior Frontal Activation During Alcohol-Specific Inhibition Increases With Craving and Predicts Drinking Outcome in Alcohol Use Disorder. *Frontiers in Psychiatry*. 2022; 13.
90. Suárez-Suárez S, Doallo S, Pérez-García JM, Corral M, Rodríguez Holguín S, Cadaveira F. Response Inhibition and Binge Drinking During Transition to University: An fMRI Study. *Frontiers Psychiatry*. 2020; 11: 535.
91. Almeida-Antunes N, Crego A, Carbia C, Sousa SS, Rodrigues R, Sampaio A, López-Caneda E. Electroencephalographic signatures of the binge drinking pattern during adolescence and young adulthood: A PRISMA-driven systematic review. *NeuroImage: Clinical*. 2021; 29: 102537.
92. Molnar SM, Beaton LE, Happer JP, Holcomb LA, Huang S, Arienzo D, Marinkovic K. Behavioral and brain activity indices of cognitive control deficits in binge drinkers. *Brain Science*. 2018; 8: 9.
93. Wetherill RR, Squeglia LM, Yang TT, Tapert SF. A longitudinal examination of adolescent response inhibition: Neural differences before and after the initiation of heavy drinking. *Psychopharmacology*. 2013; 230: 663–671.

94. Osipova D, Takashima A, Oostenveld R, Fernández G, Maris E, Jensen O. Theta and gamma oscillations predict encoding and retrieval of declarative memory. *Journal of Neuroscience*. 2006 26: 7523-7531.
95. Sederberg P et al. Gamma oscillations distinguish true from false memories. *Psychological Science*. 2007; 18, 927–932
96. Gruber T, Müller MM, Keil A, Elbert T. Selective visual-spatial attention alters induced gamma band responses in the human EEG. *Clinical Neurophysiology*. 1999; 110:2074 –2085
97. Fries P, Reynolds JH, Rorie AE, Desimone R. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science*. 2001; 291:1560 –1563.
98. Friese U, Daume J, Göschl F, König P, Wang P, Engel AK. Oscillatory brain activity during multisensory attention reflects activation, disinhibition, and cognitive control. *Scientific Reports*. 2016; 6: 1-11.
99. Tallon-Baudry C, Bertrand O, Hénaff MA, Isnard J, Fischer C. Attention modulates gamma-band oscillations differently in the human lateral occipital cortex and fusiform gyrus. *Cerebral Cortex*. 2005; 15: 654-662.
100. Cohen-Gilbert JE, Nickerson LD, Sneider JT, Oot EN, Seraikas AM, Rohan M et al. College Binge Drinking Associated with Decreased Frontal Activation to Negative Emotional Distractors during Inhibitory Control. *Frontiers in Psychology*, 2017; 8.

PART IV: DISCUSSION

CHAPTER 7: General Discussion

The present dissertation aimed to expand the knowledge about the effects of BD on young adults' brain by filling some existing gaps in the literature that may have important implications for alcohol research and clinical practice. More specifically, we aimed to deeply understand the BD effects on the brain electrical activity of adolescents and young adults by systematically reviewing, for the first time, the EEG studies conducted so far (Chapter 2). Aiming to grasp more comprehensively the mechanisms underlying the processing of alcohol-related stimuli, the first empirical study provided the first body of knowledge regarding the brain connectivity underlying alcohol-cue reactivity in young BDs (Chapter 5). On the other hand, the second empirical study was pioneering in exploring the behavioral and FC patterns underlying the memory suppression mechanisms, especially those related to the suppression of alcohol-related memories in young BDs (Chapter 6). This chapter presents the main findings of these studies, discussing their contributions to BD research, and integrating them within the approach outlined in the narrative review (Chapter 3).

7.1. BD and its Effects on Brain Electrical Activity

The systematic review (Almeida-Antunes et al., 2021) included 34 studies and showed that BDs have abnormal EEG activity during cognitive tasks and resting state conditions, which supports both the continuum and the compensation hypothesis. Specifically, BDs seem to exhibit enhanced resting EEG activity (Affan et al., 2018; Courtney & Polich, 2010; López-Caneda, Cadaveira, et al., 2017), reduced activity during error detection (Kim & Kim, 2019; Smith & Mattick, 2013; Smith et al., 2016), and increased neural reactivity toward alcohol-related stimuli (Petit et al., 2012, 2013, 2014; Ryerson et al., 2017). These neural alterations resemble those observed in individuals with AUD, being thus in accordance with the continuum hypothesis, which claims that BD and AUD are two successive steps of the same phenomenon (Enoch, 2006; Lannoy et al., 2014, 2019). On the other hand, BDs display enhanced brain activity associated with several cognitive processes, being the increased P3 amplitude elicited during attention (Crego et al., 2012; López-Caneda et al., 2013), working memory (Park & Kim, 2018; Schroder et al., 2019), and response inhibition (López-Caneda et al., 2012, 2014; Smith & Mattick, 2013; Smith et al., 2016) tasks the most solid EEG finding. This augmented brain activity suggests the recruitment of additional neural resources to perform the task at adequate/successful levels, which supports the neurocompensation hypothesis.

Overall, the BDs' EEG profile appears to resemble that of individuals with alcohol dependence during more automatic cognitive processes (e.g., early pre-conscious error detection) and low-demanding conditions (e.g., resting state and visualization of alcohol pictures). However, when the demands of the task increase, BDs seem to activate additional brain regions to counteract underpinning neural decline and to maintain cognitive performance, being indexed by augmented brain activity. Additional factors, such as the characteristics of the task (i.e., the complexity of the stimuli used) and the consumption severity (e.g., high- versus moderate-BDs), were proposed to explain why BDs can sometimes compensate for deficits caused by the drinking pattern, while in other instances, they cannot, mirroring the patterns observed in individuals with AUD. BDs reporting larger amounts of alcohol consumed per drinking occasion (i.e., high-BDs) seem to be more likely to exhibit alterations (i.e., reduced brain activity) close to that exhibited by individuals with AUD (Lannoy et al., 2020; Maurage et al., 2012), since both present similar levels of alcohol consumption. In turn, BDs with lower alcohol use are still able to compensate for the alcohol-related damage, recruiting additional neural resources to maintain normative performance (Crego et al., 2009; López-Caneda et al., 2012; Schroder et al., 2019). Supporting this hypothesis, neuroimaging studies also revealed that decreased brain activity was associated with the intensity of the alcohol consumption pattern (Cservenka et al., 2015; Jones et al., 2016; Maurage et al., 2013; Squeglia et al., 2012; Whelan et al., 2014).

Likewise, and despite further investigation being needed, evidence from recent neuroimaging studies seems to be in line with the assumption that young BDs recruit additional neural resources during tasks requiring augmented cognitive effort. Accordingly, a neuroimaging study employing a Go/No-Go task (i.e., a highly demanding task) showed that BDs performed equally well as light-drinkers; however, they exhibit enhanced error-related negativity in the anterior and posterior cingulate cortices and augmented connectivity among prefrontal regions, suggesting a compensatory mechanism to properly inhibit their responses (Myers et al., 2021). In the same vein, the study of Molnar and colleagues (2018) showed that BDs exhibited heightened ventrolateral PFC activation specifically in response to conflict during a Stroop task, which was linked to their perceived task difficulty, suggesting that as the demands of the task increase the recruitment of additional neural resources also increases (Molnar et al., 2018).

In line with our results, a recent systematic review of the neuroimaging studies conducted in BD revealed that the hyperactivation of the insula, DLPFC, and ACC as well as the recruitment of additional areas during task performance – particularly during inhibition - were the most common patterns observed in BDs (Pérez-García, Suárez-Suárez, et al., 2022). Also, the results of this work revealed no differences in the behavioral performance in most of the cognitive tasks, reinforcing the

neurocompesation hypothesis (Pérez-García, Suárez-Suárez, et al., 2022). Interestingly, these authors hypothesized that the direction of the abnormalities observed in BDs may vary according to the tasks employed and the brain regions recruited, since some studies revealed both increased and decreased neural activity in different regions (Pérez-García, Suárez-Suárez, et al., 2022).

Similarly to what we observed in the EEG literature, there are few fMRI studies exploring certain cognitive functions in BDs, such as working memory and emotional processing, and others were not even addressed (e.g., verbal episodic memory) (Pérez-García, Suárez-Suárez, et al., 2022). Therefore, future studies should focus on the study of these cognitive abilities in this population to corroborate the results observed so far. Recently, an EEG study showed altered ERPs amplitude in BDs during a verbal episodic memory (Rodríguez Holguín et al., 2023). In line with the results of Smith et al.'s (2017), BDs exhibited an augmented LPC amplitude for new pairs when compared to controls, indicating the recruitment of additional neural sources to recognize and recollect the context of the cue and generate a response for slightly processed word pairs, in order to achieve a similar level of performance (Rodríguez Holguín et al., 2023; Smith et al., 2017). Moreover, BDs displayed poor behavioral performance in a demanding verbal episodic memory task, particularly during a short-term cued-recall trial (Rodríguez Holguín et al., 2023); however, the EEG activity during this task was not collected, which does not enable a more comprehensive interpretation of the results in light of the hypothesis discussed above.

Notably, in the absence of data predicting the onset of BD, it remains unclear whether the observed electrophysiological abnormalities in BDs result from the maintenance of the drinking pattern or constitute a pre-existing neural marker. Although there is still a long way to go to understand whether there are brain characteristics that could predict future involvement in BD and what are the long-term effects of this pattern, the evidence discussed in our systematic review suggests that the two assumptions (cause vs consequence) are not mutually exclusive. In accordance with the neuroimaging research (Squeglia et al., 2012; Wetherill et al., 2013), the few EEG studies assessing BDs longitudinally seem to point to a deterioration and/or emergence of neural alterations with the maintenance or transition to this pattern (López-Caneda et al., 2012, 2013; Maurage et al., 2009; Petit et al., 2014). Consistent with these findings, a sustained pattern of BD in the early stages of adulthood also seems to lead to gray matter alterations in regions involved in reward processing, emotional regulation, and executive functions (Pérez-García, Cadaveira, et al., 2022). Concerning abnormalities preceding BD, despite the only EEG study exploring BDs prior to the engagement in this pattern has not shown any significant results (Maurage et al., 2009), several neuroimaging studies reported atypical brain functioning - mainly characterized by reduced activity in frontal and parietal regions - before the beginning of BD (Jones et al., 2016; Norman

et al., 2011; Wetherill et al., 2013). Likewise, recent longitudinal studies using magnetoencephalography also revealed abnormalities in FC networks prior to alcohol misuse (Antón-Toro et al., 2021, 2022, 2023). Specifically, adolescents who engaged in BD two years later seem to exhibit hyperconnectivity patterns at rest (Antón-Toro et al., 2022) as well as among crucial regions of IC networks (Antón-Toro et al., 2021), and between prefrontal and temporal regions (Antón-Toro et al., 2023) during inhibitory tasks prior to BD. Overall, this evidence underlines the existence of neurofunctional abnormalities before the involvement in binge alcohol consumption - particularly in regions associated with cognitive control (Antón-Toro et al., 2021; Norman et al., 2011; Wetherill et al., 2013) – which could potentially serve as a crucial neurophysiological marker of predisposition to hazardous drinking in adolescents.

The extent to which BDs can compensate for potential deficits caused by excessive and intermittent alcohol use is also a question that remains to solve. Therefore, additional studies are required to understand for how long or under which conditions BDs can compensate for potential underlying deficits caused by alcohol misuse. Importantly, some studies revealed that abandoning BD may act as a brake on the neurofunctional (Brumback et al., 2015; López-Caneda et al., 2014) and neuropsychological impairments (Carbia, Cadaveira, Caamaño-Isorna, et al., 2017; Carbia, Cadaveira, López-Caneda, et al., 2017; Mota et al., 2013; Winward, Bekman, et al., 2014; Winward, Hanson, et al., 2014). However, future studies should explore further the recovery after BD to verify if the cessation of the pattern may effectively mitigate the dysfunctions caused by alcohol consumption.

In general, our systematic review showed that EEG is sensitive to subtle brain function alterations potentially resulting from alcohol use that can be compensated to achieve typical performance levels. The most solid EEG finding was the augmented P3 amplitude particularly during response inhibition which align with neuroimaging evidence showing enhanced activity in prefrontal regions during inhibitory processes. Importantly, BDs seem to exhibit commonalities with those dealing with AUD, being the heightened response to alcohol-related cues specially worrying, since it has been strongly associated with the craving experience (Bollen et al., 2020; Flaudias et al., 2019). The increased motivational reactivity to alcohol-related information leads to increased alcohol craving levels, which could play a role in maintaining or even intensifying the drinking behavior over time (Field & Eastwood, 2005; Manchery et al., 2017). Noteworthy, this enhanced attention for alcoholic cues coupled with altered IC may constitute a risk factor for the escalation of the pattern towards more severe forms of alcohol misuse, such as AUD. Trying to shed light on the neural communication underlying the processing of alcohol-related stimuli, the first experimental study of the present dissertation (Chapter 5) focused on the assessment of FC patterns during the visualization of alcohol and no-alcohol stimuli in young BDs.

Furthermore, aiming to examine the interplay between alcohol attentional bias and inhibition, the second experimental study (Chapter 6) explored the behavioral and neurofunctional memory suppression mechanisms, especially those related to the suppression of alcohol-related memories in BDs.

7.2. Alcohol Attentional Bias and BD

The experimental study presented in the Chapter 5 was the first to explore the FC patterns underlying alcohol attentional bias in young BDs. When processing alcohol-related stimuli, we observed that BDs exhibit a beta-band hyperconnectivity, relative to N/LDs. This hyperconnectivity pattern was observed over right fronto-parietal, fronto-occipital and fronto-temporal networks, suggesting that young BDs show an overactivation of brain attentional networks involved in the processing of relevant/desired stimuli, which lead to enhanced processing of alcohol-related information. In contrast, during the processing of non-alcoholic cues, BDs displayed a theta-band hypoconnectivity in a left-lateralized fronto-occipital network in comparison to N/LDs (Figure 24). This decreased FC suggests that young BDs process non-alcoholic information in a lesser degree than N/LDs, tentatively because they perceive this type of cues as low-rewarding stimuli. Interestingly, these hyper- and hypoconnectivity patterns were associated with augmented craving levels.

Overall, these findings are in line with the results reported in the systematic review, supporting that young BDs present an attentional bias for alcohol-related information, characterized by enhanced neural processing of alcohol-related cues, which is translated by increased brain activity and augmented neural communication over attentional networks. These data are especially concerning since several studies have shown that augmented attention to alcohol-related information may contribute to enhanced alcohol craving and consumption levels, ultimately reinforcing the drinking pattern (Fadardi & Cox, 2009; Field et al., 2008; Koob & Volkow, 2010; Langbridge et al., 2019; Pennington et al., 2020; Simon et al., 2022; Townshend & Duka, 2001).

In addition, our findings suggest that young BDs have decreased attention towards non-alcoholic stimuli, which is in accordance with recent evidence showing that BDs exhibit a reduction in the encoding of signals related to non-alcoholic cues, indicating that the motivational aspects of non-alcohol stimuli are blunted in this population (Tolomeo et al., 2023). Further support comes from neuroimaging studies reporting reduced brain response among subcortical and cortical regions in BDs while they performed tasks involving the anticipation and reception of rewards (Chen et al., 2020; Cservenka et al., 2015; Jones et al., 2016; Whelan et al., 2014), which suggest that BDs have decreased reward processing of non-alcohol stimuli.

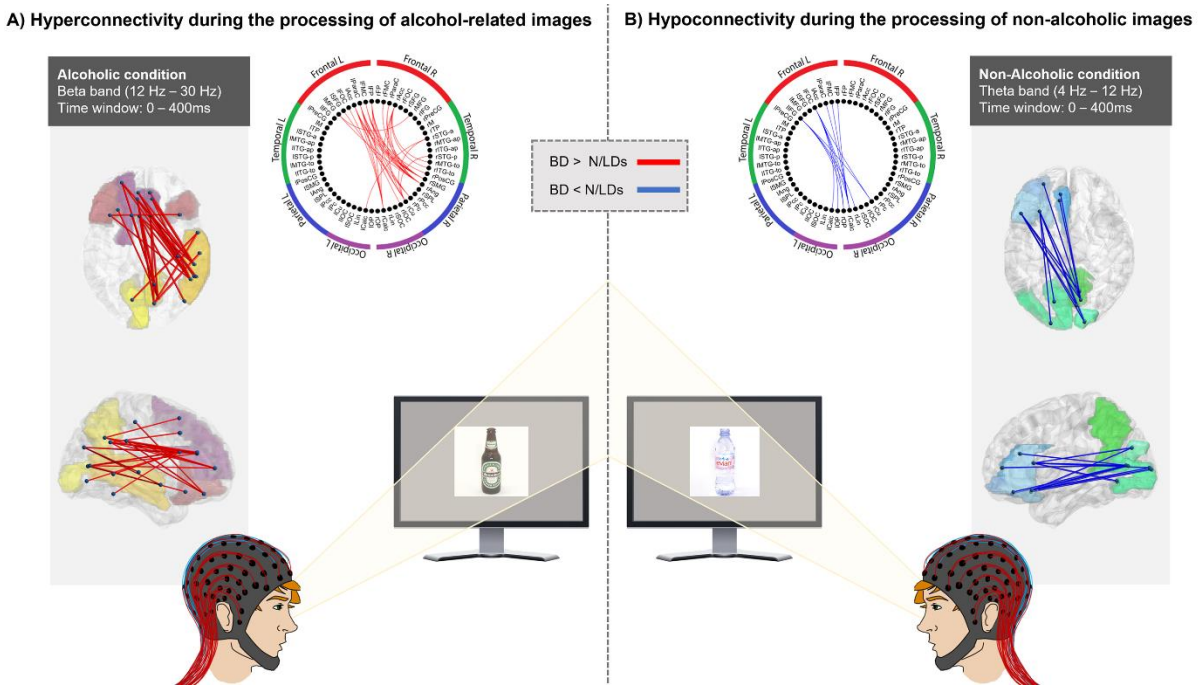
Taken together, these findings indicate that BDs exhibit deficits in attentional processing unless the stimuli being processed are related to alcohol. Accordingly, BD has already been associated with attentional impairments, indexed by decreased connectivity between regions of prefrontal network during attentional processes (Correas et al., 2019) as well as abnormal rest connectivity among networks responsible for redirecting attention towards significant and behaviorally relevant stimuli in the environment (Herman et al., 2019; Tong et al., 2021). More importantly, these data might indicate that BD, similar to alcohol/drug dependence, may be associated with decreased motivational value and reduced attention to natural rewards (Koob & Volkow, 2010; Volkow et al., 2004).

In this regard, the findings reported in this study are in line with what is observed in alcohol dependence and postulated in the neurobiological models of addiction, i.e., while alcohol/drug-related stimuli have increased salience attribution, non-alcohol/drug-related ones become devaluated, receiving reduced attention (Cox et al., 2017; Koob & Volkow, 2010; Volkow et al., 2006; Zilverstand et al., 2018). This increased and decreased motivational value of alcoholic and non-alcoholic stimuli, respectively, arise from dysregulations on the salience/reward systems that underly the transition from impulsive to compulsive consumption (Le Moal & Koob, 2007). Consequently, repeated alcohol exposure may lead to alterations in the salience and reward networks of young BDs, putting these individuals at risk of transit from impulsive to compulsive consumption and developing AUD. Supporting this assumption, evidence reveal that BDs - similarly to individuals with AUD - exhibit enhanced resting FC between regions involved in the salience and reward networks, suggesting augmented salience for alcohol-related rewards that may facilitate increased alcohol-seeking behavior as consumption progresses from impulsive to compulsive (Arienzo et al., 2020).

This increased attention or sensitivity to alcohol-related stimuli in BDs may lead them to experience increased craving (Koob & Volkow, 2010), a phenomenon intricately linked with the retrieval of alcohol-related memories and thoughts. Consequently, the investigation into the suppression of these memories in BDs becomes especially pertinent in order to comprehend potential mechanisms that underlie the maintenance of this pattern, and potentially the transition from impulsive consumption to a more compulsive pattern. Moreover, it may offer valuable insights into possible approaches for alleviating craving, ultimately contributing to more effective interventions for individuals struggling with alcohol and drug-related issues. As such, our second experimental study was designed with the aim of delving into this critical topic.

Figure 24.

Graphical depiction of the BD's FC patterns in response to alcohol-related and non-alcoholic stimuli



Note. (A) Distribution of significant FC links in beta band (12–30 Hz) during the alcoholic condition within the 0–400 ms time window. The red links represent higher connectivity between right fronto-parietal, fronto-occipital and fronto-temporal networks in BDs while processing alcohol-related images. (B) Distribution of significant FC links in theta band (4–12 Hz) for the non-alcoholic condition within the 0–400 ms time window. The blue links indicate lower connectivity in a left-lateralized fronto-occipital network in BDs during the processing of non-alcoholic images.

7.3. Memory Suppression and BD

The second experimental study (Chapter 6) provided the first evidence regarding memory suppression brain mechanisms in young BDs. This study showed that BDs have difficulties in suppressing non-alcohol memories, but similar performance during the suppression of alcoholic ones when compared with N/LDs. At the neural level, results revealed a hypoconnectivity pattern between the ACC and the lFusiG while BDs were suppressing no-alcohol memories, indicating a reduced top-down control over visual representations from non-alcoholic images which may be contributing to the unsuccessful forgetting of those memories. In contrast, BDs showed a hyperconnectivity pattern between the right IC network and memory regions (i.e., right hippocampus, parahippocampus and fusiform cortex) during attempts to suppress alcohol-related memories, indicating an enhanced top-down control aiming at purging intruding alcohol memories from their awareness (Figure 23).

Overall, these findings indicate that BD individuals may exhibit compromised memory suppression abilities, likely stemming from diminished top-down IC, a function previously demonstrated

to be affected by binge alcohol use (Carbia et al., 2018; Holcomb et al., 2019; López-Caneda, Rodríguez Holguín, et al., 2017). Likewise, a recent study proposed deficits in the suppression of intrusive thoughts in BDs, showing reduced resting FC between the inferior frontal cortex and the hippocampus (Arienzo et al., 2020). We proposed that the dysfunctional suppression of non-alcohol related stimuli, associated with decreased FC between IC-memory regions, may result from reduced attention towards these stimuli (Figure 25). Besides it has been shown that memories require attention and access to conscious to be suppressed effectively (Legrand et al., 2022), it is well known that attention is a key component of executive functions, being particularly important in IC processes (Diamond, 2013). Likewise, evidence revealed that memory suppression – an ability mediated by the cognitive control network - is also attention dependent (Anderson & Hulbert, 2021). Accordingly, research has showed that individuals suffering from attention-deficit/hyperactivity disorder exhibit poor memory suppression ability (Depue et al., 2010; Storm & White, 2010). Therefore, the lower attentional processing of non-alcohol-related memories may be compromising the ability to suppress those memories.

Contrarily to what was hypothesized, BDs were able to suppress alcohol-related memories in a similar way to N/LDs; however, at neural level, they exhibited increased FC between the IC and memory networks. This hyperconnectivity pattern was interpreted as a neurocompensatory mechanism indexed by increased communication between regions involved in memory suppression to countermand highly salient alcoholic memories. According to the assumption discussed above, alcohol-related memories probably arouse the BDs' attention, which may facilitate memory suppression mechanisms. Similar results were found in a study using a Go/No-Go task with alcoholic and non-alcoholic stimuli, where BDs exhibited increased FC during the inhibition of alcoholic stimuli (Blanco-Ramos et al., 2022). In addition, fMRI studies also revealed augmented brain activity in regions responsible for cognitive control (i.e., DLPFC, ACC and right inferior frontal cortex) during effective inhibition of the motor response to alcohol-related stimuli in BDs (Ames, Grenard et al., 2014; Suárez-Suárez et al., 2020). According to the dual-process model (Bechara, 2005; Lannoy et al., 2014, 2020; Noël et al., 2010), these findings suggest that the BDs' reflective system may be recruiting additional resources during the suppression of alcohol-related cues or memories to compensate the overactivation of the affective-automatic system caused by the motivational value of this type of stimuli (Figure 25).

As discussed in our systematic review, BDs may be able to recruit compensatory mechanisms to achieve proper performance depending on their drinking habits. Therefore, in BDs with high/intensive alcohol use, the neurocompensation may no longer be available. Accordingly, a study revealed that heavier recent BD episodes were associated with decreased activation of regions involved in executive

control (and memory suppression), namely the DLPFC and ACC (Cohen-Gilbert et al., 2017). In the same line, evidence has shown that alcohol attentional bias may compromise task performance in BDs (Czapla et al., 2015; Lannoy et al., 2018) except if additional cognitive control resources are recruited (Blanco-Ramos et al., 2019; Fleming & Bartholow, 2014). In light of this, when BDs are involved in more severe BD episodes, the increased neural communication during the suppression of alcoholic memories may not be recruited, leading to impaired suppression of those memories, which in turn may contribute to increased craving levels and increased drinking behavior (Bernard et al., 2021; Field & Eastwood, 2005; Manchery et al., 2017).

Furthermore, this neurocompensation may also be recruited probably because BDs realize of the need to inhibit alcohol-related memories due to the No-Think cue. As suggested by the results of the systematic review, BDs seem not exhibit neurocompensation mechanisms during more automatic or low-demanding processes, likely because they are not aware that it is necessary to employ cognitive resources. In daily-life situations, the need to suppress alcohol-related memories may be not so evident as in the laboratory setting and BDs might not recruit additional neural resources to effectively suppress those memories. In these cases, the occurrence of alcohol-related memories may be a more unconscious and automatic process, for instance, when individuals pass by a cafe or bar, memories of drinking alcohol with friends or a past party may come to mind. Consequently, there is no clear intention or an external cue to suppress those memories/thoughts and they may remain in BD's minds, potentially increasing their desire to consume.

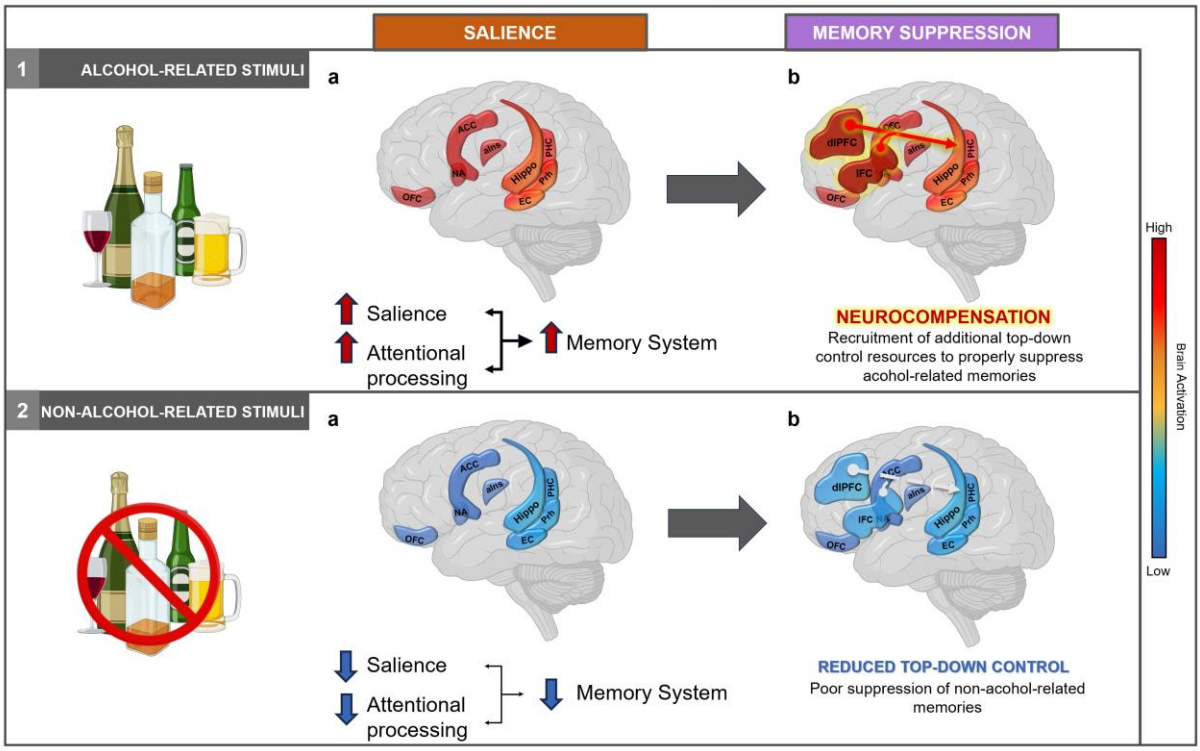
In general, these findings suggest that young BDs may have difficulties in memory suppression due to attentional and IC deficits potentially resulting from alcohol misuse. However, their attentional bias for alcohol-related stimuli may lead to the recruitment of additional cognitive control resources that allowed them to effectively suppress memories associated with alcohol (Figure 25). Nevertheless, the recruitment of this neurocompensatory mechanism may rely on the BDs' intentionality to suppress those memories as well as the severity of their drinking habits. Consequently, if the recruitment of additional neural resources is not available, the augmented reactivity to alcohol-related information may compromise the suppression of these memories, which could contribute to the escalation of the drinking pattern or development of AUD.

In accordance with the results from the first experimental study, this evidence indicates that BDs exhibit enhanced salience of alcohol-related stimuli, decreased processing of non-alcohol information and reduced top-down executive control. In line with the neurobiological models of addiction, these dysregulations in salience/reward and executive networks mediate the progression from recreational to

compulsive drug use, which may put BDs at risk of developing alcohol abuse (Everitt & Robbins, 2016; Goldstein & Volkow, 2011; Koob & Volkow, 2016; Volkow et al., 2004; Zilverstand et al., 2018; Zilverstand & Goldstein, 2020).

Figure 25.

Neural responses to alcohol and non-alcohol cues in BDs: implications for memory suppression mechanisms



Note. (1a) BDs display heightened reactivity to alcohol-related cues potentially indicating an overactivation of the reward/salience systems (depicted in red/orange brain regions). This overactivation may result in an intensified processing of such stimuli and an increased activation of the memory system, leading to the retrieval of alcohol-related memories. (1b) The heightened focus on alcohol-related memories may prompt BDs to engage additional top-down inhibitory control (depicted by the red arrow) from prefrontal regions, particularly the DLPFC and IFC, towards memory structures such as the hippocampus and parahippocampus, in order to counteract the highly salient alcoholic memories. (2a) BDs exhibit diminished attention towards non-alcohol-related cues, potentially reflecting reduced activity in the reward/salience systems (depicted in blue brain regions). This reduced activation of these systems may result in a decreased processing of such stimuli and a lowered activation of the memory system. (2b) The reduced attention towards non-alcohol related memories, coupled with potential inhibitory control deficits due to alcohol misuse, may lead to a reduced ability to suppress this type of memories (indicated by the dashed grey line). ACC: Anterior Cingulate Cortex; aIns: anterior insula; dlPFC: dorsolateral Prefrontal Cortex; EC: Entorhinal Cortex; Hippo: Hippocampus; IFC: Inferior Frontal Cortex; NA: Nucleus Accumbens; OFC: Orbitofrontal Cortex; PHC: Parahippocampal Cortex; Prh: Perirhinal Cortex.

7.4. Hyperactivity and Hyperconnectivity: A Worrying Compensation Mechanism?

The findings of the present dissertation suggest that young BDs exhibit neurocompensatory mechanisms as indicated by heightened neural response and hyperconnectivity in the absence of behavioral deficits. We hypothesized that the recruitment of additional neural resources could rely on BD's drinking habits, with a severe/high-intensity of drinking possibly leading to an incapacity to recruit such mechanisms. In addition, we postulated that BDs engage this neurocompensation when undertaking highly demanding tasks or when they deliberately exert significant cognitive effort. However, it is unknown to what extent this neurocompensation may pose a risk for BDs over the long term.

It is worth noting that hyperconnectivity has emerged as a prevalent response to neurological disruption, being often observed across several conditions including, Parkinson's (Georges et al., 2014; Fernández-Seara et al., 2015), traumatic brain injury (Hillary et al., 2014; Iraji et al., 2016), and multiple sclerosis (Tona et al., 2014; Faivre et al., 2012), where the brain seeks to adapt to significant disturbances by adjusting its connectivity patterns to effectively communicate and respond to environmental demands (Hillary et al., 2015; Hillary & Grafman, 2017). Likewise, compensatory mechanisms have also been observed in individuals with chronic alcoholism (Chanraud & Sullivan, 2014). These mechanisms usually involve a reorganization of brain systems -either by the recruitment of additional regions or alternative pathways, to maintain normal performance despite alcohol-induced disruptions (Camchong et al., 2013; Chanraud et al., 2011, 2013; Chanraud-Guillermo, 2009; Desmond et al., 2003; Pfefferbaum et al., 2011; Tapert et al., 2001; Marinkovic et al., 2009; Muller-Oehring et al., 2013; Pitel et al., 2013). However, the recruitment of *extra* regions for a specific task reduces their availability for concurrent tasks, potentially indicating difficulties for chronic alcoholics in multitasking (Chaunraud et al., 2011). This may represent one of the possible costs of compensation -i.e., the engagement of additional neural resources could potentially strain the system, leading to an overload of cognitive resources (Chanraud & Sullivan, 2014).

In the same vein, existing literature on hyperconnectivity in neurological conditions suggests that while this adaptive response facilitates continued communication during significant network disruptions to maximize information transfer and minimize behavioral deficits, it may also impact behavior, leading to reduced processing speed and cognitive fatigue (Hillary et al., 2015). Additionally, this augmented hyperconnectivity also comes at a metabolic cost. This cost, the energy expended in maintaining heightened neural activity and connectivity, poses doubts about the viability of such a response over extended periods (Hillary & Grafman, 2017). Balancing network cost, efficiency, and metabolic demands becomes crucial for optimizing functional recovery. Concerningly, there is converging

evidence that increased brain metabolism, through local activity and increased network burden, is associated with neurodegeneration, emphasizing the importance of not exclusively interpreting hyperconnectivity patterns as an adaptive compensatory mechanism (Hillary & Grafman, 2017). Therefore, the investigation into the duration and impact of sustained compensatory mechanisms has become a focal point of research interest.

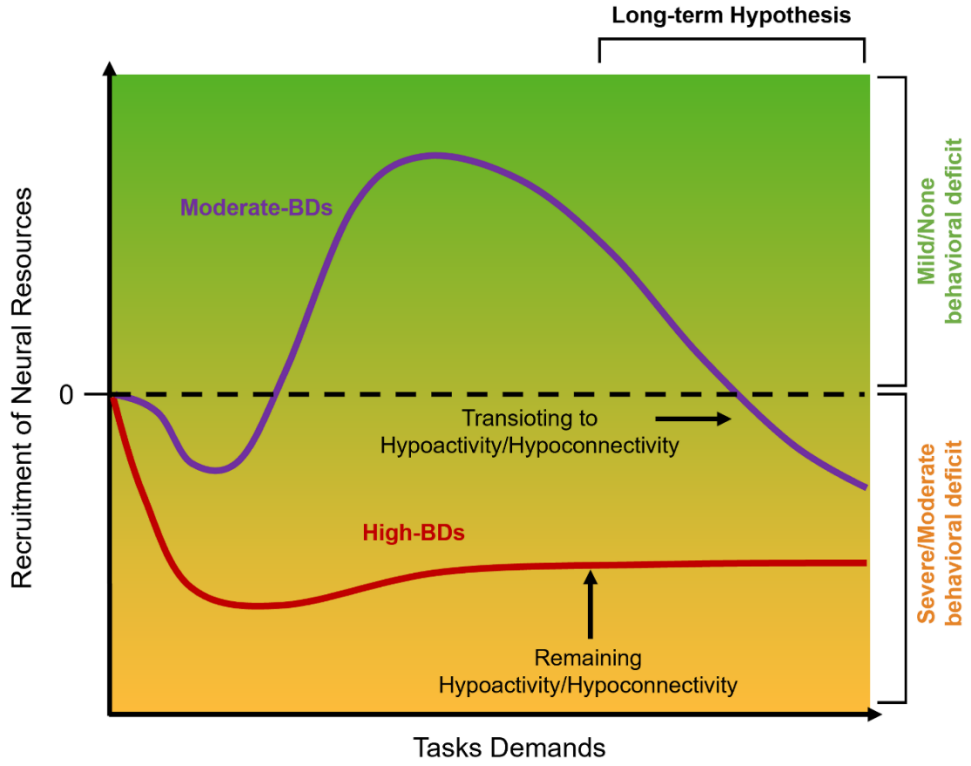
It was proposed that hyperconnectivity in injury and disease is influenced by factors such as demands, injury severity, and available resources (Hillary and Grafman, 2017). Changes in connectivity follow a non-linear pattern, reaching a (hyperconnectivity) peak before transitioning into hypoconnectivity upon a critical loss of structural resources (Aswendt & Hoehn, 2023). Regarding the compensatory mechanisms in chronic alcoholism, it was suggested that in line with the compensation-related utilization of neural circuits hypothesis (Reuter-Lorenz & Park, 2010), alcoholics may engage more neural resources at lower demand levels, which results in a reduction of available resources for handling higher-demand tasks (Chanraud & Sullivan, 2014). However, the sustained capacity for neurocompensation depends on the overall processing capacity of the brain as well as in the availability of reserve resources. In individuals with chronic alcoholism, neurocompensatory processes lead to regional and network functional changes, which are primarily associated with prolonged effects, but it is likely that these stem from initial, rapid short-term adjustments that occur at cellular and molecular levels (e.g., alteration in gray and white matter) (Sullivan & Pfefferbaum, 2019)

Taken together, in the case of young BDs, they showed to be able to compensate during demanding tasks (Almeida-Antunes et al., 2021; Ames, Wong et al., 2014; Campanella et al., 2013; Molnar et al., 2018; Myers et al., 2021, Suárez-Suárez et al., 2020). However, the extent to which this compensation might eventually hinder concurrent processing, as well as the potential changes in brain structure and function it may induce remains unexplored. Importantly, persisting in a BD pattern may potentially lead to an inability to engage a neurocompensatory response, which could result in the emergence of functional deficits (Figure 26). Therefore, individuals with BD may potentially transit from a phase of neurocompensation to a depletion of neural resources, resulting in reduced brain activity and hypoconnectivity patterns (Chen et al., 2020; Lannoy et al., 2020; Maurage et al., 2012, 2013; Squeglia et al., 2011). However, future studies should explore further this hypothesis, as the existing literature on this topic is limited.

Bearing this in mind, the long-term consequences of sustained neurocompensation -including hyperconnectivity- in young BDs became a matter of concern. This adaptive response to the challenges posed by BD behavior, while facilitating continued communication and brain functioning, may introduce

future challenges at the cerebral and behavioral levels. Furthermore, it can evolve into a pattern of decreased brain function, which can lead to functional deficits. Thus, exploring the factors influencing the onset and persistence of hyperactivity/hyperconnectivity in young BDs is a critical avenue for future research. This investigation will shed light on the underlying mechanisms driving this neural adaptation and potentially unveil opportunities for targeted interventions.

Figure 26. *Illustration of the recruitment of neural resources according to task demands in Moderate (purple) and High-BDs (red)*



Note. Moderate-BDs (represented by the purple line) engage additional neural resources to maintain normal behavioral performance. In contrast, High-BDs (depicted by the red line) struggle to activate such compensatory mechanisms, leading to reduced availability of brain resources and subsequent behavioral impairments. Over the long term, it appears that moderate-BDs may transition from a state of neurocompensation (i.e., hyperactivity/hyperconnectivity), towards a pattern of diminished utilization of neural resources, resembling the hypoactivity/hypoconnectivity pattern observed in high-BDS, which is associated with behavioral deficits.

7.5. Limitations and Future Directions

This section focuses on the limitations of the present thesis as well on the future directions for research concerning BD. One important limitation transversal to the studies included in the present dissertation is the characteristics of the sample. Firstly, all the participants were university students and,

consequently, individuals with high cognitive functioning, which could potentially restrict the generalization of the findings to other populations (Guerra-Carrillo et al., 2017). In addition, the effort to control some factors associated with brain functioning abnormalities, such as polydrug use of other substances and presence of psychopathological disorders and/or traits, has conditioned the study of a significant part of the BDs population. As a result, our findings are confined to clinically healthy individuals who have a binge alcohol consumption. Consequently, as the evidence provided by the studies of this dissertation reveals abnormal neural communication in young BDs even in the presence of these protective factors (i.e., high education levels, no polydrug use, and absence of psychopathological disorders), investigating a more representative sample of BDs becomes particularly relevant to observe whether such population exhibit a different pattern of results perhaps characterized by worsen behavioral and brain activity abnormalities. Furthermore, additional variables should be included to control for potential confounders, such as the socioeconomic status and baseline measures of inhibition and episodic memory abilities. Concerning the BD group, it should be relevant to have more detailed drinking variables, particularly a measure of recent BD episodes since evidence has been shown that heavier recent BD is associated with decreased activation of regions involved in executive control (Cohen-Gilbert et al., 2017).

Finally, the use of EEG in the two experimental studies does not allow us to measure the activity of deeper subcortical regions and the communication between these structures and cortical regions due to its limited spatial resolution (Nunez & Srinivasan, 2006). Therefore, future research should consider the use of EEG-fMRI simultaneously -a methodology that allows noninvasive recording of human brain activity with both high spatial and temporal resolution (Debener et al., 2006)– in order to have more reliable results about the FC patterns underlying both alcohol attentional bias and memory suppression.

Regarding the study of memory suppression, there are some aspects of the TNTA that should be considered. Apart from the lack of a measure of memory intrusions, the experimental procedure also did not include a measure to verify if the participants understand the instructions. Despite the instructions for the No-Think condition were more consistent with direct suppression (i.e., to inhibit the retrieval process directly) we did not confirm the exact strategy that participants used during memory suppression; consequently, we do not know whether BDs and N/LDs used similar strategies to complete the task or even if they were doing the effort to suppress the memories. Participants may have used distinct strategies during the No-Think condition, including thought substitution (i.e., generating alternative thoughts to avoid thinking about the image), rehearsing a distractor, or attending to present-moment sensations (Sullivan et al., 2019). Studies showed that the use of different strategies is associated with the involvement of distinct prefrontal regions (Benoit & Anderson, 2012), which could compromise the interpretation of our

results. Therefore, future studies exploring memory suppression through this task should include proper measures to ensure participants' accurate comprehension and application of TNT instructions and provide more strong and controlled results (Nardo & Anderson, 2023). As previously mentioned, an intrusion report should also be included. However, as the neuroimaging procedures are more complex and usually have long-lasting protocols, the inclusion of a trial-by-trial measure may constitute a challenge for researchers. In these cases, a more general measure should be considered (e.g., at the end of the experiment, participants would be asked to rate, for each item, their difficulty in suppressing the memory; Schmitz et al., 2017). Furthermore, behavioral studies -with fewer limitations than EEG/fMRI research- should use a trial-by-trial intrusions report in BDs and individuals with alcohol-related problems, since assessing the occurrence of alcohol-related memory intrusions in this population seems particularly relevant to understand the mechanisms underlying the suppression of these memories. Overall, these modifications in the TNTA task will provide a better interpretation of the participants' experience during task performance, and, more importantly, during memory suppression.

Although the present dissertation provides the first insights about memory suppression in young BDs, further investigation exploring these mechanisms in this population as well as individuals with AUD is needed to better understand how this ability may be implicated in the maintenance or escalation of drinking behavior. As some studies have already observed SIF with autobiographical memories (Lu et al., 2023; Noreen & MacLeod, 2014; Pennington et al., 2020; Stephens et al., 2013), future studies exploring memory suppression mechanisms in young BDs or other populations with alcohol-related problems should consider including personal memories associated with alcohol consumption in order to enhance the ecological validity of the results and, consequently, extend its relevance to daily-life situations. In the same vein, it would be pertinent to assess whether BDs have positive or negative memories associated with alcohol. In the case of individuals with severe AUD, craving experience may be triggered by the need to alleviate negative feelings or sensations caused by the alcohol withdrawal (i.e., negative reinforcement). Therefore, these individuals may have negative alcohol-related memories, while BDs may still have positive ones since they do not have a pathological pattern of consumption yet. In this way, the valence of these memories should be further explored both in AUDs and BDs to understand whether suppression of alcohol-related memories may be affected by the aversion/attraction levels of such memories. Moreover, studies should also assess the intrusiveness of these memories in BDs during their daily life, aiming to understand if persistent alcohol-related memories occur in this subclinical population and, subsequently, may constitute a major factor for the perpetuation and escalation of the pattern.

To prove whether the hyperconnectivity pattern observed in BDs during the suppression of alcohol-related memories is only elicited by information associated with alcohol, future studies should also include other high-salient or other pleasant stimuli (e.g., high-caloric food, erotic pictures). This approach will allow to compare the FC patterns underlying the suppression of alcohol-related memories and other stimuli with increased motivational value, which could hold important implications for theories that suggest a general reduction in reward value for stimuli not directly related to alcohol/substance of abuse. Evidence from this type of investigation could unravel potentially unique neural mechanisms underlying the processing of alcohol-related memories/stimuli, which may influence how individuals with BD respond to and manage cravings or triggers related to alcohol. Therefore, it could provide insights into the mechanisms contributing to binge alcohol consumption.

Given that the few studies exploring memory suppression in substance misuse have been focused on populations with alcohol-related problems (i.e., AUD, BD, and heavy drinkers), future investigation need to explore this ability in other substance use disorders as well as other addictive/compulsive behaviors (e.g., binge eating, internet addiction, gambling). In line with the protocol presented in the Chapter 4, the TNTA task may be adapted to populations with other substance/behavioral addictions and be used as a training tool to potentiate memory inhibition ability and potentially reduce compulsive behaviors.

The study of memory suppression may be a new and promising avenue to better understand BD and addictive behaviors in general; however, the present dissertation also emphasizes the need to conduct additional longitudinal studies in young BDs to explore whether the observed behavioral and neural alterations evolve over extended periods of maintaining (or ceasing) BD. Longitudinal studies would also allow to further explore the sustainability of BDs' neurocompensation over time, providing insight into its potential enduring effects on brain function and behavior as well as uncovering any disruptions caused by binge alcohol consumption. Furthermore, collecting data prior to the engagement in this pattern would provide further insights into the contributing risk factors associated with alcohol use.

7.6. Conclusion

The current dissertation showed that the involvement in BD during young adulthood is associated with abnormal EEG activity. Specifically, the systematic review revealed that young BDs display increased brain activity at rest and augmented neural reactivity for alcohol-related information, resembling some of the EEG abnormalities observed in individuals with AUD. Conversely, BDs exhibit enhanced brain activity - particularly increased P3 amplitude – during attention, working memory, and response inhibition

tasks. This incremented brain activity suggests the recruitment of additional neural resources to compensate for underlying deficits caused by the intensive and intermittent alcohol use. Aligned with these findings, the first experimental study supported the presence of an attentional bias for alcohol-related information in young BDs, by revealing an increased neural communication between areas involved in attentional networks during the processing of alcohol-related stimuli. This hyperconnectivity may suggest augmented motivational reactivity towards alcohol-related cues and, consequently, enhanced processing of this type of information. In contrast, they displayed reduced processing of non-alcoholic images, translated by a hypoconnectivity in attentional networks, which support the idea that the motivational aspects of non-alcohol stimuli may be blunted in young BDs. Results from the second experimental study also showed that BDs exhibit a hypoconnectivity pattern between regions involved in memory suppression during the inhibition of non-alcohol-related memories, while during the suppression of alcohol-related memories, BDs display an increased communication between these brain regions. These results suggested that while the decreased attention towards non-alcohol-related memories may compromise top-down control processes and, consequently, the suppression of these memories, the augmented reactivity to highly salient alcohol-related memories may lead to the recruitment of additional neural resources to compensate the overactivation of the salience/reward systems resulting from the increased motivational value and/or intrusiveness of these memories.

Collectively, the results of the present work are consistent with neurobiological models of addiction revealing that BD may be associated with increased salience attribution for alcohol-related information, reduced processing of non-alcohol rewards and reduced top-down control mechanisms. As postulated by these models, this dysfunction of the reward/salience and IC networks underlies the transition from recreational to compulsive alcohol use. Therefore, this evidence suggests that young BDs are at risk of developing compulsive alcohol use or alcohol dependence, supporting the continuum hypothesis, which proposes that BD constitutes a first step towards the development of alcohol abuse. Thus, the EEG abnormalities exhibited by BDs could serve as potential indicators/markers for the development of alcohol addiction, possibly offering clinical insights for intervention prior to the escalation of alcohol-seeking behavior towards a more severe pattern.

Concluding, FC assessment might uncover dysfunctional networks linked to BD, offering understanding into a possible transitional phase in the progression of AUD. In addition, this work reinforces the EEG value to explore subtle alterations caused by BD or excessive alcohol use which usually are not detected at the behavioral level. It is noteworthy that the findings of the present dissertation are the first body of knowledge about memory suppression in young BDs, consequently, this preliminary

evidence might encourage research on this field in order to better understand how memory suppression mechanisms may be involved in substance misuse.

7.7. References

Affan, R. O., Huang, S., Cruz, S. M., Holcomb, L. A., Nguyen, E., & Marinkovic, K. (2018). High-intensity binge drinking is associated with alterations in spontaneous neural oscillations in young adults. *Alcohol*, *70*, 51–60. https://doi.org/10.1016/j.alcohol.2018.01.002

Alderson Myers, A. B., Arienzo, D., Molnar, S. M., & Marinkovic, K. (2021). Local and network-level dysregulation of error processing is associated with binge drinking. *NeuroImage: Clinical*, *32*, 102879. https://doi.org/10.1016/j.nicl.2021.102879

Ames, S. L., Grenard, J. L., He, Q., Stacy, A. W., Wong, S. W., Xiao, L., Xue, G., & Bechara, A. (2014). Functional imaging of an alcohol-Implicit Association Test (IAT): Imaging alcohol IAT. *Addiction Biology*, *19*(3), 467–481. https://doi.org/10.1111/adb.12071

Ames, S. L., Wong, S. W., Bechara, A., Cappelli, C., Dust, M., Grenard, J. L., & Stacy, A. W. (2014). Neural correlates of a Go/NoGo task with alcohol stimuli in light and heavy young drinkers. *Behavioural Brain Research, 274*, 382–389. https://doi.org/10.1016/j.bbr.2014.08.039

Anderson, M. C., & Green, C. (2001). Suppressing unwanted memories by executive control. *Nature*, *410*(6826), 366–369. https://doi.org/10.1038/35066572

Anderson, M. C., & Hulbert, J. C. (2021). Active Forgetting: Adaptation of Memory by Prefrontal Control. *Annual Review of Psychology*, *72*(1), 1–36. https://doi.org/10.1146/annurev-psych-072720-094140

Anderson, M. C., Reinholz, J., Kuhl, B. A., & Mayr, U. (2011). Intentional suppression of unwanted memories grows more difficult as we age. *Psychology and Aging*, *26*(2), 397–405. https://doi.org/10.1037/a0022505

Antón-Toro, L. F., Bruña, R., Del Cerro-León, A., Shpakivska, D., Mateos-Gordo, P., Porras-Truque, C., García-Gómez, R., Maestú, F., & García-Moreno, L. M. (2022). Electrophysiological resting-state hyperconnectivity and poorer behavioural regulation as predisposing profiles of adolescent binge drinking. *Addiction Biology*, *27*(4), e13199. https://doi.org/10.1111/adb.13199

Antón-Toro, L. F., Bruña, R., Suárez-Méndez, I., Correas, Á., García-Moreno, L. M., & Maestú, F. (2021). Abnormal organization of IC functional networks in future binge drinkers. *Drug and Alcohol Dependence*, *218*, 108401. https://doi.org/10.1016/j.drugalcdep.2020.108401

Antón-Toro, L. F., Shpakivska-Bilan, D., Del Cerro-León, A., Bruña, R., Uceta, M., García-Moreno, L. M., & Maestú, F. (2023). Longitudinal change of IC functional connectivity associated with the development of heavy alcohol drinking. *Frontiers in Psychology*, *14*, 1069990. https://doi.org/10.3389/fpsyg.2023.1069990

Arienzo, D., Happer, J. P., Molnar, S. M., Alderson-Myers, A., & Marinkovic, K. (2020a). Binge drinking is associated with altered resting state functional connectivity of reward-salience and top down control networks. *Brain Imaging and Behavior*, *14*(5), 1731–1746. https://doi.org/10.1007/s11682-019-00107-6

Arienzo, D., Happer, J. P., Molnar, S. M., Alderson-Myers, A., & Marinkovic, K. (2020b). Binge drinking is associated with altered resting state functional connectivity of reward-salience and top down control networks. *Brain Imaging and Behavior*, *14*(5), 1731–1746. https://doi.org/10.1007/s11682-019-00107-6

Aswendt, M., & Hoehn, M. (2023). Functional hyperconnectivity related to brain disease: Maladaptive process or element of resilience? *Neural Regeneration Research*, *18*(7), 1489. https://doi.org/10.4103/1673-5374.361541

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. *Nature Neuroscience*, *8*(11), 1458–1463. https://doi.org/10.1038/nn1584

Benoit, R. G., & Anderson, M. C. (2012). Opposing Mechanisms Support the Voluntary Forgetting of Unwanted Memories. *Neuron*, *76*(2), 450–460. https://doi.org/10.1016/j.neuron.2012.07.025

Bernard, L., Cyr, L., Bonnet-Suard, A., Cutarella, C., & Bréjard, V. (2021). Drawing alcohol craving process: A systematic review of its association with thought suppression, inhibition and impulsivity. *Heliyon*, *7*(1), e05868. https://doi.org/10.1016/j.heliyon.2020.e05868

Blanco-Ramos, J., Antón-Toro, L. F., Cadaveira, F., Doallo, S., Suárez-Suárez, S., & Rodríguez Holguín, S. (2022). Alcohol-related stimuli modulate functional connectivity during response inhibition in young binge drinkers. *Addiction Biology*, *27*(2), e13141. https://doi.org/10.1111/adb.13141

Blanco-Ramos, J., Cadaveira, F., Folgueira-Ares, R., Corral, M., & Rodríguez Holguín, S. (2019). Electrophysiological Correlates of an Alcohol-Cued Go/NoGo Task: A Dual-Process Approach to Binge Drinking in University Students. *International Journal of Environmental Research and Public Health*, *16*(22), 4550. https://doi.org/10.3390/ijerph16224550

Bollen, Z., Masson, N., Salvaggio, S., D'Hondt, F., & Maurage, P. (2020). Craving is everything: An eye-tracking exploration of attentional bias in binge drinking. *Journal of Psychopharmacology*.

Brumback, T., Squeglia, L. M., Jacobus, J., Pulido, C., Tapert, S. F., & Brown, S. A. (2015). Adolescent heavy drinkers' amplified brain responses to alcohol cues decrease over one month of abstinence. *Addictive Behaviors*, *46*, 45–52. https://doi.org/10.1016/j.addbeh.2015.03.001

Camchong, J., Stenger, V. A., & Fein, G. (2013). Resting-State Synchrony in Short-Term Versus Long-Term Abstinent Alcoholics. *Alcoholism: Clinical and Experimental Research, 37*(5), 794–803. https://doi.org/10.1111/acer.12037

Carbia, C., Cadaveira, F., Caamaño-Isorna, F., Rodríguez-Holguín, S., & Corral, M. (2017). Binge drinking during adolescence and young adulthood is associated with deficits in verbal episodic memory. *PLOS ONE*, *12*(2), e0171393. https://doi.org/10.1371/journal.pone.0171393

Carbia, C., Cadaveira, F., López-Caneda, E., Caamaño-Isorna, F., Rodríguez Holguín, S., & Corral, M. (2017). Working memory over a six-year period in young binge drinkers. *Alcohol*, *61*, 17–23. https://doi.org/10.1016/j.alcohol.2017.01.013

Carbia, C., López-Caneda, E., Corral, M., & Cadaveira, F. (2018). A systematic review of neuropsychological studies involving young binge drinkers. *Neuroscience & Biobehavioral Reviews*, *90*, 332–349. https://doi.org/10.1016/j.neubiorev.2018.04.013

Catarino, A., Küpper, C. S., Werner-Seidler, A., Dalgleish, T., & Anderson, M. C. (2015). Failing to Forget: Inhibitory-Control Deficits Compromise Memory Suppression in Posttraumatic Stress Disorder. *Psychological Science*, *26*(5), 604–616. https://doi.org/10.1177/0956797615569889

Chanraud, S., Pitel, A.-L., Muller-Oehring, E. M., Pfefferbaum, A., & Sullivan, E. V. (2013). Remapping the Brain to Compensate for Impairment in Recovering Alcoholics. *Cerebral Cortex, 23*(1), 97–104. https://doi.org/10.1093/cercor/bhr381

Chanraud, S., Pitel, A.-L., Pfefferbaum, A., & Sullivan, E. V. (2011). Disruption of Functional Connectivity of the Default-Mode Network in Alcoholism. *Cerebral Cortex, 21*(10), 2272–2281. https://doi.org/10.1093/cercor/bhq297

Chanraud, S., & Sullivan, E. V. (2014). Compensatory recruitment of neural resources in chronic alcoholism. *Alcohol and the Nervous System*, 369–380. https://doi.org/10.1016/b978-0-444-62619-6.00022-7

Chanraud-Guillermo, S., Andoh, J., Martelli, C., Artiges, E., Pallier, C., Aubin, H., Martinot, J., & Reynaud, M. (2009). Imaging of Language-Related Brain Regions in Detoxified Alcoholics. *Alcoholism: Clinical and Experimental Research, 33*(6), 977–984. Portico. https://doi.org/10.1111/j.1530-0277.2009.00918.x

Chen, H., Nebe, S., Mojtahedzadeh, N., Kuitunen-Paul, S., Garbusow, M., Schad, D. J., Rapp, M. A., Huys, Q. J. M., Heinz, A., & Smolka, M. N. (2021). Susceptibility to interference between Pavlovian and instrumental control is associated with early hazardous alcohol use. *Addiction Biology*, *26*(4), e12983. https://doi.org/10.1111/adb.12983

Cohen-Gilbert, J. E., Nickerson, L. D., Sneider, J. T., Oot, E. N., Seraikas, A. M., Rohan, M. L., & Silveri, M. M. (2017). College Binge Drinking Associated with Decreased Frontal Activation to Negative Emotional Distractors during IC. *Frontiers in Psychology*, *8*, 1650. https://doi.org/10.3389/fpsyg.2017.01650

Courtney, K. E., & Polich, J. (2010). Binge Drinking Effects on EEG in Young Adult Humans. *International Journal of Environmental Research and Public Health*, *7*(5), 2325–2336. https://doi.org/10.3390/ijerph7052325

Correas, A., López-Caneda, E., Beaton, L., Rodríguez Holguín, S., García-Moreno, L., Antón-Toro, L., Cadaveira, F., Maestú, F., & Marinkovic, K. (2019). Decreased event-related theta power and phase-synchrony in young binge drinkers during target detection: An anatomically-constrained MEG approach. *Journal of Psychopharmacology*, *33*(3), 335–346. https://doi.org/10.1177/0269881118805498

Cox, S. M. L., Yau, Y., Larcher, K., Durand, F., Kolivakis, T., Delaney, J. S., Dagher, A., Benkelfat, C., & Leyton, M. (2017). Cocaine Cue-Induced Dopamine Release in Recreational Cocaine Users. *Scientific Reports*, *7*(1), 46665. https://doi.org/10.1038/srep46665

Crego, A., Cadaveira, F., Parada, M., Corral, M., Caamaño-Isorna, F., & Rodríguez Holguín, S. (2012). Increased amplitude of P3 event-related potential in young binge drinkers. *Alcohol*, *46*(5), 415–425. https://doi.org/10.1016/j.alcohol.2011.10.002

Crego, A., Holguín, S. R., Parada, M., Mota, N., Corral, M., & Cadaveira, F. (2009). Binge Drinking Affects Attentional and Visual Working Memory Processing in Young University Students. *Alcoholism: Clinical and Experimental Research*, *33*(11), 1870–1879. https://doi.org/10.1111/j.1530-0277.2009.01025.x

Cservenka, A., Jones, S. A., & Nagel, B. J. (2015). Reduced cerebellar brain activity during reward processing in adolescent binge drinkers. *Developmental Cognitive Neuroscience*, *16*, 110–120. https://doi.org/10.1016/j.dcn.2015.06.004

Czapla, M., Simon, J. J., Friederich, H.-C., Herpertz, S. C., Zimmermann, P., & Loeber, S. (2015). Is Binge Drinking in Young Adults Associated with an Alcohol-Specific Impairment of Response Inhibition? *European Addiction Research*, *21*(2), 105–113. https://doi.org/10.1159/000367939

Debener, S., Ullsperger, M., Siegel, M., & Engel, A. K. (2006). Single-trial EEG–fMRI reveals the dynamics of cognitive function. *Trends in Cognitive Sciences*, *10*(12), 558–563. https://doi.org/10.1016/j.tics.2006.09.010

Depue, B. E., Burgess, G. C., Willcutt, E. G., Ruzic, L., & Banich, M. T. (2010). IC of memory retrieval and motor processing associated with the right lateral prefrontal cortex: Evidence from deficits in individuals with ADHD. *Neuropsychologia*, *48*(13), 3909–3917. https://doi.org/10.1016/j.neuropsychologia.2010.09.013

Desmond, J. E., Chen, S. H. A., DeRosa, E., Pryor, M. R., Pfefferbaum, A., & Sullivan, E. V. (2003). Increased frontocerebellar activation in alcoholics during verbal working memory: an fMRI study. *NeuroImage, 19*(4), 1510–1520. https://doi.org/10.1016/s1053-8119(03)00102-2

Diamond, A. (2013). Executive Functions. *Annual Review of Psychology*, *64*(1), 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Everitt, B. J., & Robbins, T. W. (2016). Drug Addiction: Updating Actions to Habits to Compulsions Ten Years On. *Annual Review of Psychology*, *67*(1), 23–50. https://doi.org/10.1146/annurev-psych-122414-033457

Fadardi, J. S., & Cox, W. M. (2009). Reversing the sequence: Reducing alcohol consumption by overcoming alcohol attentional bias. *Drug and Alcohol Dependence*, *101*(3), 137–145. https://doi.org/10.1016/j.drugalcdep.2008.11.015

Faivre, A., Rico, A., Zaaraoui, W., Crespy, L., Reuter, F., Wybrecht, D., Soulier, E., Malikova, I., Confort-Gouny, S., Cozzone, P. J., Pelletier, J., Ranjeva, J.-P., & Audoin, B. (2012). Assessing brain connectivity at rest is clinically relevant in early multiple sclerosis. *Multiple Sclerosis Journal, 18*(9), 1251–1258. https://doi.org/10.1177/1352458511435930

Fernández-Seara, M. A., Mengual, E., Vidorreta, M., Castellanos, G., Irigoyen, J., Erro, E., & Pastor, M. A. (2015). Resting state functional connectivity of the subthalamic nucleus in Parkinson's disease assessed using arterial spin-labeled perfusion fMRI. *Human Brain Mapping, 36*(5), 1937–1950. Portico. https://doi.org/10.1002/hbm.22747

Field, M., & Eastwood, B. (2005). Experimental manipulation of attentional bias increases the motivation to drink alcohol. *Psychopharmacology*, *183*(3), 350–357. https://doi.org/10.1007/s00213-005-0202-5

Field, M., Schoenmakers, T., & Wiers, R. (2008). Cognitive Processes in Alcohol Binges: A Review and Research Agenda. *Current Drug Abuse Reviewse*, *1*(3), 263–279. https://doi.org/10.2174/1874473710801030263

Flaudias, V., Heeren, A., Brousse, G., & Maurage, P. (2019). Toward a Triadic Approach to Craving in Addictive Disorders: The Metacognitive Hub Model. *Harvard Review of Psychiatry*, *27*(5), 326–331. https://doi.org/10.1097/HRP.0000000000000225

Fleming, K. A., & Bartholow, B. D. (2014). Alcohol cues, approach bias, and IC: Applying a dual process model of addiction to alcohol sensitivity. *Psychology of Addictive Behaviors*, *28*(1), 85–96. https://doi.org/10.1037/a0031565

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*, *12*(11), 652–669. https://doi.org/10.1038/nrn3119

Gorges, M., Müller, H.-P., Lulé, D., Pinkhardt, E. H., Ludolph, A. C., & Kassubek, J. (2015). To rise and to fall: functional connectivity in cognitively normal and cognitively impaired patients with Parkinson's disease. *Neurobiology of Aging, 36*(4), 1727–1735. https://doi.org/10.1016/j.neurobiolaging.2014.12.026

Guerra-Carrillo, B., Katovich, K., & Bunge, S. A. (2017). Does higher education hone cognitive functioning and learning efficacy? Findings from a large and diverse sample. *PLOS ONE*, *12*(8), e0182276. https://doi.org/10.1371/journal.pone.0182276

Herman, A. M., Critchley, H. D., & Duka, T. (2019). Binge drinking is associated with attenuated frontal and parietal activation during successful response inhibition in fearful context. *European Journal of Neuroscience*, *50*(3), 2297–2310. https://doi.org/10.1111/ejn.14108

Hillary, F. G., & Grafman, J. H. (2017). Injured Brains and Adaptive Networks: The Benefits and Costs of Hyperconnectivity. *Trends in Cognitive Sciences*, *21*(5), 385–401. https://doi.org/10.1016/j.tics.2017.03.003

Hillary, F. G., Rajtmajer, S. M., Roman, C. A., Medaglia, J. D., Slocomb-Dluzen, J. E., Calhoun, V. D., Good, D. C., & Wylie, G. R. (2014). The Rich Get Richer: Brain Injury Elicits Hyperconnectivity in Core Subnetworks. *PLoS ONE, 9*(8), e104021. https://doi.org/10.1371/journal.pone.0104021

Hillary, F. G., Roman, C. A., Venkatesan, U., Rajtmajer, S. M., Bajo, R., & Castellanos, N. D. (2015). Hyperconnectivity is a fundamental response to neurological disruption. *Neuropsychology*, *29*(1), 59–75. https://doi.org/10.1037/neu0000110

Holcomb, L. A., Huang, S., Cruz, S. M., & Marinkovic, K. (2019). Neural oscillatory dynamics of IC in young adult binge drinkers. *Biological Psychology*, *146*, 107732. https://doi.org/10.1016/j.biopsycho.2019.107732

Iraji, A., Benson, R. R., Welch, R. D., O'Neil, B. J., Woodard, J. L., Ayaz, S. I., Kulek, A., Mika, V., Medado, P., Soltanian-Zadeh, H., Liu, T., Haacke, E. M., & Kou, Z. (2015). Resting State Functional Connectivity in Mild Traumatic Brain Injury at the Acute Stage: Independent Component and Seed-Based Analyses. *Journal of Neurotrauma, 32*(14), 1031–1045. https://doi.org/10.1089/neu.2014.3610

Jones, S. A., Cservenka, A., & Nagel, B. J. (2016). Binge drinking impacts dorsal striatal response during decision making in adolescents. *NeuroImage*, *129*, 378–388. https://doi.org/10.1016/j.neuroimage.2016.01.044

Kim, E.-H., & Kim, M.-S. (2019). An Event-related Potential Study of Error-monitoring Deficits in Female College Students Who Participate in Binge Drinking. *Clinical Psychopharmacology and Neuroscience*, *17*(1), 80–92. https://doi.org/10.9758/cpn.2019.17.1.80

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of Addiction. *Neuropsychopharmacology*, *35*(1), 217–238. https://doi.org/10.1038/npp.2009.110

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8

Langbridge, J. E., Jones, R. D., & Canales, J. J. (2019). A Neurophysiological and Behavioral Assessment of Interventions Targeting Attention Bias and Sense of Control in Binge Drinking. *Frontiers in Human Neuroscience*, *12*, 538. https://doi.org/10.3389/fnhum.2018.00538

Lannoy, S., Billieux, J., & Maurage, P. (2014). Beyond Inhibition: A Dual-Process Perspective to Renew the Exploration of Binge Drinking. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00405

Lannoy, S., Dormal, V., Billieux, J., Brion, M., D'Hondt, F., & Maurage, P. (2020). A dual-process exploration of binge drinking: E vidence through behavioral and electrophysiological findings. *Addiction Biology*, *25*(2), e12685. https://doi.org/10.1111/adb.12685

Lannoy, S., Maurage, P., D'Hondt, F., Billieux, J., & Dormal, V. (2018). Executive Impairments in Binge Drinking: Evidence for a Specific Performance-Monitoring Difficulty during Alcohol-Related Processing. *European Addiction Research*, *24*(3), 118–127. https://doi.org/10.1159/000490492

Le Moal, M., & Koob, G. F. (2007). Drug addiction: Pathways to the disease and pathophysiological perspectives. *European Neuropsychopharmacology*, *17*(6–7), 377–393. https://doi.org/10.1016/j.euroneuro.2006.10.006

Legrand, N., Etard, O., Viader, F., Clochon, P., Doidy, F., Eustache, F., & Gagnepain, P. (2022). Attentional capture mediates the emergence and suppression of intrusive memories. *iScience*, *25*(12), 105516. https://doi.org/10.1016/j.isci.2022.105516

Levy, B. J., & Anderson, M. C. (2012). Purging of Memories from Conscious Awareness Tracked in the Human Brain. *The Journal of Neuroscience*, *32*(47), 16785–16794. https://doi.org/10.1523/JNEUROSCI.2640-12.2012

López-Caneda, E., Cadaveira, F., Correas, A., Crego, A., Maestú, F., & Rodríguez Holguín, S. (2017). The Brain of Binge Drinkers at Rest: Alterations in Theta and Beta Oscillations in First-Year College Students with a Binge Drinking Pattern. *Frontiers in Behavioral Neuroscience*, *11*, 168. https://doi.org/10.3389/fnbeh.2017.00168

López-Caneda, E., Cadaveira, F., Crego, A., Doallo, S., Corral, M., Gómez-Suárez, A., & Rodríguez Holguín, S. (2013). Effects of a Persistent Binge Drinking Pattern of Alcohol Consumption in Young People: A Follow-Up Study Using Event-Related Potentials. *Alcohol and Alcoholism*, *48*(4), 464–471. https://doi.org/10.1093/alcalc/agt046

López-Caneda, E., Cadaveira, F., Crego, A., Gómez-Suárez, A., Corral, M., Parada, M., Caamaño-Isorna, F., & Rodríguez Holguín, S. (2012). Hyperactivation of right inferior frontal cortex in young binge

drinkers during response inhibition: A follow-up study: Response inhibition in young binge drinkers. *Addiction*, *107*(10), 1796–1808. https://doi.org/10.1111/j.1360-0443.2012.03908.x

López-Caneda, E., Rodríguez Holguín, S., Corral, M., Doallo, S., & Cadaveira, F. (2014). Evolution of the binge drinking pattern in college students: Neurophysiological correlates. *Alcohol*, *48*(5), 407–418. https://doi.org/10.1016/j.alcohol.2014.01.009

López-Caneda, E., Rodríguez Holguín, S., Corral, M., Doallo, S., & Cadaveira, F. (2014). Evolution of the binge drinking pattern in college students: Neurophysiological correlates. *Alcohol*, *48*(5), 407–418. https://doi.org/10.1016/j.alcohol.2014.01.009

López-Caneda, E., Rodríguez Holguín, S., Correas, Á., Carbia, C., González-Villar, A., Maestú, F., & Cadaveira, F. (2017). Binge drinking affects brain oscillations linked to motor inhibition and execution. *Journal of Psychopharmacology*, *31*(7), 873–882. https://doi.org/10.1177/0269881116689258

Lu, F., Yang, W., & Qiu, J. (2023). Neural bases of motivated forgetting of autobiographical memories. *Cognitive Neuroscience*, *14*(1), 15–24. https://doi.org/10.1080/17588928.2022.2136150

Manchery, L., Yarmush, D. E., Luehring-Jones, P., & Erblich, J. (2017). Attentional bias to alcohol stimuli predicts elevated cue-induced craving in young adult social drinkers. *Addictive Behaviors*, *70*, 14–17. https://doi.org/10.1016/j.addbeh.2017.01.035

Marinkovic, K., Oscar-Berman, M., Urban, T., O'Reilly, C. E., Howard, J. A., Sawyer, K., & Harris, G. J. (2009). Alcoholism and Dampened Temporal Limbic Activation to Emotional Faces. *Alcoholism: Clinical and Experimental Research,* *33*(11), 1880–1892. Portico. https://doi.org/10.1111/j.1530-0277.2009.01026.x

Maurage, P., Bestelmeyer, P. E. G., Rouger, J., Charest, I., & Belin, P. (2013). Binge drinking influences the cerebral processing of vocal affective bursts in young adults. *NeuroImage: Clinical*, *3*, 218–225. https://doi.org/10.1016/j.nicl.2013.08.010

Maurage, P., Joassin, F., Speth, A., Modave, J., Philippot, P., & Campanella, S. (2012). Cerebral effects of binge drinking: Respective influences of global alcohol intake and consumption pattern. *Clinical Neurophysiology*, *123*(5), 892–901. https://doi.org/10.1016/j.clinph.2011.09.018

Maurage, P., Pesenti, M., Philippot, P., Joassin, F., & Campanella, S. (2009). Latent deleterious effects of binge drinking over a short period of time revealed only by electrophysiological measures. *Journal Psychiatry Neuroscience.*

Molnar, S., Beaton, L., Happer, J., Holcomb, L., Huang, S., Arienzo, D., & Marinkovic, K. (2018). Behavioral and Brain Activity Indices of Cognitive Control Deficits in Binge Drinkers. *Brain Sciences*, *8*(1), 9. https://doi.org/10.3390/brainsci8010009

Mota, N., Parada, M., Crego, A., Doallo, S., Caamaño-Isorna, F., Rodríguez Holguín, S., Cadaveira, F., & Corral, M. (2013). Binge drinking trajectory and neuropsychological functioning among university students: A longitudinal study. *Drug and Alcohol Dependence*, *133*(1), 108–114. https://doi.org/10.1016/j.drugalcdep.2013.05.024

Müller-Oehring, E. M., Jung, Y. C., Sullivan, E. V., Hawkes, W. C., Pfefferbaum, A., & Schulte, T. (2013). Midbrain-driven emotion and reward processing in alcoholism. *Neuropsychopharmacology, 38*(10), 1844-1853.

Na, E., Jang, K.-M., & Kim, M.-S. (2019). An Event-Related Potential Study of Decision-Making and Feedback Utilization in Female College Students Who Binge Drink. *Frontiers in Psychology*, *10*, 2606. https://doi.org/10.3389/fpsyg.2019.02606

Nardo, D., & Anderson, M. (2023). *Everything You Ever Wanted to Know About the Think/No-Think task, But Forgot to Ask* [Preprint]. PsyArXiv. https://doi.org/10.31234/osf.io/t3dn4

Noël, X., Bechara, A., Brevers, D., Verbanck, P., & Campanella, S. (2010). Alcoholism and the Loss of Willpower: A Neurocognitive Perspective. *Journal of Psychophysiology*, *24*(4), 240–248. https://doi.org/10.1027/0269-8803/a000037

Noreen, S., & MacLeod, M. D. (2014). To think or not to think, that is the question: Individual differences in suppression and rebound effects in autobiographical memory. *Acta Psychologica*, *145*, 84–97. https://doi.org/10.1016/j.actpsy.2013.10.011

Norman, A. L., Pulido, C., Squeglia, L. M., Spadoni, A. D., Paulus, M. P., & Tapert, S. F. (2011). Neural activation during inhibition predicts initiation of substance use in adolescence. *Drug and Alcohol Dependence*, *119*(3), 216–223. https://doi.org/10.1016/j.drugalcdep.2011.06.019

Paz-Alonso, P. (2009). Memory suppression is an active process that improves over childhood. *Frontiers in Human Neuroscience*, *3*. https://doi.org/10.3389/neuro.09.024.2009

Nunez, P. L., & Srinivasan, R. (2006). *Electric fields of the brain: the neurophysics of EEG*. Oxford University Press, USA.

Park, S., & Kim, M.-S. (2018). An event-related potential study of spatial working memory in binge drinking college students. *PLOS ONE*, *13*(9), e0203696. https://doi.org/10.1371/journal.pone.0203696

Paz-Alonso, P., Ghetti, S., Matlen, B. J., Anderson, M. C., & Bunge, S. A. (2009). Memory suppression is an active process that improves over childhood. *Frontiers in Human Neuroscience*, *3*. https://doi.org/10.3389/neuro.09.024.2009

Pennington, C. R., Shaw, D. J., Adams, J., Kavanagh, P., Reed, H., Robinson, M., Shave, E., & White, H. (2020). Where's the wine? Heavy social drinkers show attentional bias towards alcohol in a visual conjunction search task. *Addiction*, *115*(9), 1650–1659. https://doi.org/10.1111/add.14997

Pérez-García, J. M., Cadaveira, F., Canales-Rodríguez, E. J., Suárez-Suárez, S., Rodríguez Holguín, S., Corral, M., Blanco-Ramos, J., & Doallo, S. (2022). Effects of Persistent Binge Drinking on Brain Structure in Emerging Adults: A Longitudinal Study. *Frontiers in Psychiatry*, *13*, 935043. https://doi.org/10.3389/fpsyt.2022.935043

Pérez-García, J. M., Suárez-Suárez, S., Doallo, S., & Cadaveira, F. (2022). Effects of binge drinking during adolescence and emerging adulthood on the brain: A systematic review of neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *137*, 104637. https://doi.org/10.1016/j.neubiorev.2022.104637

Petit, G., Kornreich, C., Dan, B., Verbanck, P., & Campanella, S. (2014). Electrophysiological correlates of alcohol- and non-alcohol-related stimuli processing in binge drinkers: A follow-up study. *Journal of Psychopharmacology*, *28*(11), 1041–1052. https://doi.org/10.1177/0269881114545663

Petit, G., Kornreich, C., Maurage, P., Noël, X., Letesson, C., Verbanck, P., & Campanella, S. (2012). Early attentional modulation by alcohol-related cues in young binge drinkers: An event-related potentials study. *Clinical Neurophysiology*, *123*(5), 925–936. https://doi.org/10.1016/j.clinph.2011.10.042

Petit, G., Kornreich, C., Verbanck, P., & Campanella, S. (2013). Gender differences in reactivity to alcohol cues in binge drinkers: A preliminary assessment of event-related potentials. *Psychiatry Research*, *209*(3), 494–503. https://doi.org/10.1016/j.psychres.2013.04.005

Pfefferbaum, A., Desmond, J. E., Galloway, C., Menon, V., Glover, G. H., & Sullivan, E. V. (2001). Reorganization of Frontal Systems Used by Alcoholics for Spatial Working Memory: An fMRI Study. *NeuroImage, 14*(1), 7–20. https://doi.org/10.1006/nimg.2001.0785

Pitel, A.-L., Chanraud, S., Müller-Oehring, E. M., Pfefferbaum, A., & Sullivan, E. V. (2012). Modulation of limbic-cerebellar functional connectivity enables alcoholics to recognize who is who. *Brain Structure and Function, 218*(3), 683–695. https://doi.org/10.1007/s00429-012-0421-6

Rodríguez Holguín, S., Folgueira-Ares, R., Crego, A., López-Caneda, E., Corral, M., Cadaveira, F., & Doallo, S. (2023). Neurocognitive effects of binge drinking on verbal episodic memory. An ERP study in university students. *Frontiers in Pharmacology*, *14*, 1034248. https://doi.org/10.3389/fphar.2023.1034248

Ryerson, N. C., Neal, L. B., & Gable, P. A. (2017). Attenuating the alcohol allure: Attentional broadening reduces rapid motivational response to alcohol pictures. *Psychopharmacology*, *234*(8), 1247–1254. https://doi.org/10.1007/s00213-017-4557-1

Schmitz, T. W., Correia, M. M., Ferreira, C. S., Prescot, A. P., & Anderson, M. C. (2017). Hippocampal GABA enables IC over unwanted thoughts. *Nature Communications*, *8*(1), 1311. https://doi.org/10.1038/s41467-017-00956-z

Schroder, E., Dousset, C., Noel, X., Kornreich, C., & Campanella, S. (2019). Increased Neural Activity in Hazardous Drinkers During High Workload in a Visual Working Memory Task: A Preliminary Assessment Through Event-Related Potentials. *Frontiers in Psychiatry*, *10*, 248. https://doi.org/10.3389/fpsyt.2019.00248

Simon, J., Grogna, D., Rivard, M.-C., Heck, M., Bouchard, S., & Quertemont, E. (2022). Assessing attentional bias for alcohol-related cues using eye tracking in a virtual reality environment. *Frontiers in Virtual Reality*, *3*, 849840. https://doi.org/10.3389/frvir.2022.849840

Smith, R., Alkozei, A., Lane, R. D., & Killgore, W. D. S. (2016). Unwanted reminders: The effects of emotional memory suppression on subsequent neuro-cognitive processing. *Consciousness and Cognition*, *44*, 103–113. https://doi.org/10.1016/j.concog.2016.07.008

Smith, J. L., De Blasio, F. M., Iredale, J. M., Matthews, A. J., Bruno, R., Dwyer, M., Batt, T., Fox, A. M., Solowij, N., & Mattick, R. P. (2017). Verbal Learning and Memory in Cannabis and Alcohol Users: An Event-Related Potential Investigation. *Frontiers in Psychology*, *8*, 2129. https://doi.org/10.3389/fpsyg.2017.02129

Smith, J. L., & Mattick, R. P. (2013). Evidence of deficits in behavioural inhibition and performance monitoring in young female heavy drinkers. *Drug and Alcohol Dependence*, *133*(2), 398–404. https://doi.org/10.1016/j.drugalcdep.2013.06.020

Squeglia, L. M., Schweinsburg, A. D., Pulido, C., & Tapert, S. F. (2011). Adolescent Binge Drinking Linked to Abnormal Spatial Working Memory Brain Activation: Differential Gender Effects. *Alcoholism: Clinical and Experimental Research, 35*(10), 1831–1841. https://doi.org/10.1111/j.1530-0277.2011.01527.x

Squeglia, L. M., Sorg, S. F., Schweinsburg, A. D., Wetherill, R. R., Pulido, C., & Tapert, S. F. (2012). Binge drinking differentially affects adolescent male and female brain morphometry. *Psychopharmacology*, *220*(3), 529–539. https://doi.org/10.1007/s00213-011-2500-4

Stephens, E., Braid, A., & Hertel, P. T. (2013). Suppression-Induced Reduction in the Specificity of Autobiographical Memories. *Clinical Psychological Science*, *1*(2), 163–169. https://doi.org/10.1177/2167702612467773

Storm, B. C., & White, H. A. (2010). ADHD and retrieval-induced forgetting: Evidence for a deficit in the IC of memory. *Memory*, *18*(3), 265–271. https://doi.org/10.1080/09658210903547884

Suárez-Suárez, S., Doallo, S., Pérez-García, J. M., Corral, M., Rodríguez Holguín, S., & Cadaveira, F. (2020). Response Inhibition and Binge Drinking During Transition to University: An fMRI Study. *Frontiers in Psychiatry*, *11*, 535. https://doi.org/10.3389/fpsyt.2020.00535

Sullivan, D. R., Marx, B., Chen, M. S., Depue, B. E., Hayes, S. M., & Hayes, J. P. (2019). Behavioral and neural correlates of memory suppression in PTSD. *Journal of Psychiatric Research*, *112*, 30–37. https://doi.org/10.1016/j.jpsychires.2019.02.015

Sullivan, E. V., & Pfefferbaum, A. (2019). Brain-behavior relations and effects of aging and common comorbidities in alcohol use disorder: A review. *Neuropsychology, 33*(6), 760–780. https://doi.org/10.1037/neu0000557

Tapert, S. F., Brown, G. G., Kindermann, S. S., Cheung, E. H., Frank, L. R., & Brown, S. A. (2001). fMRI Measurement of Brain Dysfunction in Alcohol-Dependent Young Women. *Alcoholism: Clinical and Experimental Research, 25*(2), 236–245. https://doi.org/10.1111/j.1530-0277.2001.tb02204.x

Tolomeo, S., Baldacchino, A., & Steele, J. D. (2023). Blunted Expected Reward Value Signals in Binge Alcohol Drinkers. *The Journal of Neuroscience*, *43*(31), 5685–5692. https://doi.org/10.1523/JNEUROSCI.2157-21.2022

Tona, F., Petsas, N., Sbardella, E., Prosperini, L., Carmellini, M., Pozzilli, C., & Pantano, P. (2014). Multiple Sclerosis: Altered Thalamic Resting-State Functional Connectivity and Its Effect on Cognitive Function. *Radiology, 271*(3), 814–821. https://doi.org/10.1148/radiol.14131688

Tong, T. T., Vaidya, J. G., Kramer, J. R., Kuperman, S., Langbehn, D. R., & O'Leary, D. S. (2021). Impact of binge drinking during college on resting state functional connectivity. *Drug and Alcohol Dependence*, *227*, 108935. https://doi.org/10.1016/j.drugalcdep.2021.108935

Townshend, J. M., & Duka, T. (2001). Attentional bias associated with alcohol cues: Differences between heavy and occasional social drinkers. *Psychopharmacology*, *157*(1), 67–74. https://doi.org/10.1007/s002130100764

Volkow, N. D., Fowler, J. S., Wang, G.-J., & Swanson, J. M. (2004). Dopamine in drug abuse and addiction: Results from imaging studies and treatment implications. *Molecular Psychiatry*, *9*(6), 557–569. https://doi.org/10.1038/sj.mp.4001507

Volkow, N. D., Wang, G.-J., Telang, F., Fowler, J. S., Logan, J., Childress, A.-R., Jayne, M., Ma, Y., & Wong, C. (2006). Cocaine Cues and Dopamine in Dorsal Striatum: Mechanism of Craving in Cocaine Addiction. *Journal of Neuroscience*, *26*(24), 6583–6588. https://doi.org/10.1523/JNEUROSCI.1544-06.2006

Wetherill, R. R., Squeglia, L. M., Yang, T. T., & Tapert, S. F. (2013). A longitudinal examination of adolescent response inhibition: Neural differences before and after the initiation of heavy drinking. *Psychopharmacology*, *230*(4), 663–671. https://doi.org/10.1007/s00213-013-3198-2

Whelan, R., Watts, R., Orr, C. A., Althoff, R. R., Artiges, E., Banaschewski, T., Barker, G. J., Bokde, A. L. W., Büchel, C., Carvalho, F. M., Conrod, P. J., Flor, H., Fauth-Bühler, M., Frouin, V., Gallinat, J., Gan, G., Gowland, P., Heinz, A., the IMAGEN Consortium, ... Garavan, H. (2014). Neuropsychosocial profiles of current and future adolescent alcohol misusers. *Nature*, *512*(7513), 185–189. https://doi.org/10.1038/nature13402

Winward, J. L., Bekman, N. M., Hanson, K. L., Lejuez, C. W., & Brown, S. A. (2014). Changes in Emotional Reactivity and Distress Tolerance Among Heavy Drinking Adolescents During Sustained Abstinence. *Alcoholism: Clinical and Experimental Research*, *38*(6), 1761–1769. https://doi.org/10.1111/acer.12415

Winward, J. L., Hanson, K. L., Bekman, N. M., Tapert, S. F., & Brown, S. A. (2014). Adolescent Heavy Episodic Drinking: Neurocognitive Functioning during Early Abstinence. *Journal of the International Neuropsychological Society*, *20*(2), 218–229. https://doi.org/10.1017/S1355617713001410

Worbe, Y., Irvine, M., Lange, I., Kundu, P., Howell, N. A., Harrison, N. A., Bullmore, E. T., Robbins, T. W., & Voon, V. (2014). Neuronal Correlates of Risk-Seeking Attitudes to Anticipated Losses in Binge Drinkers. *Biological Psychiatry*, *76*(9), 717–724. https://doi.org/10.1016/j.biopsych.2013.11.028

Xiao, L., Bechara, A., Gong, Q., Huang, X., Li, X., Xue, G., Wong, S., Lu, Z.-L., Palmer, P., Wei, Y., Jia, Y., & Johnson, C. A. (2013). Abnormal affective decision making revealed in adolescent binge drinkers using a functional magnetic resonance imaging study. *Psychology of Addictive Behaviors*, *27*(2), 443–454. https://doi.org/10.1037/a0027892

Zilverstand, A., & Goldstein, R. Z. (2020). Dual models of drug addiction. Em *Cognition and Addiction* (pp. 17–23). Elsevier. https://doi.org/10.1016/B978-0-12-815298-0.00003-4

Zilverstand, A., Huang, A. S., Alia-Klein, N., & Goldstein, R. Z. (2018). Neuroimaging Impaired Response Inhibition and Salience Attribution in Human Drug Addiction: A Systematic Review. *Neuron*, *98*(5), 886–903. https://doi.org/10.1016/j.neuron.2018.03.048

APPENDIXES

Appendix A. Supplementary Material Chapter 2

Table A.1

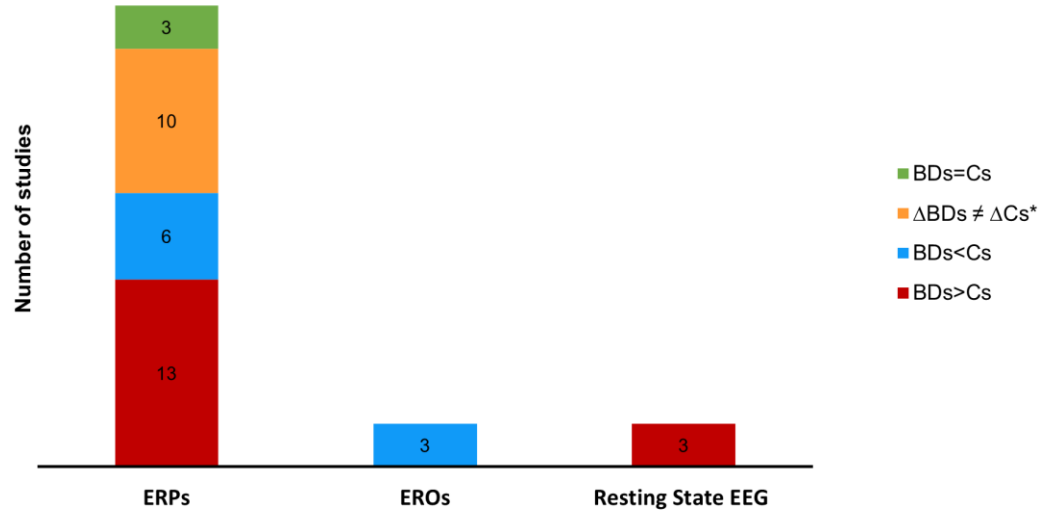
Adaptation of questions number 5 and number 14 of the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Question	Parameters	Description/Example
Q5	Number of subjects	To have a reasonable sample size for EEG studies (i.e., n ≥ 20 per group).
	Justification	To take into account several statistical parameters such as justification of sample size, estimation of effect size, etc.
Q14	Criterion A	To have proper inclusion/exclusion criteria (e.g., control of drug use, family or personal history of psychopathological disorders - including alcoholism).
	Criterion B	To explore sex-related differences.
	Criterion C	To carry out statistical analysis with potential confounding variables.

Note. If the studies did not meet criterion A, answer to Q14 was "No". In case the study fulfilled two of the three criteria mentioned above and one of them was criterion A, answer to Q14 was "Yes".

Figure A.1

Number of studies, using the different methods of EEG analysis, that found increased (BDs>Cs), decreased (BDs<Cs), different (ΔBDs ≠ ΔCs), and similar (BDs=Cs) brain activity in BDs when compared to Cs (control group or non/low drinkers).

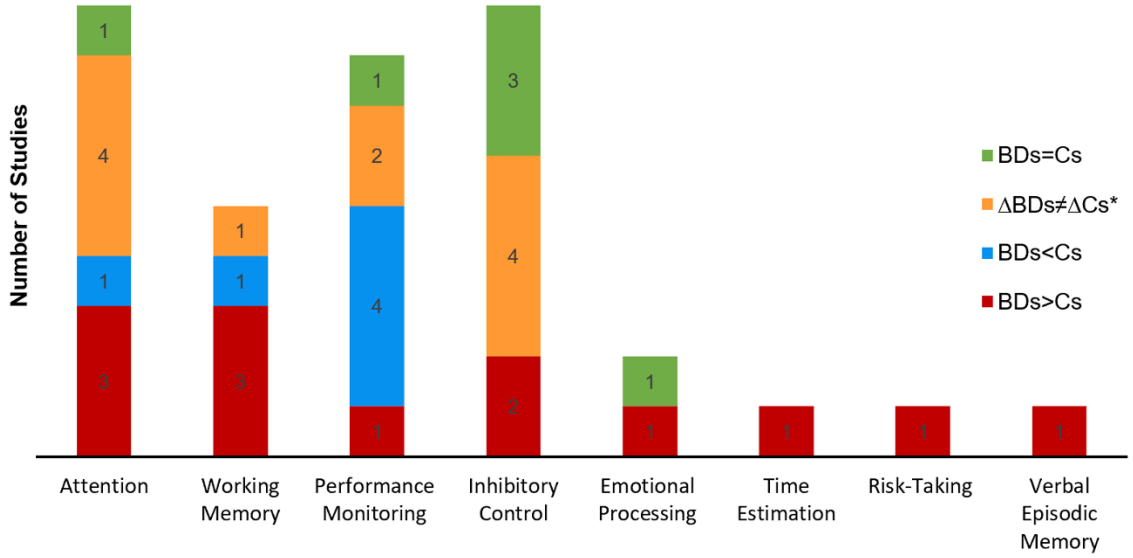


Note. One ERO study also explored ERP components, being included in the ERPs studies.

*Significant differences between conditions only in one group.

Figure A.2

Number of ERP studies, for each of the cognitive functions explored, that found increased (BDs>Cs), decreased (BDs<Cs), different (ΔBDs ≠ ΔCs), and similar (BDs=Cs) electrophysiological activity (i.e., amplitude) in BDs when compared to Cs (control group or non/low drinkers).



*Significant differences between conditions only in one group.

A.1. Alcohol variables and ERPs

A.1.2. Age of drinking onset

Only five studies conducted correlational analysis between the age of drinking onset and electrophysiological measures. Four of them found that this variable was associated with alterations in neural activity (Affan et al., 2018; Blanco-Ramos et al., 2019; López-Caneda et al, 2013, 2014b).

Specifically, the age of onset of regular drinking was negatively correlated with P3b (oddball task) and NoGo-P3 (Go/NoGo task) amplitudes, suggesting that the earlier the start of alcohol use the larger the impact on the electrophysiological measures (López-Caneda et al., 2013, 2014b). Likewise, the age of drinking onset was negatively correlated with the P1 amplitude for the Go-Alcohol and NoGo-NoAlcohol stimuli in the study by Blanco-Ramos et al. (2019). In the resting-state study by Affan et al. (2018), alpha slowing was positively correlated with the age of drinking onset, indicating that the alpha peak frequency was slower among subjects who started to consume alcohol early.

A.1.3. Quantity and Intensity of Drinking

Eleven studies showed that abnormal EEG activity may also be associated with measures of quantity and intensity of alcohol consumption (Affan et al., 2018; Blanco-Ramos et al., 2019; Holcomb et al., 2019; Kim & Kim, 2019; López-Caneda et al., 2013, 2014b; Maurage et al., 2009; Petit et al.,2012, 2014b; Smith et al., 2013, 2015).

The study of Affan et al. (2018) showed that slower alpha was negatively associated with several measures of increased alcohol intake and alcohol-induced blackouts. Additionally, they found that spontaneous frontal theta power was positively associated with the number of monthly inebriated occasions and BD episodes.

Smith et al. (2015) explored a variable named alcohol involvement, which measures the onset, duration and intensity of alcohol use. This variable was positively correlated with the N2 conflict adaptation effect, namely the higher the involvement with alcohol consumption the larger this conflict adaptation effect. Similarly, Blanco-Ramos et al. (2019) showed that NoGo-N2 for NoAlcohol pictures was negatively correlated with the number of BD episodes and the total number of drinks in the last 180 days. Thus, having more BD episodes and consuming higher amounts of alcohol may be related to increased conflict monitoring activity when subjects are in a context of predominant alcohol cues. Additionally, regression analysis revealed that those individuals with a short history of BD –but with a high frequency and intensity of alcohol use- showed the largest NoGo-N2 amplitude.

In the study of López-Caneda et al. (2013), the quantity and intensity of alcohol consumption was positively correlated with parietal P3b amplitude in the second evaluation. Likewise, enhanced NoGo-P3 was associated with a greater speed and weekly amount of alcohol consumption (López-Caneda et al., 2014b). These findings suggest that increased quantity and intensity of drinking may lead to an augmented neural activity linked to attentional/inhibitory processes. Furthermore, regression analyses showed that earlier age of regular drinking and greater speed of alcohol consumption predicted larger NoGo-P3 amplitude over the frontal region in the second evaluation moment (López-Caneda et al., 2014b). Also, higher levels of drinking may be associated with abnormal oscillatory activity during response inhibition (Holcomb et al., 2019)

In addition, Maurage et al. (2009) reported a positive correlation between mean alcohol intake and the latency of each ERP component analyzed during emotional processing (i.e. P1, N2 and P3b), suggesting a relationship between alcohol use and slowing of brain activity. Moreover, Petit et al. (2012) found that an elevated number of weekly alcohol use as well as prolonged duration of BD habits correlated with enlarged P1 amplitude to alcohol-related cues, indicating that these measures of excessive alcohol

use can be associated with a cognitive bias to alcoholic stimuli. In the follow-up study, Petit et al. (2014b) observed that the number of alcohol doses per occasion was the best predictor of the reduced P3 amplitude to non-alcoholic pictures in the second evaluation. Consequently, greater alcohol doses per drinking occasion may predict a cognitive bias during the processing of alcohol-related information after one-year maintaining BD.

Regarding the AUDIT scores, Smith et al. (2013) found that reduced ERN amplitude and larger successful > failed P3 effect were correlated with a greater total score in this questionnaire, indicating that BD can be associated with impaired performance monitoring and inhibitory control abilities, respectively. In the same vein, greater AUDIT scores as well as increased binge score on the Alcohol Use Questionnaire were associated with decreased ERN amplitude in the study of Kim and Kim (2019). Again, an intensive pattern of alcohol consumption was related with reduced brain activity during performance monitoring processes.

Figure B.1

Table describing the questionnaires and tasks administered throughout the different steps of protocol.

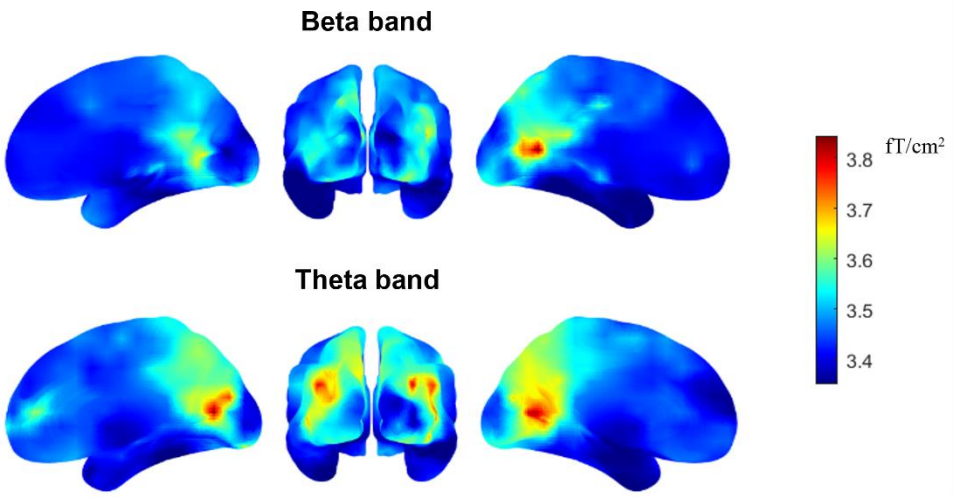
	T1: Clinical History Interview	T2: Pre-training EEG assessment	T3: Training Sessions	T4: Post-training EEG assessment	T5.1: 10-days follow-up	T5. 2: 3-months follow-up
Alcohol and other Substance use	AUDIT + **5 alcohol use questions**: • Speed of Drinking • Consumption in a standard week • Percentage of times getting drunk • Age of onset of regular drinking • Age of onset of BD DUDIT-E	AUDIT + **1 alcohol use question**: • Speed of Drinking TLFB DUDIT-E			AUDIT + **1 alcohol use question**: • Speed of Drinking TLFB	AUDIT + **1 alcohol use question**: • Speed of Drinking TLFB TADD
Alcohol Craving	ACQ-SF-R PACS	ACQ-SF-R PACS			ACQ-SF-R PACS	ACQ-SF-R PACS
Other	EHI UPPS-P BIS-11 SCL-90-R	Breathalyzer test EEG Session Checklist tDCS Screening Questionnaire	Breathalyzer test VAS	Breathalyzer test EEG Session Checklist		
Computerized Tasks		ACR Task TNTA Task	Variations of the TNTA task	ACR Task TNTA Task		

Note: ACQ-SF-R - Alcohol Craving Questionnaire-Short Form Revised; ACR – Alcohol Cue Reactivity task; AUDIT - Alcohol Use Disorder Identification Test; BDs – Binge Drinkers; BIS-11 - Barratt Impulsivity Scale-11; CT – cognitive training; DUDIT-E - Drug Use Disorders Identification Test-Extended; EEG – electroencephalogram; GSI - Global Severity Index; N/LDs – Non-/Low Drinkers; PACS – Penn Alcohol Craving Scale; SCL-90-R - Symptom Checklist-90-Revised questionnaire; TADD - Typical and Atypical Drinking Diary; TLFB - Alcohol Timeline Followback; UPPS-P - Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency.

Appendix C. Supplementary Material Chapter 5

Figure C.1

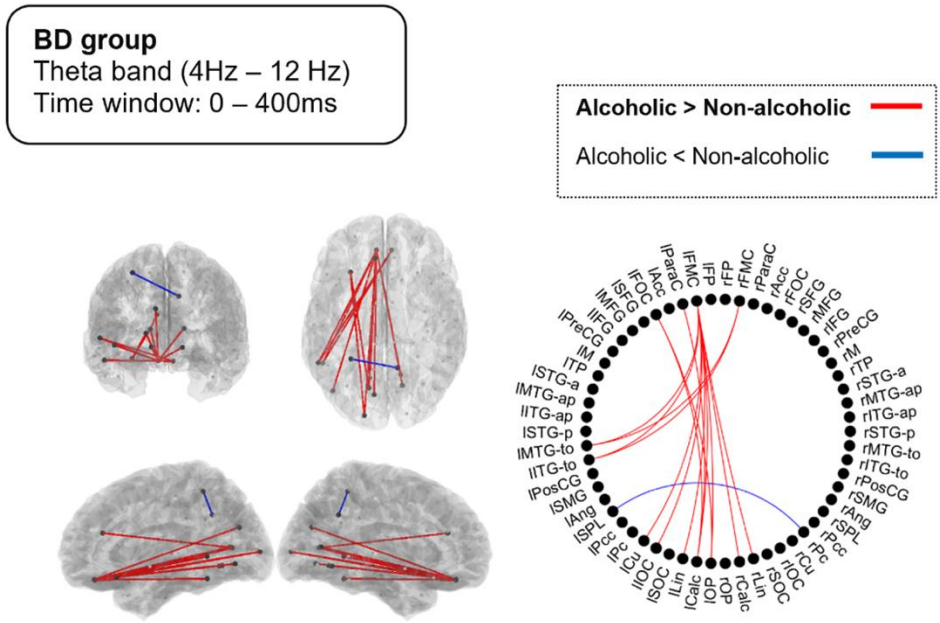
Representation of the source reconstruction of the P100 visual component using the beamformer spatial filter for beta (up) and theta (bottom) bands.



Note. Left column: Ventral view of the right hemisphere. Middle column: Posterior view of both hemispheres. Right column: Ventral view of the left hemisphere.

Figure C.2

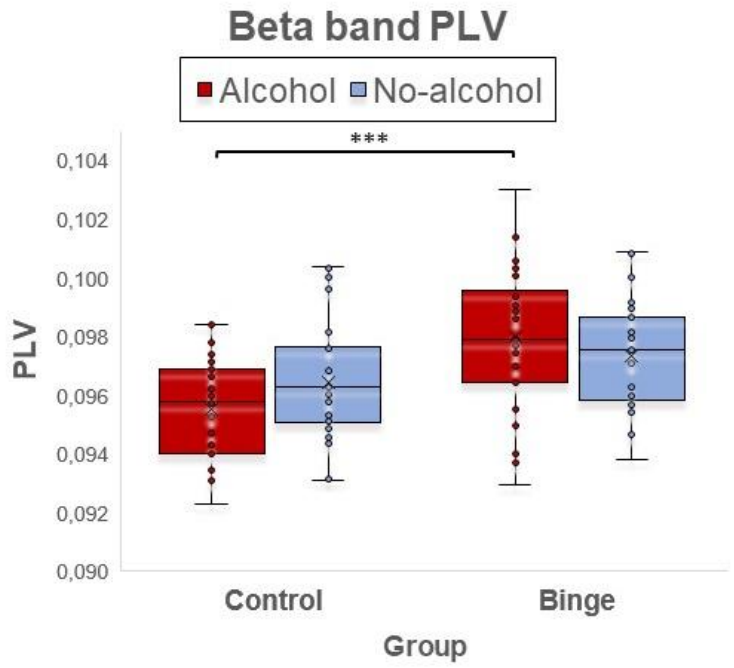
Distribution of significant FC links in theta band for the BD group.



Note. Red links represent higher connectivity between pairs of cortical regions for alcoholic condition. Blue links represent higher connectivity between pairs of cortical regions for non-alcoholic condition. All links were corrected for multiple comparisons by FDR method and for source leakage effects.

Figure C.3

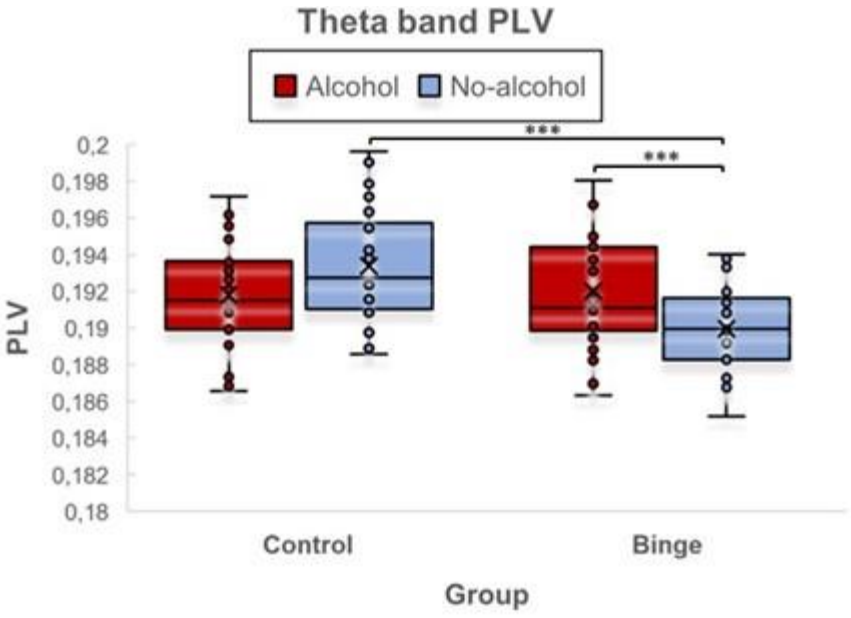
Boxplots of PLV values for each group and condition in beta band. Link between boxes highlight significant differences between groups in alcoholic condition.



**** = p < 0.001*

Figure C.4

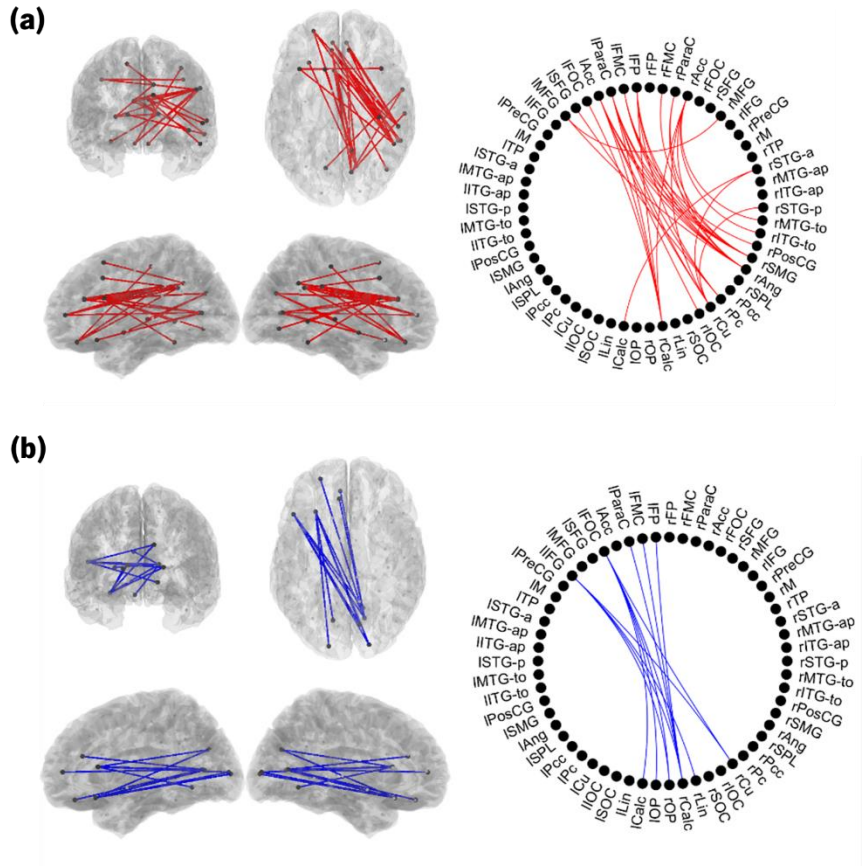
Boxplots of PLV values for each group and condition in theta band. Link between boxes highlight significant differences between groups in non-alcoholic condition and within BD group.



**** = p < 0.001*

Figure C.5

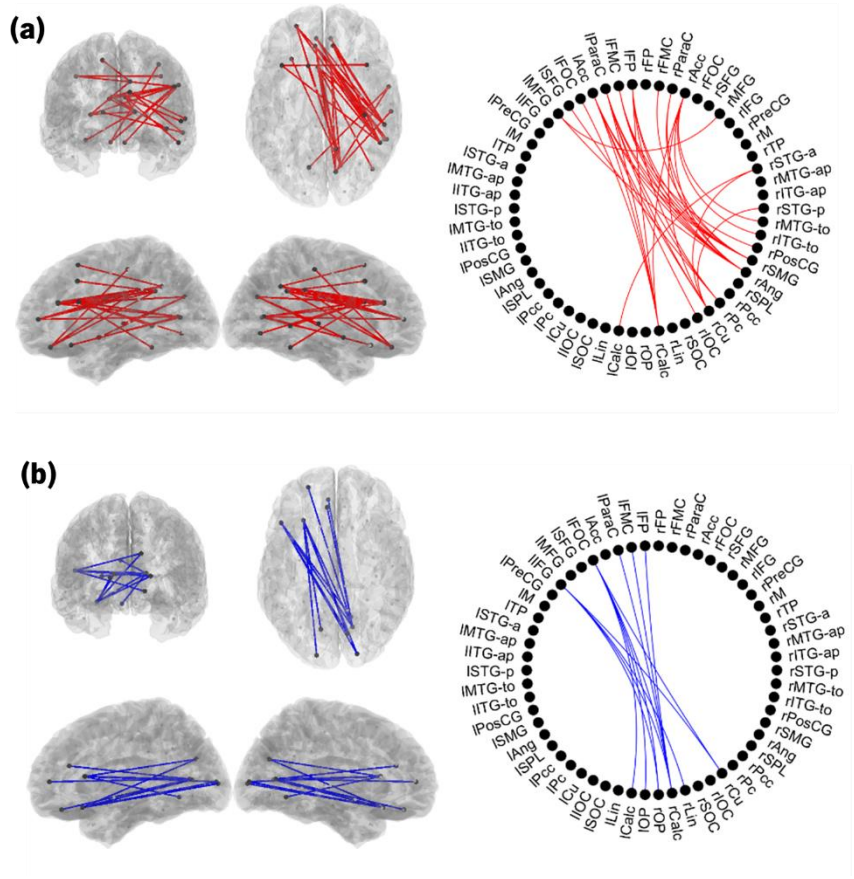
Distribution of significant links in (a) beta band (12Hz – 30Hz) for alcoholic condition and (b) theta band (4Hz – 12Hz) for non-alcoholic condition, once cannabis consumption is corrected.



Note. Red links represent higher connectivity between pairs of cortical regions (colored areas) for BD group. Blue links represent lower connectivity between pairs of cortical regions (colored areas) for BD group.

Figure C.6

Distribution of significant links in (a) beta band (12Hz – 30Hz) for alcoholic condition and (b) theta band (4Hz – 12Hz) for non-alcoholic condition, once tobacco consumption is corrected.

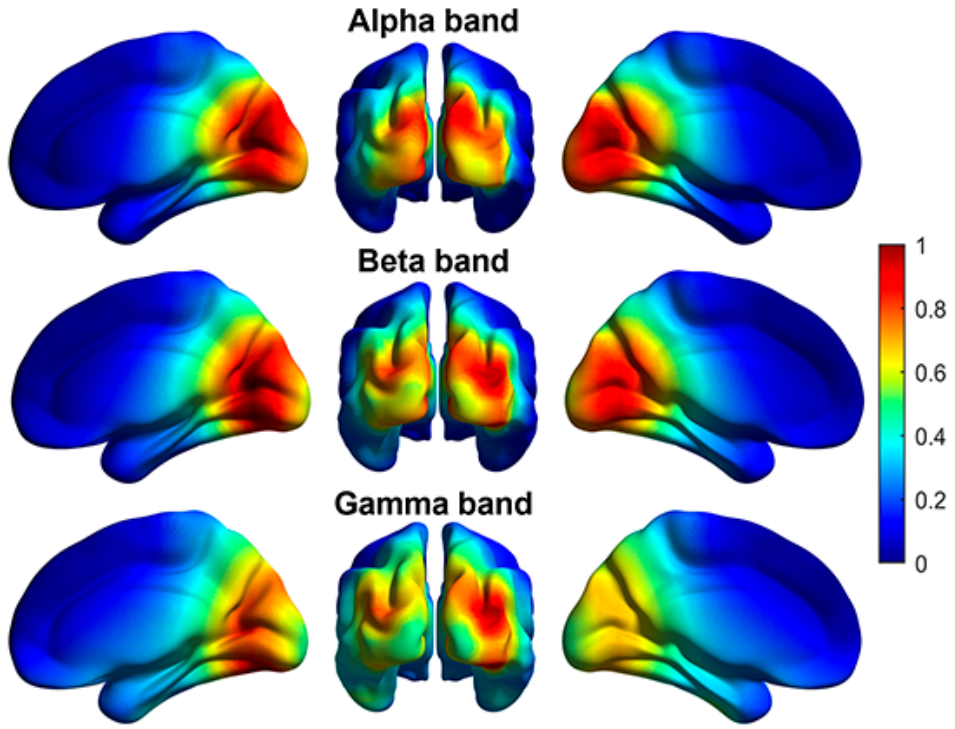


Note. Red links represent higher connectivity between pairs of cortical regions (colored areas) for BD group. Blue links represent lower connectivity between pairs of cortical regions (colored areas) for BD group.

Appendix D. Supplementary Material Chapter 6

Figure D.1

Source reconstruction representation of the P100 visual component using the beamformer spatial filter for alpha (up), beta (middle) and gamma (bottom) bands.



Note. Left column: Ventral view of the right hemisphere. Middle column: Posterior view of both hemispheres. Right column: Ventral view of the left hemisphere.

D.1. Event Related Potentials (ERPs) Analysis

EEG signal –processed by the BrainVision Analyzer 2.2 software (BrainVision Analyzer, 2021)- was corrected for vertical and horizontal ocular artifacts by independent component analysis and re-referenced to the average reference. It was then digitally filtered offline with a 0.1 to 30 Hz band-pass filter (12 dB/octave) and segmented into epochs of 2100 ms (from -100 to 2000 ms after stimulus onset). Baseline correction was applied and epochs exceeding ±80μV at any scalp electrode were rejected. Only trials corresponding to originally learned items during the learning phase were considered. There were no significant differences in the number of trials between the Think (119.72±38.56) and No-Think (116.30±38.24) conditions. In addition, these epochs were averaged separately according to the type of picture to be recalled or suppressed, thus obtaining four conditions: Think Alcohol, Think No-Alcohol, No-Think Alcohol, and No-Think No-Alcohol. The number of trials were similar across the four conditions: 59.16±21.38 (Think Alcohol), 60.56±20.57 (Think No-Alcohol), 57.09±20.40 (No-Think

Alcohol), and 59.21±22.17 (No-Think No-Alcohol). To quantify the ERP data frequently observed in TNT paradigms, we calculated the mean amplitudes of the three ERP components typically linked to memory suppression, namely, N2 (200-400 ms time window), Late Parietal Positivity (LPP; 400-700 ms time window) and Frontal Slow Wave (FSW; 600-1000 ms time window). With the aim of exploring the N2 and the FSW amplitudes, we extracted the ERP data from 6 electrodes placed at left (F3, FC3), midline (Fz, FCz), and right (F4, FC4) frontal regions. To assess the LPP waveform, statistical analyses were based on left (P3, PO3), midline (Pz, POz), and right (P4, PO4) parietal electrodes.

D.1.1. Statistical Analysis

A 2 x 2 x 3 x 2 analysis of variance (ANOVA) was conducted on the mean amplitude of each component separately. Factors were Condition (Think, No-Think), Content (Alcohol, No-Alcohol), Region (Left, Midline, Right), and Electrode (2 electrodes). In all cases, where appropriate, degrees of freedom were corrected by the Greenhouse–Geisser estimate, and post-hoc paired comparisons were performed with the Bonferroni adjustment for multiple comparisons (alpha level≤0.05)

D.2. ERPs Results

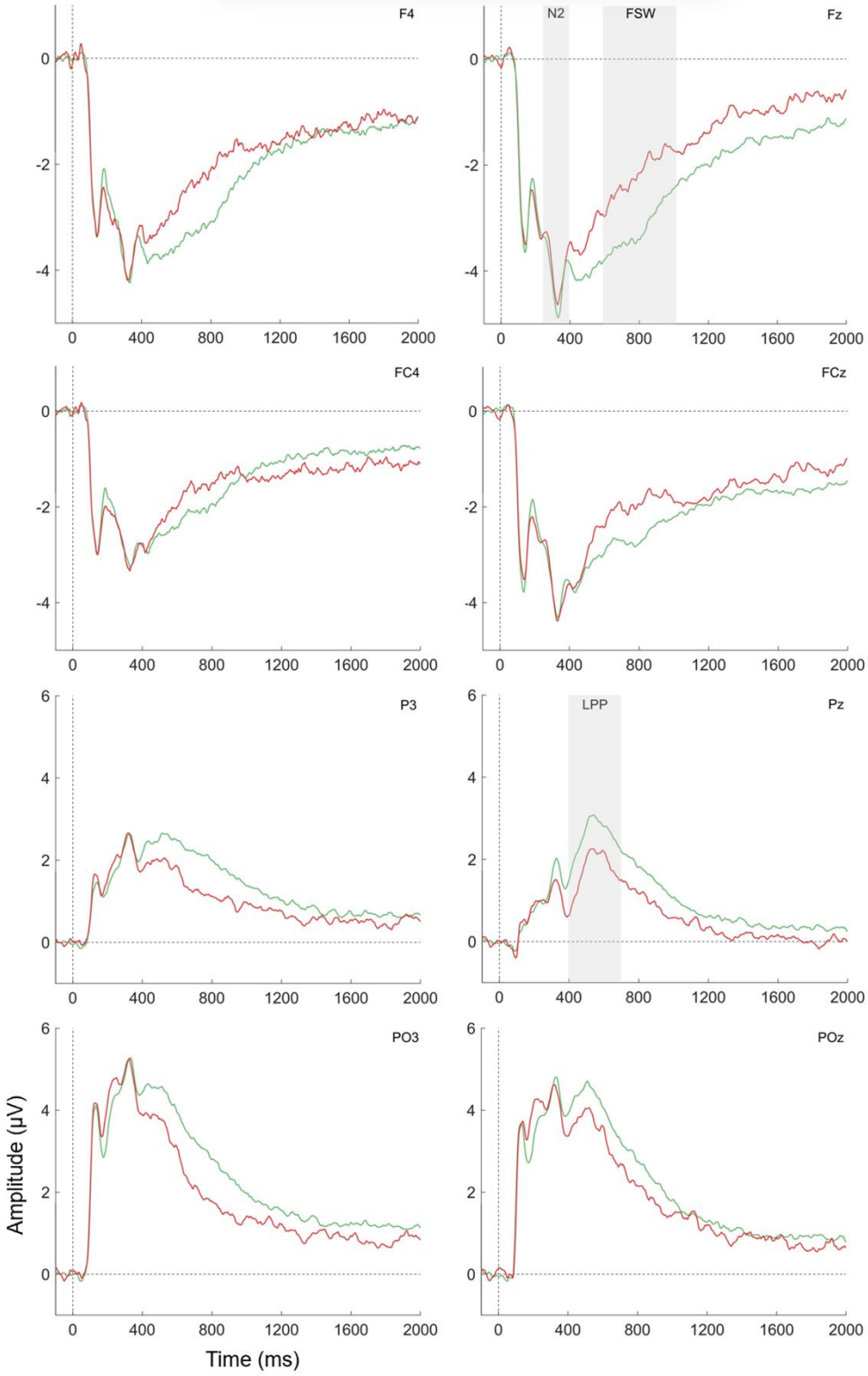
The grand averages of ERPs for Think (Alcohol and No-Alcohol) and No-Think (Alcohol and No-Alcohol) conditions are shown in Figures D.2 and D.3. Only effects involving Condition (Think vs No-Think) factor were of interest and thus reported. Analysis of the N2 component did not show significant main effects or interactions involving the Condition factor.

Analysis of the LPP component revealed a significant main effect of Condition [$F(1, 80) = 42.33$, $p < 0.001$, $\eta 2 = 0.346$)], with larger LPP amplitudes for Think in comparison to No-Think trials. In addition, a significant Condition x Region interaction was found, [$F(1.53, 122.10) = 50.55$, $p < 0.001$, $\eta 2 = 0.387$)]. Post hoc analysis revealed that amplitudes were larger for Think than No-Think condition in midline [$F(1, 80) = 67.59$, $p < 0.001$, $\eta 2 = 0.458$)] and right [$F(1, 80) = 78.30$, $p < 0.001$, $\eta 2 = 0.495$)] parietal regions. Finally, there was a significant Condition x Content x Region interaction, [$F(1.69, 135.42) = 15.76$, $p < 0.001$, $\eta^2 = 0.165$)]. Post hoc analysis revealed that in midline and right locations, LPP amplitudes were larger for Think than No-Think condition, independently of the content. In both conditions, amplitudes were larger for Alcohol than No-Alcohol images but only in the right region [$F(1, 80) = 13.80$, $p < 0.001$, $\eta^2 = 0.147$)].

Analysis of the FSW revealed a significant main effect of Condition [$F(1, 80) = 24.71$, $p < 0.001$, $\eta 2 = 0.236$)], with larger FSW negativity for the Think trials in comparison with No-Think trials. No other significant interactions involving the Condition factor were found regard to the FSW component.

Figure D.2

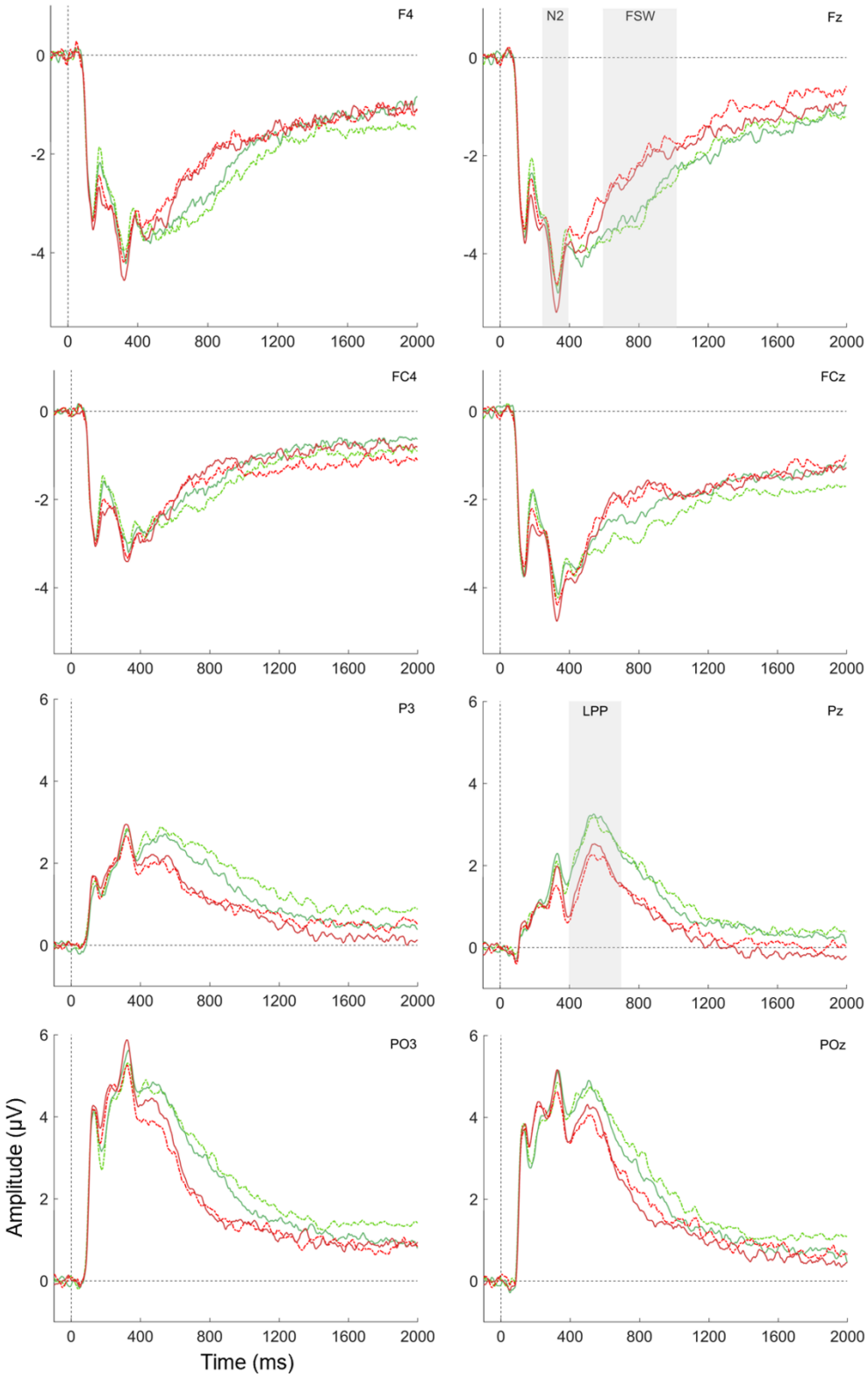
Grand average of event-related potentials for Think (green line) and No-Think (red line) conditions.



Note. Shaded in grey are depicted the time-windows of the three components analyzed: N2, frontal slow wave (FSW) and late parietal positivity (LPP). Averages are presented for Fz, F4, FCz, FC4, P3, Pz, PO3 and POz electrodes.

Figure D.3

Grand average of event-related potentials for Think No-Alcohol (green line), Think Alcohol (dashed green line), No-Think No-Alcohol (red line) and No-Think Alcohol (dashed red line) trials.



Note. Shaded in grey are depicted the time-windows of the three components analyzed: N2, frontal slow wave (FSW) and late parietal positivity (LPP). Averages are presented for Fz, F4, FCz, FC4, P3, Pz, PO3 and POz electrodes.

D.3. FC Results

D.3.1. Think Alcohol – No-Think Alcohol

No significant effects between-groups effects were observed regarding the difference between the FC levels of the Think Alcohol and No-Think Alcohol conditions.

D.3.2. Think No-Alcohol – No-Think No-Alcohol

Results showed a significant Condition by Group interaction for No-Alcohol content. When comparing the difference between the FC level of the Think No-Alcohol and No-Think No-Alcohol conditions between groups, seven significant clusters from three regions of the memory network were observed over three different time-windows (300-900ms, 1200-1800ms and 1400-2000ms). From the seven clusters, five –three from lHip-lParahip and two from rHip-rParahip- were observed in the low beta frequency-band. The remaining two clusters involved the lFusiG and were found in the alpha band. The spatial distribution of these clusters is depicted in Figure D.4.

Within the 300-900ms time-window, the lHip-lParahip was significantly connected with the rIFG (p=0.0056), the rMFG (p=0.0062) and the rSFG (p=0.0166) in low beta band. Also, in this time window and within the same frequency band, the rHip-rParahip was significantly connected with the rMFG (p=0.0150) and the rSFG (p=0.0222). In the 1200-1800ms time-window, the lFusiG was significantly connected with rSFG (p=0.0104) in the alpha band. In the last time-window from 1400 to 2000ms, the lFusiG was significantly connected with lSFG (p=0.0280) also in the alpha band. The results for the seed-based analysis are summarized in Table D.1. Pairwise comparisons revealed that, in the 300-900ms time-window, BDs exhibited increased low beta-band FC between the bilateral hippocampal and parahippocampal regions and right prefrontal areas (i.e., rIFG, rMFG and rSFG) during the Think No-Alcohol relative to the No-Think No-Alcohol condition. Over the 1200-1800ms and 1400-2000ms time-windows, BDs displayed increased alpha-band FC between the lFusiG and the right and left SFG, respectively, for the No-Think No-Alcohol condition in comparison with the Think No-Alcohol condition. Results also revealed significant differences between groups for Think No-Alcohol condition. Specifically, in the 300-900ms time-window, BDs showed increased low beta-band FC between the lHip-lParahip and the three right prefrontal regions, and between the rHip-rParahip and the rSFG, when compared with N/LDs. In the 1200-1800ms and 1400-2000ms time-windows, BDs exhibited decreased alpha-band FC between the lFusiG and the right and left SFG, respectively, in comparison to N/LDs.

Table D.1

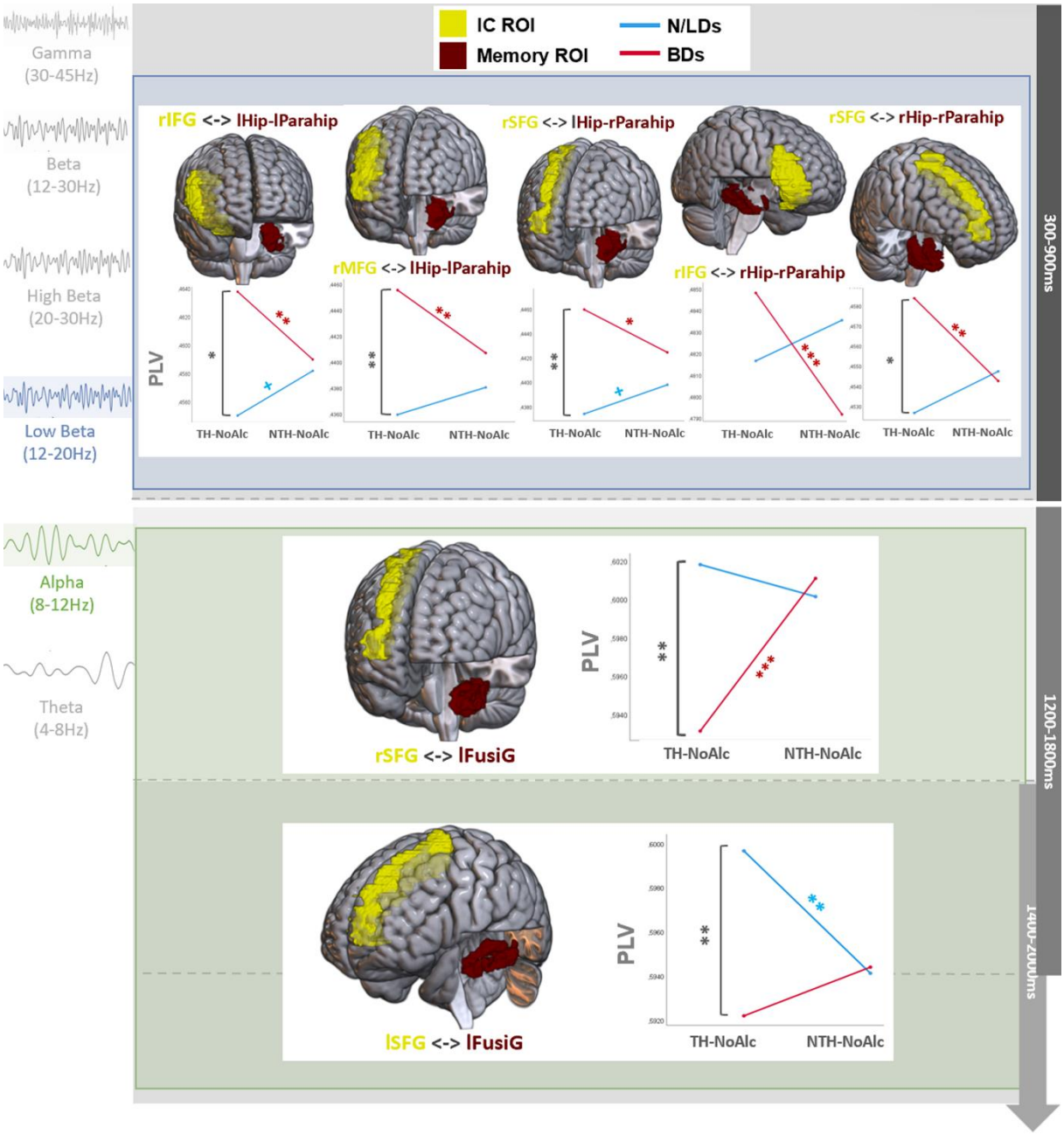
Seed-based FC results summary (No-Alcohol content - Condition by Group interaction)

Time Window	Frequency band	IC Seed	Memory Region	% sources	p	Cluster α
300-900ms	Low-Beta (12-20 Hz)	rIFG	lHip-lParahip	46.15%	0.0104	0.01
			rHip-rParahip	47.06%	0.0150	0.01
300-900ms	Low-Beta (12-20 Hz)	rMFG	lHip-lParahip	46.15%	0.0102	0.01
300-900ms	Low-Beta (12-20 Hz)	rSFG	lHip-lParahip	46.15%	0.0166	0.01
			rHip-rParahip	47.06%	0.0222	0.01
1200-1800ms	Alpha (8-12 Hz)		lFusiG	33.33%	0.0104	0.01

Note. The percentage of sources of the statistically significant clusters were calculated by dividing the number of sources that constituted the cluster by the total number of memory ROI sources.

Figure D.4

Think No-Alcohol versus No-Think No-Alcohol seed-based FC results depiction.

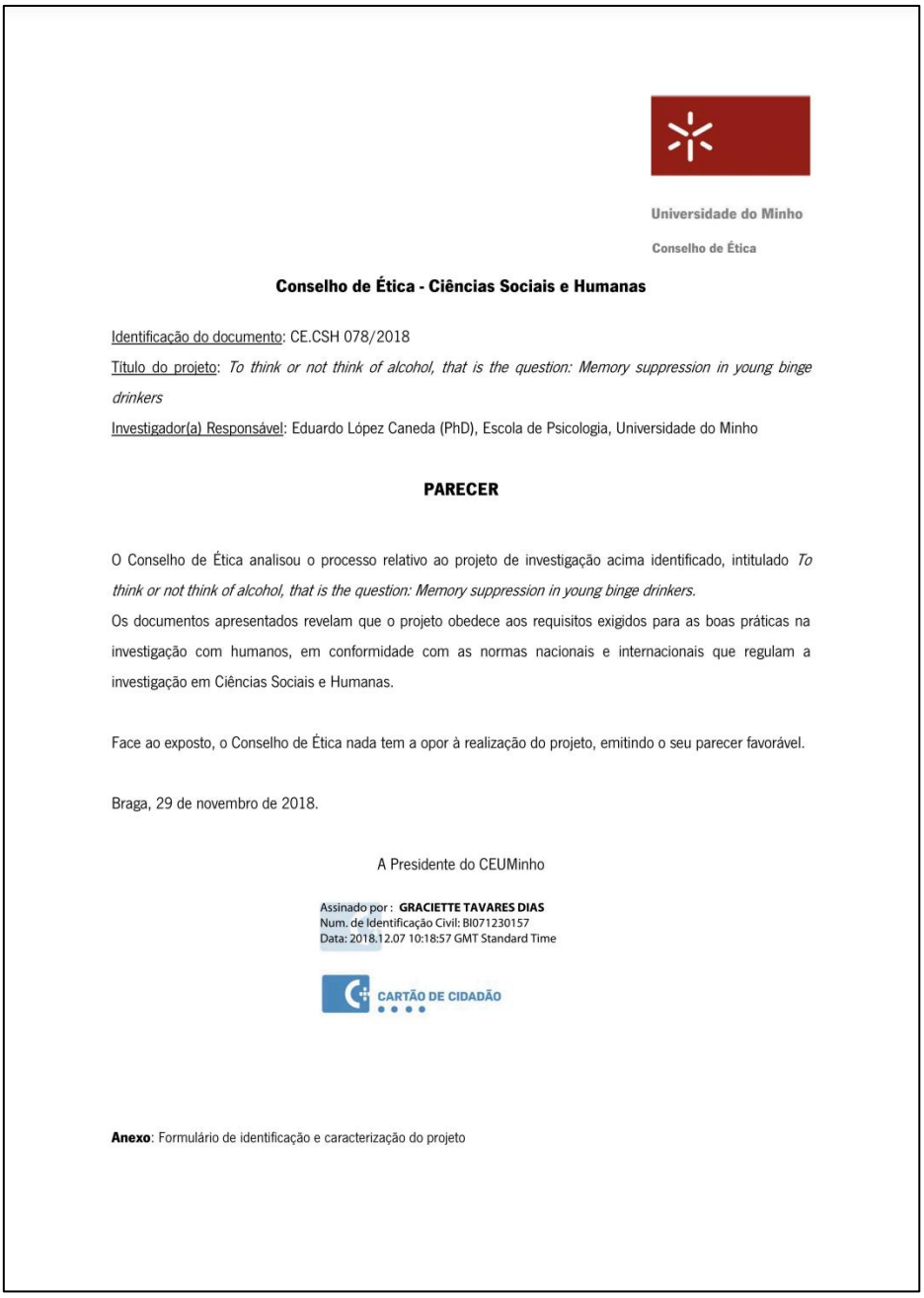


Note. Left: Six frequency-bands used in the FC analysis. Colored frequency-bands represent those where significant clusters were observed, in the gray ones there were no significant results. The brains contain the clusters from the memory network (dark red regions) significantly connected with the inhibitory control (IC) seeds (yellow regions) along the 300-900ms time-window in low-beta frequency-band, and along the 1200-1800ms and 1400-2000ms time-windows in alpha band. The graphics near the brains represent the FC level (i.e., Phase Locking Value [PLV]) between the corresponding IC seed and the target memory ROI per condition (Think No-Alcohol and No-Think No-Alcohol) for both groups, BDs (red line) and N/LDs (blue line). rIFG: right inferior frontal gyrus; rMFG: right middle frontal gyrus; rSFG: right superior frontal gyrus; lFusiG: left Fusiform gyrus; rHip-rParahip: right hippocampus and parahippocampus; lHip-lParahip: left hippocampus and parahippocampus.
*p < .05; **p < .01; ***p<.001 significant differences; +p < .100 marginally significant differences

Appendix E. Project Ethical Approval

The studies presented in Chapter 5 and 6 in the current thesis were approved by *Comissão de Ética para a Investigação em Ciências da Vida e da Saúde* (CE.CSH 078/2018), as shown below.

.



Universidade do Minho

Conselho de Ética

Conselho de Ética - Ciências Sociais e Humanas

Identificação do documento: CE.CSH 078/2018

Título do projeto: *To think or not think of alcohol, that is the question: Memory suppression in young binge drinkers*

Investigador(a) Responsável: Eduardo López Caneda (PhD), Escola de Psicologia, Universidade do Minho

PARECER

O Conselho de Ética analisou o processo relativo ao projeto de investigação acima identificado, intitulado *To think or not think of alcohol, that is the question: Memory suppression in young binge drinkers.*
Os documentos apresentados revelam que o projeto obedece aos requisitos exigidos para as boas práticas na investigação com humanos, em conformidade com as normas nacionais e internacionais que regulam a investigação em Ciências Sociais e Humanas.

Face ao exposto, o Conselho de Ética nada tem a opor à realização do projeto, emitindo o seu parecer favorável.

Braga, 29 de novembro de 2018.

A Presidente do CEUMinho

Assinado por : **GRACIETTE TAVARES DIAS**
Num. de Identificação Civil: BI071230157
Data: 2018.12.07 10:18:57 GMT Standard Time

CARTÃO DE CIDADÃO

Anexo: Formulário de identificação e caracterização do projeto