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Behavioral Neuroscience of Alcohol Addiction

Translational Studies and
Human Phenotypes

Current Topics in Behavioral Neurosciences

Volume 72

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Springer

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Preface

A dozen years has passed since the first edition of *Behavioral Neurobiology of Alcohol Addiction* was published. At the time, our primary goal was to provide a comprehensive resource that served as a touchstone for researchers and a catalyst for reflection in the field of alcohol addiction. The perspectives of eminent scholars, coupled with a broad synthesis of knowledge, created a volume that was widely embraced—not only for its scholarly impact, as evidenced by numerous citations and downloads, but also for its utility in teaching and training future scientists. Yet, the field has since undergone major shifts that demand a fresh appraisal of where we stand and where we are headed.

We have sought to capture the evolving landscape of alcohol addiction research by curating a collection of Current Topics that exemplify recent methodological and conceptual advancements. These topics have not only substantially contributed to the field but have also profoundly influenced the way we think about alcohol addiction and its underlying mechanisms.

With this guiding principle, we have selected four Current Topics in Behavioral Neurobiology of Alcohol Addiction, which form the thematic backbone of this new edition. The current edition of *Behavioral Neurobiology of Alcohol Addiction* is organized into two volumes and four parts. The first volume, titled *Basic Mechanisms and Animal Studies*, focuses on foundational insights into the conceptualization of addiction and the neurobiological mechanisms that sustain it. The second volume, *Translational Studies and Human Phenotypes*, shifts focus to the interface of human and translational research.

In Volume 1, Part I begins with a chapter where we briefly sketch the current landscape of alcohol research (Sommer and Spanagel 2025). Then, Koob and Vendruscolo (2023) provide a comprehensive synthesis of the predominant theoretical framework. They delve into how reward deficits, the overactivation of stress systems, and chronic pain contribute to the persistence of alcohol addiction.

This theoretical overview is complemented by a series of chapters that explore various animal models of AUD, highlighting their strengths and limitations for uncovering mechanisms and guiding medication development. Becker and Lopez

(2024) provide a comprehensive review of five rodent models that are commonly used in alcohol research. Hitzemann et al. (2023) expand on this by showcasing the application of two such models to investigate brain gene expression, demonstrating how these findings contribute to the interpretation of human AUD-related genome-wide and transcriptome-wide association studies. Additionally, Scholz (2023) highlights the potential of invertebrate models in AUD research, underscoring their unique advantages, particularly for the efficient screening of novel therapeutic compounds.

The section concludes with a critical contribution from Meinhardt et al. (2024), who address the replication crisis that has challenged the reliability and validity of preclinical research. Their chapter not only scrutinizes the underlying causes of this crisis but extends our previous viewpoints by offering a set of practical guidelines aimed at improving research practices, ensuring greater reproducibility, and fostering confidence in preclinical findings.

Part II delves deeper into the specific mechanisms underpinning the actions of alcohol, providing a comprehensive exploration of its effects at multiple levels of biological organization. This section starts with Quintanilla and Israel (2023) focusing on the role metabolic pathways in alcohol preference, addiction, and treatment. The cellular and synaptic consequences of alcohol exposure are broadly discussed by Lovinger and Roberto (2023). This is followed by the chapter of Barbier et al. deliberating alcohol's effect on epigenetic mechanisms (Domi et al. 2023). A highlight of this part is the focus on the rise of neuronal population and circuit-based approaches, exemplified by chapters on manipulating the oxytocin system and dissecting the reward circuitry by Schimmer et al. (2023) and Doyle et al. (2023), respectively. These studies demonstrate the power of contemporary tools to refine our understanding of addiction's neural substrates. This part concludes with a forward-looking chapter by Lapish (2024) on computational methods for decoding the encoding of alcohol-related behaviors, illustrating the growing integration of data-driven approaches in addiction research.

Volume 2 starts with Part III that addresses the perennial challenge of modeling relapse in controlled laboratory settings. In their chapter, Milivojevic and Sinha discuss innovative strategies to replicate the conditions leading to relapse in human laboratory experiments (Milivojevic and Sinha 2023). Contrasting these approaches, Reichert et al. (2024) present the development and application of ecological momentary assessment (EMA), a methodology that provides real-time data on alcohol use and relapse risks in everyday life.

Bach et al. (2023) offer a compelling review of advances in molecular probes for positron emission tomography (PET), enabling precise imaging of alcohol-related phenotypes. Following this, Beck et al. (2023) synthesize findings from human PET and other neuroimaging studies, particularly focusing on dopamine's role in alcohol use and addiction. Their analysis reflects on both the coherence and the notable disparities between findings from animal and human studies, emphasizing the challenges of translating preclinical insights into human contexts.

This critical theme is further expanded by Crombag et al. (2024), who scrutinize the traditional reliance on "face validity" in translational research. They advocate for

a paradigm shift, emphasizing the importance of identifying intermediate human behavioral phenotypes that capture discrete aspects of AUD. Such phenotypes, they argue, should serve as anchors for developing homologous animal models grounded in shared psychological and neurobiological processes. This part concludes with Sommer and Canals (2025) presenting examples of objectively translatable neuro-imaging phenotypes based on diffusion tensor imaging (DTI). They discuss the implications of these phenotypes for studying AUD populations and highlight their potential for bridging the gap between animal and human research.

Part IV shifts the focus to novel concepts and advancements in the treatment of AUD. This section highlights innovative approaches aimed at reshaping therapeutic strategies. Three chapters delve into distinct learning mechanisms that hold promise for improving treatment outcomes. These include techniques such as memory retrieval and reconsolidation employed by the Kiefer and Barak Labs (Bach and Kiefer 2023; Barak and Goltseker 2023), and approach bias retraining discussed by Wiers et al. (2023), all of which leverage psychological constructs to enhance the efficacy of AUD psychotherapy. These contributions underscore the potential of targeting specific cognitive and behavioral processes to support long-term recovery.

An expert review by Ygael and Zangen (2024) provides a comprehensive examination of transcranial magnetic stimulation (TMS), an emerging neuromodulatory technique with growing evidence for its effectiveness in treating AUD and other addictions. The review offers insights into the mechanisms underlying TMS, its current clinical applications, and future directions for research in this area.

Leclercq and de Timary (2024) conclude the volume by exploring the critical role of inflammatory mechanisms in AUD. This includes a detailed discussion of the microbiome, the gut-brain axis, and the systemic inflammatory response as contributors to alcohol use disorder. These mechanisms are not only central to understanding the physiological consequences of chronic alcohol consumption but also represent promising targets for novel treatment interventions.

With this new edition of *Behavioral Neurobiology of Alcohol Addiction*, we aim to share our enthusiasm for the field of alcohol addiction research with a diverse and broad readership. Despite the challenges the field has faced, today's alcohol research generates more excitement and possibilities than ever before, offering innovative insights that continue to reshape our understanding of this complex disorder. We hope that this work not only serves as a comprehensive reference for seasoned scholars but also inspires a new generation of students and researchers to engage with the fascinating questions surrounding addiction.

Mannheim, Germany

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Part III

**Experimental Studies to Human Alcohol
Use and Addiction**

Laboratory and Real-World Experimental Approaches to Understanding Alcohol Relapse



Verica Milivojevic and Rajita Sinha

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Abstract Alcohol use disorder is highly prevalent and high risk of relapse remains a significant treatment challenge. Therefore, the utility of human laboratory models of relapse to further the understanding of psychobiological mechanisms that precipitate relapse risk and allow testing of novel interventions could be of benefit in expediting the development of effective treatments to target high relapse risk. Stress is a risk factor for the development of AUD and for relapse, and furthermore, chronic alcohol use leads to adaptations in central and peripheral stress biology. Here, we review our efforts to assess the integrity of these stress pathways in individuals with alcohol use disorder and whether adaptations in these systems play a role in relapse risk. Using

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validated human laboratory procedures to model two of the most common situations that contribute to relapse risk, namely stress and alcohol cues, we review how such models in the laboratory can predict subsequent relapse, and how we can measure specific identified biobehavioral markers of relapse effectively and ecologically in the real world. Finally, we discuss the significant implications of these findings for the development of novel and effective interventions that target stress dysregulation and craving as risk factors to treatment.

Keywords Craving · Cues · Human laboratory models · Relapse risk · Stress

1 Introduction

Alcohol use disorder (AUD) is a highly prevalent and heterogenous illness with devastating effects on the individual, extended family, and society as a whole (US Surgeon General Report 2016). Importantly, AUD is marked by high alcohol craving and anxiety and high risk of relapse (Milivojevic and Sinha 2018). Advances in preclinical and clinical research have demonstrated that neuroadaptations in biological stress pathways and their interaction with reward and motivational circuits play a key role in high alcohol craving states and such changes along with high craving perpetuate the chronic relapsing nature of AUD (Koob et al. 2004; Kreek and Koob 1998; Sinha 2001, 2007). This progress in our understanding of some of the underlying risk factors for the development of AUD as well as the risk of relapse have allowed us to move the needle to develop validated experimental approaches which directly probe these risk factors in the controlled laboratory setting, and with further validation and concurrence from the real world and in outpatient treatment contexts. This paper describes our validated human laboratory experiments modeling real-world situations in the controlled setting and assessing their contribution to alcohol relapse risk, as well as in examining relapse risk behaviors and risk factors daily in real time, in the real world. Human laboratory studies have been used often to model drug effects, drug self-administration and craving and urges for alcohol and other substances. This methodological tool has further allowed us to provoke relapse risk situations such as stress and alcohol/drug cue situations experimentally and assess whether we can induce hallmark features of alcohol seeking and consumption and assess its subsequent effects on relapse susceptibility. This experimental approach has yielded reliable and reproducible methods for modeling the relapse risk state, and has also provided us with a methodology that allows us to test and develop novel treatment interventions in individuals with AUD.

2 Stress, Cues, and Craving as Key Predictors of Relapse

Environmental stimuli previously associated with drug use, or internal cues such as stress responses, negative affect, and withdrawal-related states associated with chronic alcohol and drug use can function as conditioned stimuli capable of eliciting craving (Stewart et al. 1984) through classical and operant conditioning mechanisms by which neutral environmental cues paired with drug acquire emergent stimulus and drug response effects (Sinha 2012). These data are consistent with many human laboratory studies documenting that exposure to external drug-related stimuli, which may include people and places associated with alcohol and drug use such as beer cans, bars, smoking cigarettes and drinking alcohol, seeing drinking buddies and other alcohol-related situations that involve drinking, as well as internal drug arousal and mood and anxiety states that may result in increased drug craving and relapse risk (Sinha 2012).

A series of well-controlled experimental studies from our group have shown that exposure to stress and alcohol/drug relative to neutral cues increases craving in alcohol users, with increasing levels of alcohol and severity of alcohol use disorder associated with higher levels of alcohol and drug craving (Blaine et al. 2019; Blaine et al. 2020; Fox et al. 2005; Sinha 2013a). In the last decade, evidence has repeatedly shown that alcohol cues increase craving, and stress exposure increases craving significantly in binge and heavier drinkers (Blaine et al. 2019; Blaine et al. 2020; Chaplin et al. 2008; Wemm et al. 2022). Furthermore, in treatment-seeking patients with alcohol use disorder recent findings have replicated previously reported work (Sinha 2009, 2012) that individuals with AUD and substance use disorders (SUD) compared to healthy social drinkers show greater experimentally provoked stress- and cue-induced craving (Blaine et al. 2020; Martins et al. 2022). For example, we have shown that with increasing levels of alcohol and drug use, there appear to be greater craving responses and greater risk of higher levels for alcohol/drug intake that supports a feed-forward sensitized model of stress and drug cues that provoke craving which in turn provokes greater intake (Sinha 2013a).

In addition to cue-induced craving, adaptations in stress biology also show associations with alcohol relapse and prospective drinking outcomes (discussed in detail in Sect. 3 below). For example, HPA axis dysregulation, marked by higher basal ACTH levels and lack of stress- and cue-induced ACTH and cortisol responses, higher anxiety and higher stress- and alcohol cue-induced craving were observed in individuals with AUD exposed to experimental stress and alcohol cues, and these biomarkers were each predictive of shorter time to relapse (Sinha et al. 2011). Similarly, stress-induced ACTH and cortisol responses predicted higher amounts of cocaine use per occasion in a 90-day follow-up period in individuals with cocaine use disorder (Sinha et al. 2006). Importantly, recent findings also show that high alcohol craving at treatment entry and on a daily level increased stress-related alcohol craving prospectively predicted poor outpatient alcohol use outcomes during outpatient behavioral treatment (Martins et al. 2022; Wemm et al. 2019). These findings suggest that normalizing the multilevel alcohol-related stress

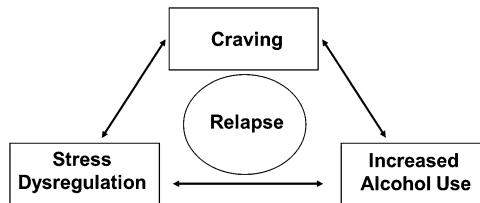


Fig. 1 Schematic diagram of the *feed-forward* interactions between stress dysregulation, craving, and increased alcohol use such that greater stress dysregulation, greater the craving, and greater risk of increases in alcohol use, with each contributing to increased relapse risk

dysregulation alongside reductions in alcohol craving may improve alcohol relapse risk and drinking outcomes (Blaine and Sinha 2017; Milivojevic and Sinha 2017). Thus, alcohol craving may serve as a powerful proxy for treatment outcome and future alcohol and drug use and relapse as shown in a recent meta-analysis (Vafaei and Kober 2022), and should therefore be investigated as a key biobehavioral marker and target of treatment development and outcome (Fig. 1).

3 Why Does Stress Matter in Addiction Risk and Relapse?

Growing evidence points to the critical role of stress in increasing the risk for the development of AUD and for relapse. For instance, population-based and clinical studies have shown a significant association between psychosocial adversity, traumatic exposure, negative affect, chronic distress, and internal deprivation states with addiction risk (Carliner et al. 2017; Laucht et al. 2009; Meaney et al. 2002; Schwabe et al. 2011; Sinha 2008). These findings underscore the impact of chronic and repeated exposure to stress and adversity on peripheral and central stress responses, increasing an individual's vulnerability to alcohol use and relapse, as detailed below.

3.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis and Addiction Risk in Children

The use of psychoactive substances actively stimulates and activates the HPA and autonomic axes in the case of psychostimulants (cocaine, nicotine, and amphetamine), alcohol, cannabis, and also with certain types of opioids (Sinha 2008; Wemm and Sinha 2019). There may also be significant variation in these responses, as assessed by plasma/serum concentrations of ACTH and cortisol (the latter also in saliva), salivary alpha amylase (a measure of autonomic adrenergic arousal), in addition to physiological assessments of heart rate (HR) and HR variability (HRV) as a function of the degree of chronic stress or trauma exposure (Dennis et al. 2014;

Hinnant et al. 2015; Sinha 2008). These responses to stress and drugs can be modulated by genes encoding HPA axis stress response markers, as well as by epigenetic changes in glucocorticoid signaling genes in response to chronic exposure to stress and adversity (Tyrka et al. 2016).

While several studies have linked greater stress reactivity in plasma and/or salivary cortisol as a risk factor for comorbidity of mood disorders and addiction (Rao 2010; Rao et al. 2009; Rao and Morris 2015), research has also shown that blunted salivary cortisol responses to stress in at-risk children with a family history of substance use disorder also constituted an addiction risk factor (Moss et al. 1999; Moss et al. 1995). Specifically, one study evaluated at-risk prepubertal (ages 10–12) boys with substance-using fathers and found that high-risk boys secreted significantly less salivary cortisol in response to an anticipated stressor compared with controls (Moss et al. 1995). In another study, it was demonstrated that 14–17-year-olds prenatally exposed to cocaine exhibited elevated basal salivary concentrations of cortisol relative to nonexposed youths; by contrast, they exhibited a blunted salivary cortisol response to specific social stressors compared with controls (Chaplin et al. 2015). Furthermore, this study showed that sex differences were associated with predicting future substance use, where self-reported sadness in girls in response to a stressor could predict future drug use relative to boys; however, in boys, reduced salivary alpha amylase concentrations in response to the same social stressor predicted future drug use relative to girls (Chaplin et al. 2012, 2015). This suggested distinct physiological and emotional stress response risk profiles for boys and girls in the context of drug use vulnerability.

In another series of studies, impaired neuroendocrine responses to alcohol were also associated with an increased motivation for binge and/or heavy alcohol intake, thereby serving as a potential risk marker for the progression from heavy drinking to alcohol use disorder (King et al. 2016). Specifically, in a longitudinal study of heavy drinkers and light drinkers exposed to an oral alcohol challenge with a follow-up of 6 years, heavy drinkers exhibited greater sensitivity to stimulating effects and lower sensitivity to the sedative effects of alcohol compared with light drinkers; moreover, heavy drinkers demonstrated lower salivary cortisol release in response to the alcohol challenge, and presented with a greater number of alcohol use disorder (AUD) symptoms 6 years later, relative to light drinkers (King et al. 2016; King et al. 2014).

3.2 Autonomic Nervous System (ANS) and Addiction Risk in Children

Altered cardiovascular responses are another possible mechanism underlying the increased risk for problematic substance use. For example, in children of parents with SUDs HR responses were measured in response to psychosocial stress in participants (ages 11–20; children with SUD parents versus children with healthy

parents) (Evans et al. 2015); the at-risk children exhibited a blunted HR recovery to the stress exposure, suggesting that children who are at high risk for developing an SUD are marked by dysregulated ANS responses (Evans et al. 2015). In another study, the same group examined the relationship of salivary cortisol concentrations in response to a social stress task with age of onset of alcohol intake in adolescents (aged 14–20 years) (Evans et al. 2012). The findings showed that teenagers who began drinking at an earlier age demonstrated lower salivary cortisol at the onset of, and during the stressful task, relative to teenagers who began drinking when older; this suggested that decreased HPA axis activity in response to stress is present (and significant) in adolescents who begin drinking at an early age (Evans et al. 2012). In nonhuman primates, chronic, moderate alcohol exposure in cynomolgus monkeys led to decreased HRV; however, when the animals were exposed to an acute stressor of removal from their home cage to a novel environment, those with a history of alcohol exposure presented higher HRs compared with controls (Shively et al. 2007).

3.3 Chronic Alcohol/Drug Use Alters Stress Responses

It has long been known that alcohol stimulates the hypothalamic-pituitary-adrenal (HPA) axis and initially stimulates the autonomic systems by provoking sympathetic arousal followed by depressing such activation (Ehrenreich et al. 1997; Lee and Rivier 1997). Dramatic adaptations of the HPA axis akin to tolerance have also been demonstrated with regular and chronic alcohol use in animals (Richardson et al. 2008; Zhou et al. 2000) and in humans (Adinoff et al. 1998; Adinoff et al. 2005; Wand and Dobs 1991). Similarly, chronic alcohol-related changes in autonomic responses, particularly in parasympathetic vagal tone have also been documented in non-human primates (Shively et al. 2007) and in humans (Ingjaldsson et al. 2003; Rechlin et al. 1996; Thayer et al. 2006). These data are consistent with changes in peripheral stress pathways which parallel other basic science findings of alcohol-related adaptations in the extrahypothalamic corticotrophin-releasing factor (CRF) systems and the noradrenergic pathways that are consistent with upregulated central CRF and noradrenergic pathways (Cleck and Blendy 2008; Koob and Kreek 2007; Koob 2009; Rasmussen et al. 2006); also see (Heilig et al. 2010) for review. These data document specific dysregulation in emotion, stress, and motivational systems in individuals with AUD and raise the question of whether these measures contribute to the high levels of emotional distress and the pathophysiology of alcohol craving and compulsive alcohol seeking associated with relapse susceptibility.

3.3.1 HPA Axis Adaptations in SUDs

In humans, enhanced stress-system activity has been associated with chronic smoking as well as with cocaine and alcohol consumption (Blaine and Sinha

2017; Mello 2010). Elevated basal plasma and salivary cortisol levels have been observed with active binge alcohol intake and recent withdrawal from alcohol in individuals with alcohol use disorder (Adinoff et al. 1991; Adinoff et al. 2003; Costa et al. 1996; Kutscher et al. 2002). Lower basal plasma ACTH levels have been found in individuals with a high risk for AUD based on family history, compared with low-risk individuals (Dai et al. 2002). Moreover, markedly reduced ACTH and cortisol concentrations in response to both pharmacological stimulation of the HPA axis with human corticotrophin-releasing hormone (CRH) and psychosocial stressors (e.g., mental arithmetic, cold pressor test, or interpersonal conflict) have also been reported in chronic alcohol users compared with controls (al'Absi et al. 2000; Costa et al. 1996; Errico et al. 1993; Inder et al. 1995; Junghanns et al. 2003; Lovallo et al. 2000). Similarly, cigarette smoking has been shown to elevate circulating plasma ACTH and cortisol in moderate smokers (Pomerleau and Pomerleau 1990; Seyler et al. 1984), and decreased plasma and salivary ACTH and cortisol in response to psychosocial stress (public speaking or mental arithmetic) have been reported in smokers during withdrawal relative to sham smokers (al'Absi et al. 2005). The stress-induced and drug or alcohol cue-induced craving state in patients with SUD has been characterized during protracted abstinence and the findings indicate that these cravings are accompanied by enhanced negative emotion and anxiety as well as by altered plasma cortisol and ACTH concentrations in early-abstinent cocaine users (Fox et al. 2006; Sinha et al. 2003), comorbid cocaine and alcohol users (Fox et al. 2005), as well as in early-abstinent individuals with alcohol use disorder relative to controls (Fox et al. 2007; Sinha et al. 2000, 2009). Together, these findings suggest that regular binge use of psychoactive substances, such as nicotine, alcohol, and cocaine, alters physiological stress pathways; that such alterations are accompanied by a greater motivation to use drugs; and that they result in higher levels of alcohol and drug use (for review see (Wemm and Sinha 2019)).

3.3.2 Autonomic Nervous System (ANS) Adaptations in SUDs

In addition to HPA axis dysregulation, chronic drug use can also lead to dysregulation of the ANS. In one clinical study, inpatient treatment-engaged, individuals with alcohol and cocaine use disorder completed research participation in 3-day controlled experimental studies where they were exposed to stress, alcohol/drug cues, or an active neutral relaxing control cue by using standardized personalized guided imagery [see method description below]. Drug craving, anxiety, HR, blood pressure, and several neurochemicals, including plasma cortisol and ACTH and other parameters, such as serum brain-derived neurotrophic factor (BDNF), plasma neuropeptide Y (NPY), and immune cytokines, were measured (D'Sa et al. 2012; Fox et al. 2007; Sinha 2009, 2012; Sinha et al. 2009, 2011; Xu et al. 2012). Early abstinent individuals with SUDs displayed persistent high basal HRs (Sinha et al. 2009), and reduced HR responses to the stress imagery conditions relative to healthy controls (Sinha 2012; Sinha et al. 2009, 2011). One of the first studies to experimentally examine the role of autonomic reactivity in stress-induced craving in

nicotine-dependent 15-h-abstinent smokers reported that blunted stress-induced high-frequency HRV (HF-HRV) was associated with less time to initiate smoking and increased craving relief and reinforcement from smoking (Ashare et al. 2012). Recent work examined HRV in nicotine- and alcohol-dependent individuals compared with age-matched controls, and found that HRV was globally decreased in the addicted subjects (Yuksel et al. 2016). Collectively, these data suggest that alterations in HR and HRV can result from chronic drug use and can increase relapse risk in SUDs. Furthermore, they might also be useful as predictive biomarkers of treatment outcome; for example, by assessing treatments that aim to normalize tonic and phasic vagal reactivities in early abstinent individuals with SUDs, it may be possible to improve cessation and abstinence outcomes. However, these possibilities remain to be tested.

3.4 Central Nervous System Response to Stress in Addiction

Several previous human studies suggest that trauma, adversity, and chronic stress alter the activity and structure of the prefrontal cortical, limbic, and striatal brain networks involved in regulating stress, emotions, reward, and higher cognitive or executive control functions (Sinha 2008). These functions can include the regulation of distress and emotions, such as controlling and inhibiting impulses, refocusing and shifting attention, working memory, monitoring conflict and behavior, linking behaviors to possible future consequences, and flexible consideration of alternatives for response selection and decision-making (Arnsten et al. 2012). Further evidence from human brain structural and magnetic resonance imaging (MRI) showed that recent life stressors, such as death in the family, divorce, relationships ending, assault, financial crisis, robbery, trauma (physical, emotional, and/or sexual abuse) as well as chronic stress (subjective experience of continuous stressors or ongoing life problems), are associated with lower gray matter volume in medial prefrontal, amygdala, hippocampus, and insula regions of the brain (Ansell et al. 2012; Van Dam et al. 2014). Similarly, recent life stress and acute stress exposure may decrease responses in the prefrontal regions, such as the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (vmPFC) (associated with working memory, reward processing, and resilient coping), and might be linked to at-risk drug use and emotional dysregulation, such as binge alcohol intake, emotional eating, and frequency of argumentation and/or fighting (Sinha et al. 2016). Thus, with increasing levels of stress, functional (f)MRI has indicated decreased prefrontal control and disrupted limbic-striatal responses to stress are associated with low behavioral and cognitive control (Sinha et al. 2016).

In another study, prenatally cocaine-exposed 14–17-year-old adolescents exhibited lower gray matter volume in limbic and frontal regions of their brains, as assessed by MRI and whole-brain voxel-based morphometry, relative to non-cocaine-exposed adolescent controls; moreover, lower gray matter volume in these brain regions was associated with substance use initiation (Rando et al. 2013),

thereby suggesting that changes in brain volume serve as biological risk markers of substance use. Indeed, low behavioral and cognitive control linked to reduced prefrontal and insular cortex activity, as well as the high activation of limbic-emotional and striatal-motivational brain regions under stress, suggest specific patterns that underlie a risk for developing addictive behaviors concomitant with a decreased ability to control rewarding behaviors (Li and Sinha 2008). Thus, motivational brain pathways appear to be key targets of disrupted central stress activity that suggest a potentially important mechanism where stress could affect susceptibility to addiction.

4 Modeling Alcohol Relapse in the Laboratory

There are many challenges to studying relapse situations and compulsive alcohol seeking in the laboratory. A key challenge is the ecological relevance of the provocation method, especially when studying psychopathological populations where the specific psychiatric illness is itself seen as a chronic distress state (Brady and Sinha 2005). For example, there are widespread individual differences in relapse situations (McKay et al. 1995; McKay et al. 1996) and hence using experimental-derived standard provocateurs may not capture drug-related associations that are likely involved in craving- and relapse-related motivational processes. Another challenge is that as relapse situations often involve drug, drug-related, emotional, or stressful stimuli and such stimuli invoke arousal of stress pathways, there is a need to address the well-known alterations in the “normal” stress responses. Of course, one way to address these issues is by designing laboratory experiments with adequate within-group control conditions and/or between-group controls such as inclusion of non-addicted healthy controls or social drinkers. In our studies, we have increasingly added both in the experimental designs so that we can examine changes in motivational state as a function of exposure to relapse situations and changes in biological stress and arousal measures in comparison to healthy non-addicted individuals using comparable methods in the laboratory. Finally, an additional consideration is that of stress and craving measurement. Ensuring sensitivity in the measurement of basal stress responses to detect tonic adaptations pertaining to disease state would be important to assess for influence on changes in motivation state and craving associated with phasic provoked or challenge responses.

4.1 *Developing Valid Laboratory Models of Relapse Situations*

In order to develop a validated method to study relapse situations in individuals with alcohol and other substance use disorders in the laboratory, the method needs to achieve four objectives as outlined in our previous review (Sinha 2009, 2013b). The

method should (a) consistently reproduce a hallmark disease symptom and proxy marker of relapse. Craving has served as such a measure in the laboratory setting, thereby providing internal validity; (b) provoke the particular disease symptom which in turn, should be associated with AUD severity; (c) be predictive of alcohol use behaviors and real-world clinical outcomes; and finally (d) be responsive to interventions, i.e., an intervention that targets that disease symptom and makes the disease outcomes worse or better. In the clinical context, patients with AUD entering outpatient substance use treatment report high levels of stress and an inability to manage distress adaptively, thereby increasing the risk of succumbing to high levels of drug craving and relapse to drug use (Sinha 2007). While patients are often successful in learning cognitive-behavioral strategies in the clinic, relapse rates remain high (Brandon et al. 2007), suggesting difficulties in applying and accessing these strategies in real-world relapse situations. The focus of our laboratory studies became the development of an ecologically relevant method that models such relapse risk in real-world situations in order to understand the biobehavioral mechanisms underlying relapse susceptibility. One key feature of our method was to provoke two of the most common relapse situations, namely emotionally stressful situations and alcohol/drug-related situations in order to develop a comparable method of provoking stress- and the alcohol/drug-related craving state. A second key aspect was to build in an experiment control condition to account for the non-specific aspects of the experimental procedures.

4.2 *Emotional Imagery Methods*

Emotional imagery paradigms have been widely used in behavioral and neuroimaging research to understand the pathophysiology of mood and anxiety disorders, including major depression, panic disorder, obsessive-compulsive disorder, and post-traumatic stress disorder (Cook et al. 1988; Foa and Kozak 1986; Mayberg et al. 1999; McNeil et al. 1993; Orr et al. 1993; Pitman et al. 1987; Shalev et al. 1993). They have also been used for anger provocation to assess anger effects on markers of cardiovascular disease (Nelson et al. 2006). There is also a body of research using imagery procedures to study the effects of affect and cues on nicotine craving in the laboratory (Drobes and Tiffany 1997; Tiffany and Drobes 1991; Tiffany and Hakenewerth 1991). Our work further adapted these methods and developed the individualized emotional imagery procedures for application in assessing specific addiction states, and for the study of stress and other challenge provocation states and these methods are further described in detail in (Sinha 2009, 2013b; Sinha and Tuit 2012).

4.3 Individualized Stress and Craving Imagery Procedures Applied in Addiction

Individualized guided imagery procedures involve an initial imagery script development session, standardized script generation, and audiotaping, followed by a habituation and imagery training session that precedes the experimental sessions [full description of procedures is provided in our manual for imagery script development procedures] (Sinha and Tuit 2012). The experimental method involves the development of scripts for stress and alcohol-related stimuli along with a non-specific control script, each based on the subject's individual experiences. Below is a sample script development session, lasting approximately 1 h, which involves developing a single script from a stressful situation, an alcohol-related craving and consumption situation, and a neutral-relaxing situation. The conditions are presented in random order and counterbalanced across subjects. Subjects remain blind to the order and type of condition until the presentation of audio recording, while the experimenters remain blind to the order and content of each audio during laboratory sessions (see Sinha 2009, 2011; Sinha and Tuit 2012 for details of the methods and procedures).

4.4 Neural Correlates of Stress and Alcohol Cue and Association with Relapse Outcomes

In previous work, we utilized motional imagery methods for stress and alcohol craving provocation and identified specific neural correlates of future relapse risk (Seo et al. 2013). However, we also identified a procedure to reliably increase subjective stress in community control volunteers and found it to be associated with alcohol use and other coping behaviors (Sinha et al. 2016). Further development of this method was undertaken to study individuals who drink socially and those who are entering treatment for current alcohol use disorder. To model relapse risk factors and brain activity in AUD, 69 treatment-entering patients with AUD were assessed for whether fMRI responses at treatment initiation were influenced by alcohol abstinence and were prospectively predictive of early heavy drinking outcomes (Blaine et al. 2020). We used a novel fMRI paradigm that consisted of brief successive exposure to three conditions: (1) a block of highly appetitive images of alcoholic beverages and people drinking alcoholic beverages alone or in social contexts; (2) a block of highly threatening, aversive, and stressful images; and (3) a no-cue control block involving neutral images (Blaine et al. 2020; Sinha et al. 2022; Sinha et al. 2016), see Fig. 2. Pictures included images from the International Affective Picture System and those developed at the Yale Stress Center; selected alcohol cue images from the web were downloaded and rated using the same rating method as the International Affective Picture System images. The alcohol cues included images of wine, beer, cocktails, champagne, and hard

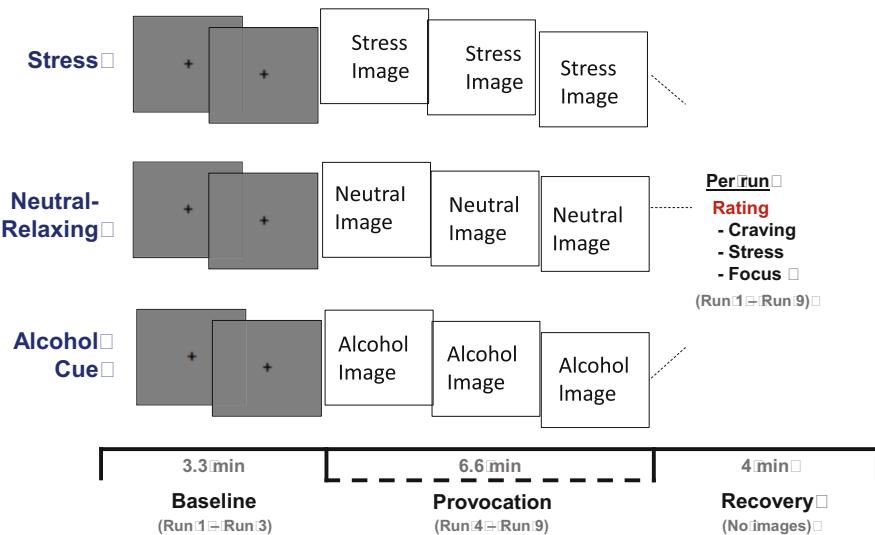


Fig. 2 A novel fMRI paradigm that consists of brief successive exposure to three conditions: (1) a block of highly appetitive images of alcoholic beverages and people drinking alcoholic beverages alone or in social contexts; (2) a block of highly threatening, aversive, and stressful images; and (3) a no-cue control block involving neutral images (adapted from Sinha et al. 2022)

liquor. The stress condition involved highly aversive images of terror, violence, mutilation, fear, disgust, and desperation. The neutral condition consisted of neutral images of mountains, grass, trees, streams, stones, and trails. During the fMRI scan, participants also had an intravenous line inserted in the nondominant forearm for repeated blood drawing for cortisol data collection during the scan. Also, a pulse oximeter was placed on the nondominant forefinger to obtain heart rate during the scan.

Following the fMRI scan, AUD patients completed daily diary assessments via a smartphone application (MetricWire). The daily surveys assessed how many glasses of beer, wine, and mixed drinks were consumed per day during the first 14 days of treatment engagement. The quantity of each type of drink was summed for each day to create an index of total drinks consumed per day. Measurements were collected during an evening survey that was available from 8:00 p.m. to 2:00 a.m. In addition, a morning survey was available from 8:00 a.m. to 2:00 p.m., which was used to estimate drinking if the participants missed the previous day's evening survey (see Fig. 4 below). We found significant hyperreactivity in the ventromedial prefrontal cortex (vmPFC) in response to neutral images, but significant hypoactivation in the vmPFC and ventral striatum in response to stress images and to alcohol cues relative to response to neutral images, replicating previous work using the emotional imagery paradigm (Seo et al. 2013) and community volunteers (Sinha et al. 2016). More importantly, this specific prefrontal-ventral striatal dysfunction was associated with fewer days of alcohol abstinence and also predicted a greater number of heavy drinking days during the subsequent 2 weeks of treatment engagement (Blaine et al. 2020).

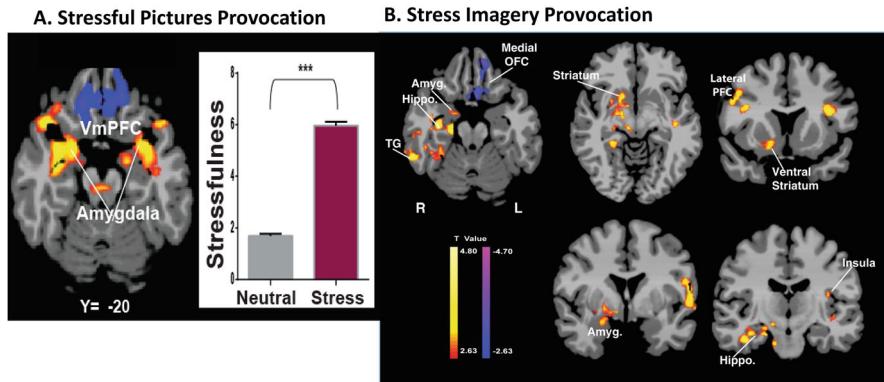


Fig. 3 Similar and replicable brain activation to stress using two different provocation paradigms of (a) Stress/Emotional visual stimuli provocation and (b) Stress imagery provocation. With both methods, exposure to stress increases subjective stress ratings and also increases activation of limbic-striatal brain stress networks, including the amygdala, hippocampus, ventral and dorsal striatum, lateral prefrontal cortex (PFC), and hypoactivation of the medial orbitofrontal cortex (OFC) and the ventromedial PFC (vmPFC) (images are from voxel-based whole brain analysis, FWE corrected at $p < 0.05$)

Notably, both the emotional imagery method (Seo et al. 2013) and the standardized visual picture fMRI (Sinha et al. 2016; Blaine et al. 2020) methods have been shown to elicit similar brain activation pathways and replicate neural activation across both methods, thereby corroborating relapse risk and treatment outcome findings (see Fig. 3 below).

5 Laboratory Responses to Relapse Situations and Subsequent Relapse

SUDs are chronic and relapsing in nature and clinical treatment studies suggest that more than two-thirds of individuals with SUD relapse within weeks to months of initiating treatment (Hyman et al. 2008; Paliwal et al. 2008). Given these high relapse rates, it is important to understand whether there is a biology underlying relapse susceptibility and, if so, whether there are specific biobehavioral markers of relapse risk that may be targeted to develop new treatments for relapse prevention. While clinical studies have repeatedly shown that stress is associated with relapse (Sinha 2012), the underlying mechanism in this relationship is not clearly understood. Using the guided imagery method described above, our laboratory tested response to personalized stress and cue imagery that models relapse situations as well as subsequent relapse outcomes in individuals with AUD and CUD.

Inpatient treatment-engaged, recovering individuals with cocaine and alcohol use disorder were exposed to personalized, guided stress, drug cues, and neutral relaxing scenarios and evaluated for craving, anxiety, and stress responses (as assessed by ANS and HPA axis markers). Individuals with SUDs in the early stages of abstinence (28 days) exhibited persistently high basal concentrations of plasma ACTH and salivary cortisol, as well as higher basal HR (Sinha et al. 2009) relative to healthy controls. However, these abstinent individuals displayed blunted plasma ACTH, salivary cortisol, and HR responses when presented with stress challenges, relative to controls (Fox et al. 2008; Fox et al. 2009; Sinha et al. 2009; Sinha et al. 2011). Moreover, after completion of the laboratory study, the patients were discharged from inpatient treatment and observed repeatedly for 90 days to assess future relapse outcomes. For the cocaine group, where altered stress responses were noted compared with controls (see above Fox et al. 2008), higher stress-induced ACTH and cortisol concentrations were not associated with time to relapse, but these responses were predictive of greater amounts of cocaine consumed during follow-up (Sinha et al. 2006). Abstinent, treatment-engaged, individuals with alcohol use disorder with high cortisol:ACTH ratios (a measure of the sensitivity of the adrenal glands to release cortisol in response to the ACTH signal) were more likely (more than double the risk) to relapse more quickly than those with low cortisol:ACTH ratios after discharge from inpatient treatment (Sinha et al. 2011). In nicotine-dependent individuals in early abstinence, other research has also shown that blunted cortisol responses may be able to predict early relapse (al'Absi et al. 2005; McKee et al. 2011). Collectively, these findings show that the somatic and behavioral response to stress and cue exposure in the laboratory can predict outcome and relapse (Sinha et al. 2009; Fox et al. 2008; Sinha et al. 2011).

6 Monitoring Alcohol Relapse in the Real World

While the numerous studies outlined above have shown that stress increases craving in individuals with AUD and predicts future alcohol relapse risk, whether stress on a particular day affects craving on that day to impact prospective alcohol intake in the real world, particularly during early treatment and recovery, is not fully understood. In one of the first such studies conducted, we collected data in two separate cohorts of individuals with AUD in which we collected daily reports of stress, craving, and alcohol intake in the real lives of the participants (Wemm et al. 2019). The first study included 85 AUD individuals who reported their daily stress, craving, and alcohol intake in the first 2 weeks of early treatment. A second validation study included 28 AUD patients monitored daily during 8 weeks of outpatient 12-step-based behavioral counseling treatment for AUD. Data were collected from telephone-based daily diaries for 903 days in Study 1 and 1,488 in Study 2, see Fig. 4 for illustration of daily diary data collection. In Study 1, participants completed a daily survey that assessed if a stress event occurred that day, their current alcohol craving, and the amount of alcohol consumed that day. In this way, data on stressors

experienced and alcohol craving on each day as well as alcohol intake per day was assessed, providing day-by-day data on predictor variables and drinking outcome. Participants were asked to respond yes or no to three questions designed to measure stressful events that day (“Did you have or nearly have an argument or disagreement with anyone?”, “Did anything else happen at home, work, or school that you felt was stressful?”, “Did anything else happen to you that most people would consider stressful?”) derived from the Daily Inventory of Stress Events (Almeida et al. 2002). Recent work has demonstrated that asking participants to recall stressful events at the day level yields similar results as asking participants to report stressful events as they occur (Preston et al. 2018). The three items were combined into a single index that indicated if a stressful event occurred that day (“1”) or not (“0”). Craving has been described as an expression of desire or wanting for alcohol or drugs (Tiffany and Wray 2012), so questions that target this desire or want tend to perform as well as questions that directly ask about craving. Thus, we opted for the average of two items used to create an index of craving, “Right now, I could really use a drink” and “Right now, the idea of a drink is appealing,” to capture aspects of desire and want. Participants indicated their agreement to these items on a 5-point Likert scale (0 = “Definitely False” and 4 = “Definitely True”). When reporting drinking behavior, participants were provided with a description of standard drinks (i.e., 12 oz. of beer, 5 oz. of wine, 1.5 oz. of liquor) and asked how many glasses of beer, wine, and mixed drinks they consumed on that day. Information about their alcohol consumption that day was supplemented by TLFB if a participant missed an evening survey in Study 1 (6.8% of drinking days). The quantity of each type of drink was summed for each day to create an index of total drinks consumed per day.

The second study used the same procedure to measure alcohol consumption, but the assessment of stressful events and craving differed slightly. As before, the TLFB was used to estimate drinking on days missing alcohol consumption reports (15.5% of days). To assess stressors that occurred that day, participants completed a more extensive version of the daily stress assessment based on work from previous ecological momentary assessment (EMA) studies (Armelia et al. 2000). Participants were asked, “Which of the following events made you feel stressed today?” to which they could check a box of 12 possible events (e.g., “Work/Education,” “Home/Family,” “Finances,” among others). Responses were dichotomized to indicate if any stressful events occurred that day (“1”) or not (“0”) in order to make the results comparable between studies. Craving was measured by asking participants about their current desire to drink (“Right now I could really use a drink”) on a Visual Analog Scale (VAS) ranging from 1 representing “Strongly disagree” up to 100, anchored at “Strongly agree.” We opted for a single question to reduce participant burden since the two items described in Study 1 were strongly correlated ($r = 0.77$).

This paradigm allowed us to test whether daily and person-averaged craving mediated the link between stressful events and next day drinking during treatment. In both studies, exposure to a stressful event on a particular day predicted increased craving on that day and such increases in craving predicted the likelihood of drinking the next day and the drinking amount (Wemm et al. 2019). Individuals who

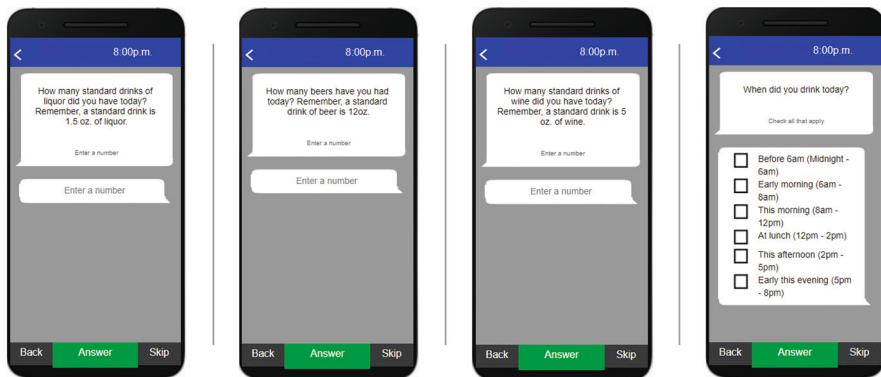


Fig. 4 Daily diaries for ecological momentary assessment (EMA) data collection of daily alcohol intake in the real world using smartphone applications

experienced more stressful events reported higher craving, and higher cravers reported greater next day drinking. The results across two studies with separate samples are the first to establish that craving directly mediates the association between stress and next day alcohol intake in individuals with AUD. These findings suggest that there is an urgent need for novel treatment approaches to address stress-induced craving to improve alcohol use outcomes.

7 Targets for Treatment Development

Research described in the previous sections using human laboratory and neuroimaging approaches has identified multilevel neural, physiologic, endocrine, and behavioral adaptations to both stress and to chronic alcohol use. Thus, we have postulated that medication or behavioral interventions that improve vmPFC function and also normalize HPA axis function (i.e., reduce basal overactivity and reinstate normal phasic stress responses) and reduce alcohol craving may improve treatment outcome in individuals with AUDs and reduce relapse risk (Milivojevic and Sinha 2017; Milivojevic and Sinha 2018). For example, naltrexone treatment can increase cortisol concentrations at baseline and decrease drug-related alcohol craving, while increasing alcohol-stimulated ACTH and cortisol responses compared with placebo in nontreatment-seeking individuals with AUD (O'Malley et al. 2002). Thus, naltrexone can reduce alcohol-related neuroendocrine tolerance and improve the effects of alcohol tolerance to stimulate the HPA axis, thereby reducing the blunted alcohol response of the HPA axis. However, these findings have also indicated that naltrexone can increase basal HPA axis tone and tonic cortisol levels relative to placebo, an effect that might be detrimental to individuals with AUD with higher subclinical and clinical HPA axis alcohol withdrawal and/or abstinence pathophysiology. This aspect of naltrexone may render it unsuitable for all individuals with AUD and

may contribute to explaining its modest efficacy in AUDs. CRF antagonists, such as pexacerfont (which directly acts on the stress axis), have been found to reduce ACTH and increase cortisol responses to stress in anxious alcoholic patients (Kwako et al. 2015). Negative results in this study, and with other CRF receptor antagonists, have been observed with regard to efficacy in reducing alcohol craving responses (Schwandt et al. 2016). However, the patient samples were not selected because of a specific alteration in biomarker and/or stress responses. Thus, future research is needed to understand whether CRF antagonists may be targeted to specific subgroups of patients and whether these might be exploited as prognostic biomarkers of high relapse risk. Recent studies have manipulated central glucocorticoids with mifepristone to normalize peripheral HPA axis responses; the drug was useful in helping to decrease alcohol intake in individuals with alcohol use disorder (Vendruscolo et al. 2015).

Noradrenergic compounds that have central effects on ANS, HPA axis, and prefrontal stress pathways have also been examined. Forty inpatient treatment-seeking individuals with AUD were randomly assigned to receive placebo ($n = 18$) or 16 mg/day, T.I.D., prazosin ($n = 22$) in a double-blind manner, titrated over 2 weeks. In week 3–4 after achieving full dose, AUD patients were exposed to three 5-min personalized guided imagery conditions (stress cue, alcohol cue, neutral/relaxing cue), on three consecutive days in a random, counterbalanced order. Alcohol craving, anxiety, heart rate, cortisol, and ACTH levels were assessed at baseline, following imagery and at repeated recovery time points. Prazosin reduced stress cue-induced alcohol craving and stress- and alcohol cue-induced anxiety. Prazosin vs. placebo increased heart rate responses in all imagery conditions and lowered basal cortisol and ACTH and attenuated stress cue-induced rises in cortisol (Milivojevic et al. 2020). In a 12-week clinical trial, 16 mg/day prazosin reduced drinking days, heavy drinking days, anxiety, depression, and craving in individuals with AUD who also had high alcohol withdrawal symptoms (Sinha et al. 2021). Importantly, prazosin also reversed mPFC-striatal dysfunction which in turn predicted fewer drinking days during a 12-week treatment period (Sinha et al. 2022). In another study, the alpha2-agonist guanfacine was reported to reduce cue-induced craving, decrease baseline cortisol, and normalize stress-induced cortisol in early abstinent cocaine- and alcohol-dependent individuals (Fox et al. 2012), and also improved cognitive performance in women with SUD specifically (Milivojevic et al. 2017).

Progesterone administration in treatment-seeking men and women with cocaine and alcohol use disorder has also been examined, indicating that progesterone can lead to reduced cue-induced cocaine craving and cortisol responses and improve prefrontal inhibitory function relative to placebo, as evidenced from the Stroop Color/Word Test (Fox et al. 2013). Similar effects have been observed with GABAergic neuroactive steroids, where men and women with cocaine and alcohol use disorder receiving progesterone were grouped based on baseline concentrations of progesterone-derived neuroactive steroid allopregnanolone (ALLO; (Milivojevic et al. 2016). The high ALLO group demonstrated reduced craving and improved cognitive performance compared with the low ALLO group, as well as both reduced

basal, and increased cortisol in response to stress (Milivojevic et al. 2016). Addressing a novel direction for neuroactive steroids, we have also included most recent work on the neuroactive precursor pregnenolone which showed reductions in stress- and cue-induced craving, select reductions in anxiety and normalizations in the HPA axis adaptations in both individuals with AUD and CUD (Milivojevic et al. 2022a, b).

8 Challenges, Limitations, and Future Directions

Research modeling relapse risk situations in the laboratory over the last two decades has been replicated across multiple studies and also shown that the procedures are highly valid not only in association/prediction of future alcohol relapse or clinical treatment outcomes, but also for treatment development in AUD. Several caveats about the emotional imagery and the standardized fMRI visual stimuli methods and procedures used to provoke relapse situations in the laboratory need to be highlighted. First, our adaptation of the emotional imagery methods is manualized, technically rigorous, and therefore time-consuming and resource-intensive. For example, individual script development sessions are conducted and then scripts for each condition per subject are developed. Only highly trained research staff who have completed a structured script development training and are certified for script development should be developing such stimuli for laboratory situations. Our procedures have been tested in treatment-engaged addicted patients and healthy individuals and hence its effectiveness in non-treatment seeking and actively using individuals are not known. Second, while the standard visual stimuli procedures have been validated in the fMRI, they have not been utilized out of the fMRI in laboratory settings and reliability and validity for use in human laboratory models remained to be established. Third, there are other experimental factors that are important to consider in studying relapse situations. For example, duration of the exposure to relapse situations may significantly affect strength of response. For example, in the laboratory studies, our script length is 5–6 min and a prolonged exposure might elicit a more enhanced response. Also, individual differences in addiction severity factors such as withdrawal symptoms, abstinence days from drug, and severity of trauma history may all impact stress and craving adaptations to impact outcome and need serious consideration in human laboratory modeling of AUD outcomes. Other factors, such as aversiveness of the relapse situation, its intensity and controllability are all factors that impact laboratory responses and ultimately affect the ability to detect individual differences in the laboratory, especially in clinical samples, with respect to clinical outcomes.

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Understanding Alcohol Consumption and Its Antecedents and Consequences in Daily Life: The Why and the How



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Abstract Most of the scientific research on alcohol consumption behavior in humans is laboratory-based, as reflected by the ratio of laboratory vs. real-life contributions to this handbook. Studies in daily life, although having a long history in addiction research (Shiffman et al., Ann Behav Med 16:203–209, 1994), are in the minority. This is surprising, given that patients with substance use disorders are suffering in daily life and not in the laboratory setting. In other words, drinking patterns and symptoms of alcohol use disorder evolve not in the lab but in daily life, where patients show difficulties in limiting their alcohol intake accompanied with all kinds of related problems. The ultimate goal of all interventions, independent of being tailored toward restricted drinking or abstinence, is again an altered behavior in real life. Translated to practice, patients' behavior in the lab may not translate to daily life, often showing minimal ecological validity. Therefore, we have to question to which degree lab-based research findings translate into daily life. Fortunately, the current digital revolution provided us with more and more tools, enabling us to monitor, analyze, and change behavior in human everyday life. Our chapter does not intend to give a comprehensive overview of the daily life research on alcohol consumption over the last few decades as others do (Morgenstern et al., Alcohol Res Curr Rev 36:109, 2014; Piasecki, Alcohol Clin Exp Res 43:564–577, 2019; Shiffman, Psychol Asses 21:486–497, 2009; Votaw and Witkiewitz, Clin Psychol Sci 9:535–562, 2021; Wray et al., Alcohol Res Curr Rev 36:19–27, 2014). Instead, we aim at the following: first, to highlight the key advantages of ecological momentary assessment to motivate scientists to add daily life research components to their laboratory research and, second, to provide some guidance on how to begin with daily life research.

Keywords Alcohol use disorder · Ambulatory assessment · Digital phenotyping · Ecological momentary assessment · Electronic diary · Experience sampling method · Just-in-time adaptive intervention · Substance use disorder

Abbreviations

AA	Ambulatory assessment
AUD	Alcohol use disorder
EC	Encouragement
EDA	Electrodermal activity
EMA	Ecological momentary assessment

ESM	Experience sampling method
GPS	Global positioning system
JITAI	Just-in-time adaptive interventions
N-back	A specific continuous performance task
SAA	Society for Ambulatory Assessment
SST	Stop signal task
T	Treatment
TAC	Transdermal alcohol concentration
WPED	Within-person-encouragement-design

1 The Definition of Daily Life Research Methods

Within the field of daily life research, multiple terms have been used to describe a quite homogenous set of methodologies. Most prominently used are ecological momentary assessment (EMA; Stone and Shiffman 1994), experience sampling method (ESM; Csikszentmihalyi and Larson 1987), ambulatory assessment (AA; Fahrenberg et al. 2007), and digital phenotyping (Insel 2018). According to the definition of the respective international societies (SAA: <http://www.ambulatory-assessment.org>), the terms highlight the different origins and ancestors rather than real distinctions in methods.

However, from a historical perspective it can be argued that research teams in the Netherlands, Germany, and the USA initiated the development of innovative approaches to assess individual experiences and behavior in everyday life toward the end of the previous century; see Wilhelm et al. (2012); for an exact definition of each method please refer to Trull and Ebner-Priemer (2013). Each group had their specific methodological foci and accordingly used different terms. The “experience sampling” researcher started with paper-pencil diaries and pagers and especially highlighted the random sampling of situations (Csikszentmihalyi and Larson 1987), criticizing time-based approach at foreseeable time points (like every full hour). Ecological momentary assessment was early on fully digital, starting with palm tops and handheld computers, and highlighted the concept of momentary assessments, to avoid recall biases (Stone and Shiffman 1994). Pure end-of-day diaries, summing up the experience of the whole day, might not fit this concept of momentary assessment. Ambulatory assessment (Fahrenberg et al. 2007), in contrast, had strong roots in ambulatory monitoring, the physiological and medical assessment in daily life. However, in our view, all these terms are commonly used to encompass a broad set of tools to assess affective experiences, cognition, behavior, and physiological processes in daily life. Importantly, they share these five key advantages: measurement in real life, real time, within-subjects, in a multimodal and context-dependent manner. In the following, we will use the term “daily life research methods” to refer to this set of methods.

2 The Key Features of Daily Life Research Methods

2.1 *Real Life*

The primary advantage of daily life research methods lies in its capacity for real-life assessment. Symptoms are investigated where they actually occur and affect patients, i.e., in their everyday lives. Daily life research methods therefore make experimental symptom-induction obsolete. In contrast, laboratory studies offer the possibility to test hypotheses under the strictest control in artificial laboratory settings. This may negatively affect ecological, construct, and external validity, accounting for laboratory-to-real life differences (Fahrenberg et al. 2007; Horemans et al. 2005; Wilhelm and Grossman 2010).

While most scientists and clinicians agree that for patients only their daily life is of importance (and not time or experience they undergo in a laboratory), there is disagreement if experimental studies in laboratory settings are valid proxies for real daily life experiences. In simple terms: Do findings from the lab translate into daily life? The most famous example refers to the phenomenon of the office hypertension, sometimes also called “white coat effect.” It is the most impressive example that phenomenology outside and inside the laboratory can differ tremendously. In particular, office hypertension is the observation that a certain percentage of patients do show (strongly) elevated blood pressure when measured in the clinical environment, while their everyday life blood pressure is physiologically harmless. This effect has been replicated in hundreds of studies during the last two decades (Franklin et al. 2013). As a result of this phenomenon, a considerable number of individuals are misdiagnosed every year and unnecessarily medicated. The importance of this effect becomes obvious when considering the prognostic value of blood pressure measurements. For example, Salles et al. (2008) demonstrated the supremacy of ambulatory blood pressure monitoring in predicting cardiovascular morbidity and mortality, while office blood pressure readings did not show any prognostic value in their study (Salles et al. 2008).

This example from internal medicine, demonstrating that laboratory and “clinic” assessments may be influenced by various biases, raises the important question whether studying alcohol intake in daily life would also lead to the detection of systematic misinterpretations or false beliefs which result from studies in artificial settings. In other terms, do studies in patients with alcohol use disorder (AUD) using experimental laboratory or questionnaire-based epidemiological approaches provide us with valid findings transferable to the daily lives of these patients? We raise serious doubts given the numerous distortion effects shown in the literature (Reis 2012).

The Collaborative Research Center TRR265 created to investigate trajectories of losing and regaining control over drug consumption in daily life may serve as an example (Heinz et al. 2020; Spanagel et al. 2024). In a large-scale German project, diary assessments were applied every second day in 746 (291 female/455 male) patients with AUD over a one-year period tracking daily alcohol consumption and

B Fluctuation of alcohol consumption

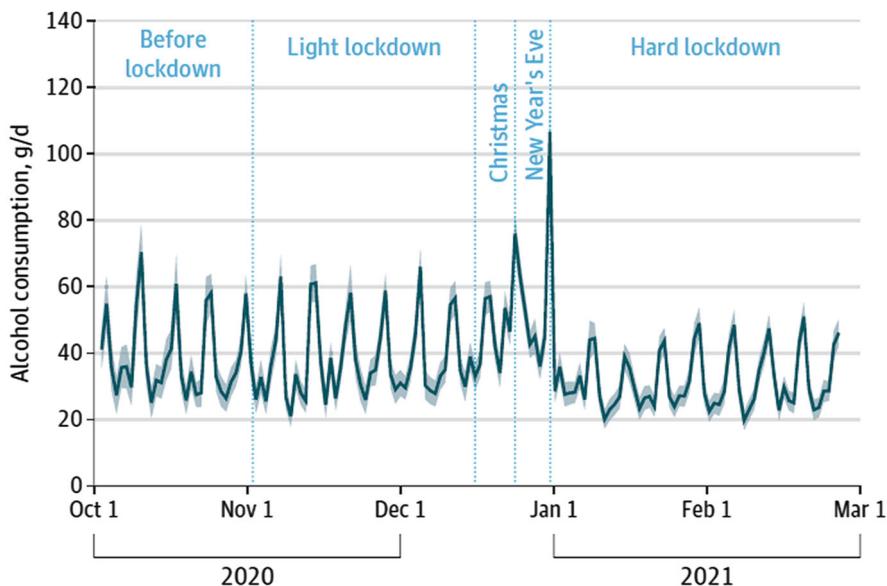


Fig. 1 Assessment of alcohol consumption and its fluctuation across time in the Collaborative Research Center TRR265. Data provided from a subset of 189 participants over a 5-month period. Republished from Deeken et al. 2022, JAMA Netw Open, e2224641. doi: <https://doi.org/10.1001/jamanetworkopen.2022.24641>

identifying behavioral and psychological correlates. As already highlighted by the name of the project “losing and regaining control over drug intake,” one central aim was to monitor increases and decreases of alcohol intake over a 12-month period in patients showing 2 to 10 AUD criteria to identify so-called tipping points of loss of control in substance use (Heinz et al. 2020; Spanagel et al. 2024). Surprisingly, such long-term fluctuations were negligible compared to a very pronounced and consistent pattern of elevated alcohol consumption during weekends compared to weekdays (see Fig. 1). On average, participants consumed 0.81 drinks more on weekend days compared to weekdays. While this might be seen as a trivial effect, we have to highlight that its size is about 15 times as large as effects revealed from individual participant data meta-analysis (Dora et al. 2023). Including individual participant data from 69 studies and more than 12,934 participants, the meta-analysis investigated associations between alcohol consumption and positive/negative affect, revealing 0.04 to 0.07 additional drinks on days with positive mood and no effect on negative mood days. In our view, these findings highlight the need to study our patient population in daily life to know how they behave in their normal habitat and which contextual factors drive their consumption.

Since daily life research evaluates experiences, attitudes, and behaviors as they unfold in natural contexts, daily life research methods data is considered to be

representative and possess construct, ecological, and external validity. However, we view daily life research methods and laboratory methods not at all as fundamentally conflicting options. Instead, we believe that daily life research methods offer a valuable supplementary approach to laboratory studies and in-office assessments by improving the generalizability of findings from controlled laboratory settings to real-world, real-life experiences. Accordingly, combining laboratory and daily life approaches is a key aspect of the before-mentioned TRR 265 (Heinz et al. 2020; Spanagel et al. 2024).

2.2 *Real Time*

Another key feature of daily life research methods is the reduction of the risk of and thus the influence of recall bias (Schwarz 2012). This bias is known to distort retrospective reporting and reconstruction of past events and experiences. Daily life research methods aim to provide a more momentary assessment of the experiences, attitudes, or behaviors of interest than is possible with retrospective self-reports in questionnaires or interview measures. Over the last few decades, many studies compared retrospective reports over, e.g., 2 weeks with momentary or daily reports of consumption (Freeman et al. 2023; Lemmens et al. 1988; Morgenstern et al. 2014). While a discussion of dis/advantages of subjective vs. objective assessments is beyond the scope of this chapter, we assume that it is fair to conclude that overall findings suggest that retrospective reporting methods assessing alcohol and cannabis consumption should not be considered a direct “substitute” for momentary or daily assessments in real life.

2.3 *Within-Subject Dynamics*

One of the features that particularly characterizes daily life research methods is the use of frequent, repeated assessments (Trull and Ebner-Priemer 2013). Through time series analysis and the time resolution provided by multiple measures, it is possible to gain a detailed understanding of dynamic constructs. This enables researchers to investigate dynamics of experiences, within-subject processes, and the interplay between environmental factors, psychopathological symptoms, and personal experiences.

A traditional example motivating a within-subject perspective focusing on dynamical indices, instead of considering mean values or a between-subject perspective, is measuring suicidality. Imagine two patients answering several times a day an electronic diary (e-diary) over the course of a week. Within the past week, both patients reported an identical mean value of suicidality. However, patient A achieves this mean via a stable mean suicidality score, while patient B reports continuously increasing suicidality over the course of the week. Despite identical

mean values, our concern for patient B would be higher as the dynamical process is more alarming. However, probably the most human symptoms are of dynamical nature, fluctuating according to internal and external stressors, demands, and regulation strategies.

A further example and a great overview of complex within-subject dynamics between affect and alcohol use is provided by the meta-analysis of Dora et al. (2023). A wealth of psychological theories hypothesized that people drink alcohol to increase positive emotions and decrease negative emotions (see Dora et al. (2024) for an overview). While experimental studies showed empirical support of the hypothesized relationship, e.g., by manipulating affect in lab settings (Bresin et al. 2018) and monitoring affect changes while drinking (Sayette 2017; Smith 2013), daily life research studies revealed inconclusive findings. Novel statistical approaches enabled most recently to combine data sets and use meta-analytical techniques on individual participant data (IPD). Instead of combining summary statistics of each study, repeated assessments of each participant of all studies can be combined into one global analysis. Applying IPD, Dora et al. (2023) integrated 353,762 days of observations from 12,394 participants across 69 studies to study within-subject processes, researching whether affect predicts alcohol use in everyday life and if those effects are stronger in certain groups of participants. In particular, the authors hypothesized that negative affect should be related to alcohol consumption on a day level, i.e., negative affect should trigger alcohol consumption, and that positive affect should be related to alcohol consumption on a day level, i.e., alcohol consumption results in better affect. Surprisingly, data analyses only confirmed the hypothesis on the positive affect—drinking relation, but did not show an association regarding negative affect. Dora et al. (2023) report in addition that their findings were consistent across multiple operationalizations of affect and subgroups of people with varying average alcohol consumption. While the paper by Dora et al. (2023) is definitely a milestone in within-subject daily life research in alcohol, it has to be critically mentioned that the achieved effect sizes were small, i.e., 0.04 to 0.07 additional drinks on days with high positive affect. In line with Dora's "Agenda for future research," we critically question the focus on day-level analyses. Since both affect and alcohol intake are strongly fluctuating within days and since specific temporal relations are assumed, such as that negative affect may vanish within an hour after starting drinking accompanied by a short to immediate increase in positive affect, within-day analyses might be superior compared to day-level analyses.

2.4 Multimodal Assessment, Including Psychological, Physiological, and Behavioral Data

Another key feature of ambulatory assessment is the possibility to include behavioral and physiological data beyond verbal and subjective reports. The limitations of subjective symptomatology reports are well documented, but the most prominent

example is provided by two meta-analyses from Adamo et al. (2009) and Prince et al. (2008), comparing subjective reports of physical activity to its objective assessment using e.g. acceleration devices or double labeled water methods. In adults, Prince et al. (2008) meta-analyzed 147 studies showing that subjective and objective assessments of physical activity are only weakly related ($r = 0.37$). The follow-up meta-analysis in children and adolescents fully replicated these findings (Prince et al. 2008). Another promising asset of objective assessments, beyond its higher reliability and validity, is the possibility of continuous measurements and ongoing real-time analyses, which can be used to trigger additional assessments (Reichert et al. 2020b), warning e-mails (Mühlbauer et al. 2018), or just-in-time adaptive interventions (JITAIs; Nahum-Shani et al. 2015). While self-reports assessed by daily life research methods are of superior reliability and validity compared to retrospective reports, they still represent a subjective evaluation by the patient. Therefore, it may be advantageous to complement these subjective measures with objective assessments of physiological and/or behavioral data.

Two studies within the TRR265 exemplify the benefits of combining self-reports with other data sources in addiction research. First, Zech et al. (2022) reviewed methodological challenges and opportunities combining cognitive tasks with daily life research data in a mobile assessment environment. They conclude that sampling should combine event-based and time-based trigger and that more frequent assessment leads to more conclusive results but could potentially be a high burden on participants. Field tests of mobile cognitive tasks in the setting of the TRR265 showed that analyzing more than one consecutive real-life assessment drastically improved reliability and mobile task performance can be related to real-life measures of drinking behavior (Zech et al. 2022, 2023). The authors analyzed the reliability and validity of four smartphone-based cognitive tasks in the TRR265 sample, i.e., response inhibition, a working memory, a risk-taking, and an information sampling task (Zech et al. 2022). While split-half reliability was high, test–retest reliability was moderate to good. However, latent variables based on factor loadings further increased test–retest reliability, demonstrating that combining several measures into latent variables is a further useful denoising step (Zech et al. 2023). These important conceptual and methodological considerations need to be further explored to increase ecological validity of cognitive tasks in real-life settings ultimately painting a more accurate picture of behavioral patterns.

Second, combining blood samples from study center visits with daily ESM data, Hoffmann et al. (2024) found that hormone concentration, specifically the progesterone-to-estradiol ratio, predicted reduced binge drinking in natural cycling female participants. Hormone levels were assessed in four in-person visits, where blood samples were taken and questions regarding the natural menstrual cycle were answered. Between assessments, participants reported their drinking behavior daily in real-life ESM assessments. Analyses were carried out using generalized and general linear mixed modeling. Menstrual cycles were associated with both binge drinking and progesterone-to-estradiol levels. In late menstrual phases with a higher predicted marginal mean of progesterone-to-estradiol ratio, binge drinking probability was 13% lower. In male participants, a higher progesterone-to-estradiol ratio

predicted less binge drinking, presenting a promising treatment target. Required ESM data in combination with biological assessments enabled us to unravel the dynamic nature of these biological processes.

2.5 *Investigations of Setting- or Context-Specific Relationships*

Traditional assessment methods, e.g., symptom questionnaires and interviews, are limited in capturing contextual information as the reported symptomatology is assessed and averaged for a particular period of time (e.g., the last week, the last month) and not related to a specific context. In contrast, in ESM both symptoms and contextual information can be repeatedly and simultaneously assessed over time, offering the opportunity to analyze their covariation, i.e., context-sensitive analyses of situational influences on symptomatology.

The most prominent empirical example of the simultaneous assessment of context and symptoms in addiction research is the study by Epstein et al. (2014). The authors aimed to investigate mood and behavior as a function of neighborhood surroundings among individuals with a history of drug misuse, using a combination of geolocation and EMA data. The researchers collected participants' time-stamped geolocation data while simultaneously assessing their mood, stress, and drug cravings over 16 weeks at randomly prompted times during the day. By integrating geographical data with EMA assessments, the study aimed to provide insights into how environmental factors influence the emotional well-being of drug misusers in real time. The results of the neighborhood analysis were completely contrary to the authors' hypotheses, stating that momentary exposure to physical disorder, social disorder, and drug activity would associate with craving, stress, and negative affect. The data showed that higher social disorder in the neighborhood was associated with lower momentary ratings of cocaine craving and that more physical disorder was associated with lower momentary ratings of cocaine craving, heroin craving, negative mood, and stress.

3 The Ambulatory Assessment Toolbox: Integrating Real-Time Analyses and Feedback

The ambulatory assessment toolbox (see Fig. 2) enables us to investigate a wide range of phenomena in daily life, as already highlighted in the previous sections above. For example, assessments comprise traditional e-diary questions, sound and video records, food diaries, cognitive tasks, wearables measuring physiological (electrocardiogram, pre-injection period, transdermal activity, etc.) and behavioral signals, contextual factors assessed by geolocation tracking, and digital phenotyping

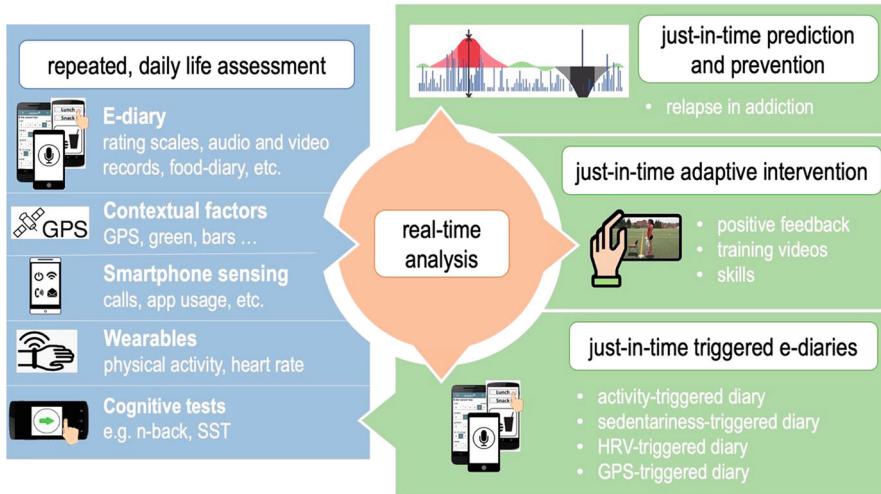


Fig. 2 The ambulatory assessment toolbox, combining the main methodological features, namely, assessment, real-time analyses, prediction and prevention, intervention, and triggered e-diaries. GPS = Global Positioning System; N-back = a specific continuous performance task; SST = Stop Signal Task, a measure of response inhibition

of parameters such as app usage and information on phone calls. For details on mobile sensing, we recommend a recently released handbook specifically devoted to this topic (Mehl et al. 2024). An often-used categorization classifies all these possibilities into passive and active sensing, describing their specific advantages and pitfalls.

Passive mobile sensing enables us to assess and collect important information of a subject's state over time with a high sampling frequency and low participant burden, which is its major advantage. The drawback of this method is that the assessed parameters (e.g., the number of steps per day) are often just raw proxies of the mental health symptoms researchers are usually interested in. Translated to AUD: What can we conclude, if we detect a suddenly altered social interaction pattern in an abstinent patient? May a missing contact to usual interaction partners, and probably the advent of new interaction partners, provide evidence for a new problematic drinking episode? Or is it a proxy for vacation, or for a physical limitation? Many digital phenotypes are unspecific and may not be closely related to the mental health symptoms of interest. To bypass this limitation, additional and important information can be provided by interlacing passive and active digital phenotyping via real-time analyses.

Enhancing passive mobile sensing with e-diary assessments enables us to better interpret findings from passive data collection. One major challenge in e-diary research lies in asking the right question at the right time point. This particularly applies if the events of interest are rare. Asking questions only when necessary might tremendously diminish patient effort and burden. This advantage can perfectly be illustrated by a possible study combining daily life research methods with

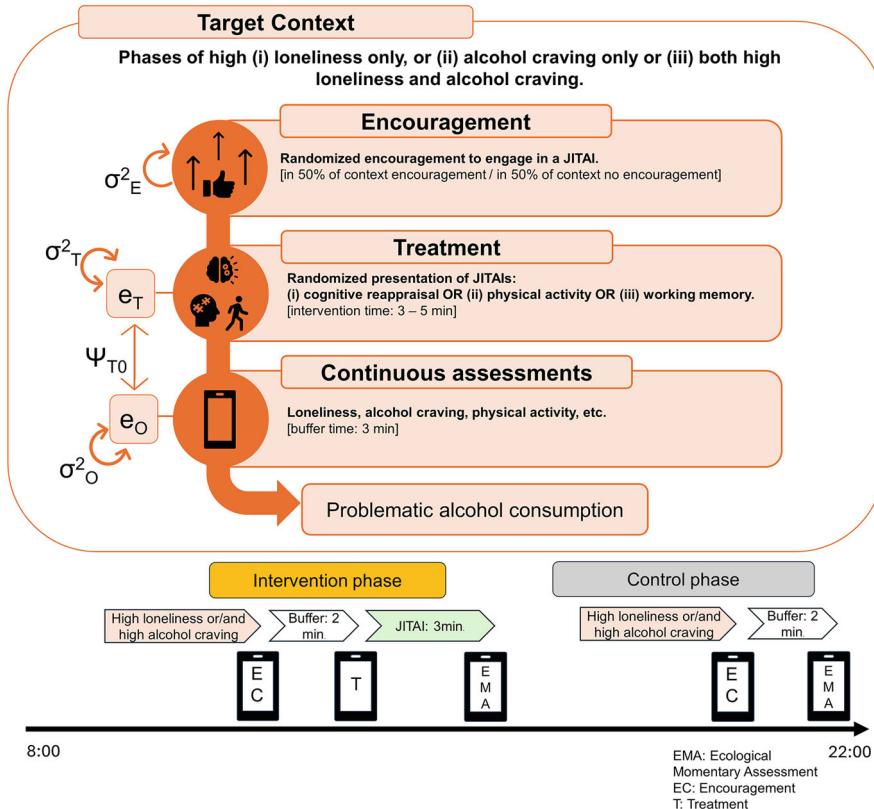


Fig. 3 Within-person-encouragement-design (WPED) in AUD for causality testing (EMA: ecological momentary assessment; T: treatment; EC: encouragement). In an instrumental variable approach and two-level structural equation framework, causal treatment effects can be estimated if a correlation between the encouragement and the treatment exists, and given the theoretical assumption that any encouragement effects on the outcome are fully mediated by the treatment

geolocation assessments. Approaching one's favorite bar can be used as a warning signal, but getting additional e-diary information, such as craving, can help to decide whether approaching the bar is indeed a high-risk situation. This approach is called *triggered diary and is visualized in the mid of Fig. 3 depicting the ambulatory assessment toolbox. In particular, real-time analyses allow us to detect events or processes as they unfold and e-diaries entries add information about related psychological processes or help to clarify the context. The advantages of such triggered e-diaries have been demonstrated in various empirical studies. Examples of triggered e-diaries include activity-triggered e-diaries (Reichert et al. 2016a, b), sedentariness-triggered e-diaries (Giurgiu et al. 2019, 2020), physiology-triggered e-diaries (heart rate: Myrtek et al. 2005; electrodermal activity (EDA): van Haleim et al. 2020; heart rate variability: Verkuil et al. 2016), geolocation-triggered e-diaries

(Epstein et al. 2014; Reichert et al. 2020a, 2021, 2016a), and audio-triggered e-diaries (Wu et al. 2021). These studies have in common that they passively capture situations of interest in real time and in real life, triggering questions only when necessary, significantly reducing patient burden. Most importantly, real-time analyses are the technological precursor of just-in-time adaptive interventions (JITAIs; (Nahum-Shani et al. 2015); see the following section for details.

4 Just-in-Time Adaptive Interventions

Intervening in everyday life to treat alcohol addiction and to intervene on drinking behavior in real-life dynamic settings has been discussed as a promising step in alcohol treatment for more than a decade (Cohn et al. 2011; Fowler et al. 2016; Quanbeck et al. 2014). Recently, researchers started to summarize and evaluate existing mobile interventions, often called ecological momentary interventions (Carpenter et al. 2020; Heron and Smyth 2010) more systematically. The term just-in-time adaptive intervention has been coined (Nahum-Shani et al. 2018) focusing on dynamic triggers of interventions based on real-life processes and adapting to individual circumstances. For example, real-time interventions have been designed to provide support in high-risk situations triggered by geolocation data (Gustafson et al. 2014) and to recommend alternative activities in high-risk situations (Kizakevich et al. 2018). Gustafson et al.'s (2014) empirical evaluation demonstrated that a smartphone application with multiple features can provide significant benefits to patients receiving continuing care for AUD.

Another intervention example is provided by Liu, Reichert, and colleagues within the TRR265, who will apply real-life interventions toward causality testing in everyday life in alcohol research. In general, AA provides researchers with intensive longitudinal data on determinants and consequences of drug consumption and enables us to investigate intra-, interindividual, and reciprocal associations. Since this data is of pure observational character, causality of associations is unknown. For example, craving and loneliness can be modeled as a predictor of alcohol consumption, but vice versa, the influence of alcohol consumption on craving and loneliness can be analyzed. Of note, causal inferences require (1) the variables of interest to be correlated with each other, (2) a temporal order to be given, (3) hidden third variables to be controlled or explained, and (4) resulting in the direction of the effect to be indispensable (Susser 1991). To test causality, experimental designs apply experimental manipulation mostly under laboratory conditions and control of potential hidden influences (Gianicolo et al. 2020). However, to test causality in everyday life, a combination of advantages from laboratory and ambulatory approaches is required to enable both ecological validity and causal inferences. In particular and toward this aim, Liu, Reichert, and colleagues will employ momentary real-life interventions in the context of loneliness and craving (Liu et al. submitted) following a within-person encouragement design (Schmiedek and Neubauer 2020). This design makes use of experimental manipulation in everyday life and mediation analysis within the

framework of combined structural equation and multilevel modeling. It takes an important step toward causality testing using JITAIs and establishes causality in daily life under a set of assumptions that are detailed in Schmiedek and Neubauer (2020). In practice, when participants report high values of craving or loneliness, a randomized encouragement will be sent, to motivate participants to engage in one of three interventions, that is, physical activity, cognitive reappraisal, or working memory (control condition). Continuous assessments will track intervention effects on craving, loneliness, and alcohol consumption. Determinants of acceptance, feasibility, and causal effects of the interventions will be examined. This study aims to further promote and explore the possibilities of using ESM assessments in combination with real-time and real-life interventions.

5 What You Need to Take Care for When Doing Daily Life Research

Daily life studies differ from laboratory and epidemiological studies, especially by their repeated measurements, which comes with additional design questions and challenges. In the following, we will provide guidance on EMA design decisions that have to be made toward study conduct and following previously published recommendations (e.g., Bolger et al. 2003; Mehl et al. 2014; Stone and Shiffman 2002; Trull and Ebner-Priemer 2020).

5.1 Sampling Design

The selection of and rationale for the sampling schedule is of utmost importance in daily life research. The most basic EMA design is an end-of-day assessment, with participants rating their daily aggregated experiences. For instance, they might report overall mood, stress level, or occurrences of specific events (e.g., interpersonal conflicts) or behaviors (e.g., alcohol consumption). Although common, this design is not very suitable for testing prominent addiction theories of interest, especially if they concern momentary experiences and processes. Usually, we aim to collect data from various daily time points, employing random, interval-based, or event-based sampling. Combining these assessment types yields a dynamic picture of processes in daily life. For instance, a researcher may uncover mood before, during, and after substance use by combining assessment schedules. There are further important considerations that may impact the sampling schedule, such as the number of necessary assessments to capture the construct of interest, the length of the study (in days) to capture enough within-subject events, the time frame of the daily assessments, and technical details of the sampling itself. A general recommendation states the need of time-based designs to fit the temporal dynamics of the process of

interest (Bolger et al. 2003; Ebner-Priemer and Sawitzki 2007; Warner 1998). For example, a nearly indiscernible increase of daily alcohol usage might develop over weeks, while a heavy drinking episode at night might be triggered by contextual stimuli (such as social contact), yet momentary craving may fluctuate over minutes or hours. Here, two issues are important to highlight: First, usually a combined protocol is superior to a pure event or time-based protocol, as various processes may be captured (e.g., adding end-of-day questions covering summarized experiences); second, a well-known default in using event-based designs is to forget the control condition (e.g., solely querying mood at drinking episodes yet not at no-drinking events), which may prevent comparisons. According to recent guidelines, researchers are encouraged to not only report on their daily life research designs, but to include the decisions toward the implementation of the design (Trull and Ebner-Priemer 2020).

5.2 Sample Selection and Size

In general, participants in daily life research studies should entail the population characteristics to which the findings will be generalized. We highly recommend to avoid selecting samples for convenience (e.g., undergraduates); instead, researchers may choose samples suitable for meaningful conclusions about relevant psychological theories or mechanisms. It's important to keep in mind that the expected within-subject relation between phenomena of interest (e.g., the temporal relationship between craving and alcohol consumption) statistically depends on the variance in both parameters. In other terms, it's not useful to include participants who do not exhibit craving and alcohol consumption. Often times the bottleneck of studies are data sets of limited quality, e.g., with regard to the time resolution of assessments of interest. Therefore, we want to encourage researchers to report basic descriptives on the variables of interest, e.g., the (mean and medium) number of drinks in a given population, the intra-class correlation coefficients of within-subject variables (such as stress and mood ratings), and to be careful when attempting to generalize to populations which differ from the own sample.

Similar to laboratory research approaches, sample size selection for daily life research methods should be based on a priori statistical power analysis. Fortunately, software tools for statistical power analyses for multilevel models exist nowadays (Lafit et al. 2021), but they depend on many unknown assumptions (e.g., random slopes, covariance structure, distribution of the outcome). In addition, there are recommendations for the minimal number of level 2 units suggested for classical multilevel models ($n = 60$) (Bolger et al. 2012) and methodological papers based on Monte-Carlo simulations that offer “rules of thumb” for a variety of classical two-level models (Arend and Schäfer 2019).

5.3 Items and Their Psychometric Properties

Previous guidelines (e.g., Shrout and Lane 2012; Stone and Shiffman 2002; Trull and Ebner-Priemer 2020) have emphasized the importance of reporting psychometric properties of items and scales used in e-diary studies. Unfortunately, relatively few self-report measures have been validated across e-diary studies and samples; instead, researchers often select items from a larger cross-sectional questionnaire and adapt the instructions to fit the desired time frame (e.g., “over the last 15 minutes”). It appears that the reliability and validity of e-diary items are assumed but not evaluated or reported. For purposes of reliability and validity within the e-diary framework, it is recommended that complex constructs are assessed with at least three items, while discrete phenomena or behavior may be assessed with a single item (Shrout and Lane 2012). Furthermore, procedures for evaluating the psychometric properties of scales used in e-diary research have been published, for reliability measures both within-subjects (i.e., across time) and between-subjects (Geldhof et al. 2014; Shrout and Lane 2012), as well as reliability of change scores within-subjects (Cranford et al. 2006).

5.4 Compliance and Reactivity

Given that research using daily life methods seeks to provide a window into the real lives of participants, nonresponse to surveys (or failure to wear sensors) will challenge the ability to generalize findings to participants’ typical daily life experiences. Beyond, compliance critically affects lagged analyses. For example, the research question whether craving precedes alcohol consumption would demand such a lagged analysis, where the previous time point (t_{-1}) is a lag of the current time point (t_0). This procedure enables us to investigate how previous craving is (statistically) related to current alcohol consumption. Here, one missing data point will disable two lagged analyses; i.e., in a worst-case scenario 20% of missing data will result in 40% missing values in the lagged analysis. Accordingly, it is important for researchers to define compliance and lack of compliance, to report (mean) compliance for each type of assessment per participant and compliance across participants. Furthermore, it is important to describe the thresholds for compliance necessary to be included in the analysis, to compare compliance rates for groups of participants, and to examine data for systematic influences on compliance rates. Fortunately, compliance is substantially enhanced if participants are trained in study procedures, use of the smartphones or software, and proper wearing of external devices and sensors. In addition, monetary compensation can uplift compliance, and, in our view, it is of utmost importance to explain to participants why a high compliance is needed. Quantitative reviews tried to extract features which drive compliance (Ottenstein and Werner 2022; Wrzus and Neubauer 2023), but they may come with bias since studies with “bad” compliance may remain unpublished.

Reactivity, i.e., the phenomenon of repeated assessment to alter the everyday life behavior itself, has been investigated empirically by studies randomly assigning the frequency of assessments per day, assuming a linear effect from having 1 to 3 to 6 to 12 assessments per day. Overall, those e-diary studies (Conner and Reid 2012; Coppersmith et al. 2022; Stone et al. 2003) do not support reactivity effects; i.e., they provide no evidence that the assessments itself alter humans' behavior. However, studies investigating physical activity via wearables do show reactivity effects, at least for the first week (Clemes et al. 2008; Clemes and Deans 2012).

Assessment of everyday life behavior like alcohol consumption naturally comes with the limitation of a potential self-report bias. One can argue that alcohol and substance use in particular are attached with a large stigma, inducing shame and motivating to downplay severity of related symptoms. A large body of literature provides evidence for a higher accuracy of momentarily assessed alcohol consumption compared to retrospective recall methods and high correlations to biological assessment methods (Del Boca and Darkes 2003; Dulin et al. 2017; Shiffman 2009). A possible objective assessment of alcohol intake could be provided by assessing transdermal alcohol concentration (TAC) measured by wearable transdermal sensors. Despite being a promising assessment method, the accuracy and validity of TAC sensors are not yet sufficiently examined (Brobbin et al. 2022) and implementation can be costly and therefore limit the potential sample size and duration of a study. Validation studies provide evidence of strong associations between TAC measured alcohol consumption and self-report in experience sampling (Russell et al. 2022; Simons et al. 2015). For a subsequent research period in the TRR265, objective and self-report measures of alcohol consumption are being combined to examine the validity of alcohol consumption assessment methods on a larger scale.

6 Future Outlook/What Can We Expect

Real-life research shows many advantages, as outlined above. However, one could argue that there are two types of daily life research methods, both showing tremendous disadvantages. That is, e-diaries provide subjective assessments, which may be a specific challenge to alcohol research, they are not without burden, and they can't measure symptomatology and behavior continuously (Kuntsche et al. 2023). Digital phenotyping parameters, on the other hand, show low validity (Ebner-Priemer et al. 2020) being only weakly correlated to the symptomatology and behavior of interest. For example, a geolocation data may be intersected with information on the amount of bars surrounding a participant at a given moment, yet it does not tell us anything about actual drinking behavior. Maybe, the participant is just working in the office above the bar or visits the office of an alcoholics anonymous group, located in this district.

Measures providing both continuous objective measurement and high validity (Wadle and Ebner-Priemer 2023) are on the cutting edge of recent daily life research. In principle, audio features reveal linguistic and paralinguistic information. For

example, patients may talk about alcohol, they may arrange happy hour drinking in a bar, and their voice may entail incidences of stress or craving. Audio recordings in daily life might track this. However, automated audio recordings are highly protected by law, e.g., in Germany specified in the General Data Protection Regulation (GDPR; Datenschutz-Grundverordnung) and the Telecommunications Act (Telekommunikationsgesetz). Real-time data processing of audio data may enable us to comply with the GDPR concurrently enabling us to extract valuable audio features for research in AUD, by neither storing raw audio data nor speech content. One example where tremendous progress in this area has been made is the Google audio set (Gemmeke et al. 2017), a large-scale dataset of 2,084,320 manually annotated and human-labeled 10-s sound clips using a structured hierarchical ontology of 632 audio event classes, covering, e.g., human sounds (speech, screaming, whispering, etc.) and acoustic environment (inside, public space, outside, etc.). Closely linked to the data set is VGGish, a pre-trained convolutional neural network from Google, which generates 128-dimensional features, which can't be back-translated to audio content or speaker identification, but are linked to the audio event classes. A similar case can be made for "screenomics," a research method taking screenshots from smartphones every 5 s, therewith violating all imaginable privacy issues, but providing valid proxies for participants' behavior, feelings, and cognitions (Reeves et al. 2020).

In conclusion, the digital mobile revolution has catapulted daily life research methods into the mainstream of alcohol research, enabling us to not only capture repeated real-life self-reports on alcohol consumption and its correlates, but also to assess digital phenotypes via wearable outputs and real-time analyses. In future, smart digital phenotypes, i.e., features extracted from an audio stream in real time using machine learning techniques, without storage of raw data thus ensuring privacy and anonymity of third parties may provide researchers with an additional layer to the real-life toolbox providing high reliability, low patient burden, and high validity. These tools will not only allow researchers and clinicians to better understand what patients are experiencing in their daily lives, but will also enable them to implement prediction, prevention, and intervention onto patients' smartphones. Given the advantages of daily life research methods in combination with rapid developments in mobile digital technologies, the field is evolving rapidly.

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The Dopamine System in Mediating Alcohol Effects in Humans



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Abstract Brain-imaging studies show that the development and maintenance of alcohol use disorder (AUD) is determined by a complex interaction of different neurotransmitter systems and multiple psychological factors. In this context, the dopaminergic reinforcement system appears to be of fundamental importance. We focus on the excitatory and depressant effects of acute versus chronic alcohol intake and its impact on dopaminergic neurotransmission. Furthermore, we describe alterations in dopaminergic neurotransmission as associated with symptoms of alcohol dependence. We specifically focus on neuroadaptations to chronic alcohol consumption and their effect on central processing of alcohol-associated and reward-related stimuli. Altered reward processing, complex conditioning processes, impaired reinforcement learning, and increased salience attribution to alcohol-associated stimuli enable alcohol cues to drive alcohol seeking and consumption. Finally, we will discuss how the neurobiological and neurochemical mechanisms of

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alcohol-associated alterations in reward processing and learning can interact with stress, cognition, and emotion processing.

Keywords Acute alcohol effects · Chronic alcohol effects · Cue-reactivity · Dopamine · Imaging · Reward system

Abbreviations

5-HT	Serotonin
ACC	Anterior cingulate cortex
AMPA	a-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors
BAC	Blood alcohol concentration
BOLD	Blood oxygen level dependent response
CNS	Central nervous system
CS	Pavlovian conditioned stimulus
DA	Dopamine
DALYs	Disability-adjusted life years
DLPFC	Dorsolateral prefrontal cortex
DRD1	Dopamine D1 receptor
DRD2	Dopamine D2 receptor
DRD3	Dopamine D3 receptor
DTI	Diffusion tensor imaging
EEG	Electroencephalography
EtOH	Ethanol
F-DOPA	[18F]Fluoro-L-dopa
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
IAPS	International Affective Picture System
LTP	Long-term potentiation
MPFC	Medial prefrontal cortex
NAc	Nucleus accumbens
NMDA	N-methyl-D-aspartate
OFC	Orbitofrontal cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
PIT	Pavlovian-to-instrumental-transfer
SNP	Single nucleotide polymorphism
SPECT	Single photon emission computed tomography
SPM	Statistical parametric mapping
SSRI	Selective serotonin reuptake inhibitors
T1	T1-weighted magnetic resonance sequence
VTA	Ventral tegmental area
WM	Working memory

1 Introduction

In animal and human research, it has been well described that an increase in dopamine release is prominent in the rewarding and positive reinforcing effects of drugs of abuse (Hansson et al. 2019; Heinz 2000; Heinz et al. 2009; Koob 1992; Tapert et al. 2004; Wise and Rompre 1989). In a pioneering study, Olds and Milner (1954) showed that rats, which accidentally had electrodes implemented into their septal area instead of formatio reticularis, would excessively stimulate their basolimbic area and even ignore hunger until complete exhaustion (Olds and Milner 1954). In 1963, Heath described two human patients under self-stimulation treatment, which stimulated regions of the brain at a high frequency (Bishop et al. 1963; Heath 1963): they chose one out of multiple electrodes that specifically stimulated the corresponding septal area and described the feeling as “building up to a sexual orgasm.” Since the activated neurocircuits included dopaminergic projections, these findings initiated investigations of the dopaminergic “reward” system, which explored how dopamine-associated reinforcement establishes persisting habits (Birbaumer and Schmidt 2003; Wise 2002; for a recent review, see Wise and Robble 2020).

Intensive research identified various neurotransmitter systems participating in the development and maintenance of increased and chronic alcohol intake in humans, e.g. dopaminergic (DA), serotonergic (5-HT), opioidergic, and glutamatergic neurotransmission (Heinz et al. 2008, 2009; Koob and Volkow 2016; Mann 2004; Nutt et al. 2015; Oscar-Berman and Bowirrat 2005). The mesocorticolimbic DA circuitry emerged to be of central importance, since alcohol and other drugs of abuse release DA in the striatum, which promote drug-seeking behavior and consecutive intake. Rodent studies showed that in comparison to primary or secondary reinforcers like food, sleep, sex, or money, the effect of drugs on DA release does not appear to habituate (Di Chiara and Bassareo 2007). Presumably, this is caused by the drugs’ unphysiologically strong and non-habituating, direct pharmacological activation of dopaminergic stimulation compared to primary rewards necessary for survival (Heinz 2017; Wise and Rompre 1989). It is, therefore, assumed that addictive drugs also “hijack” the human reward system, which preferentially responds to drug-associated reinforcement at the expense of non-drug reward (Gardner 2005; Luijten et al. 2017).

According to the “Global Status Report on Alcohol and Health” by the World Health Organization (WHO), 3.7% of the residents of the European Union and 7.7% of the United States of America meet the diagnostic criteria for alcohol dependence with worldwide 3 million deaths every year resulting from harmful alcohol use. Overall, 5.1% of the global burden of disease and injury as measured in disability-adjusted life years (DALYs) are attributable to alcohol use disorder (WHO 2018). To address alcohol-specific processes, which contribute to the development of alcohol dependence, chronic alcohol effects on the human body and the brain need to be distinguished from effects associated with acute and intermittent alcohol use.

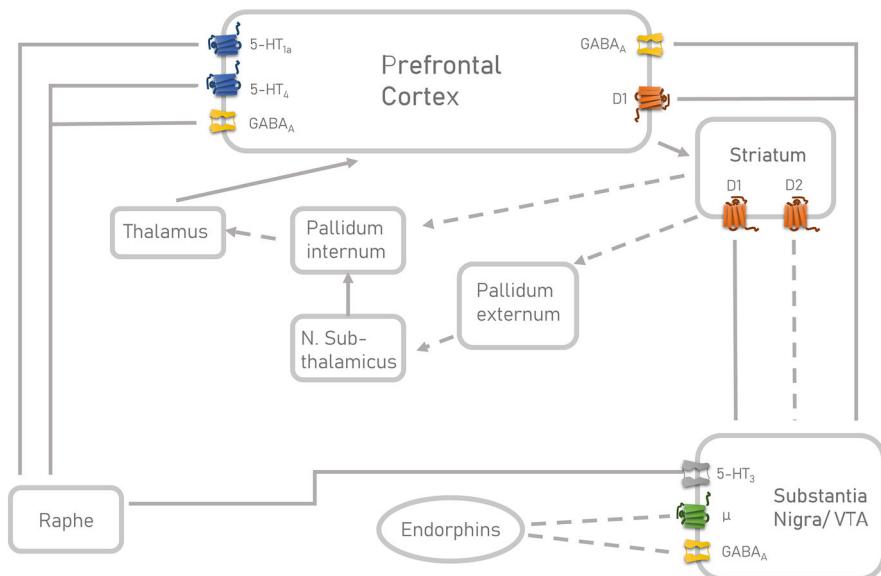


Fig. 1 Interaction of primary neurotransmitter systems involved in the acute initiation of alcohol intake. Inhibitory effects [via D₂ receptors (DRD₂) on the target cells (e.g., in the striatum) mediating GABAergic transmission] are symbolized by dotted lines and excitatory effects [via D₁ receptors (DRD₁) on the target cells (e.g., in the striatum) mediating glutamatergic transmission] by solid lines (modified according to Heinz et al. 2009). DRD₁ dopamine D₁ receptor, DRD₂ dopamine D₂ receptor, GABA gamma-aminobutyric acid

The major components of the dopaminergic mesocorticolimbic circuit consist of dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra to the ventral striatum including the nucleus accumbens (NAc), the amygdala, olfactory tubercle, and frontal and limbic cortices (for an extensive review, see Ikemoto 2007; Haber and Knutson 2010; Sesack and Grace 2010). Key limbic projections to the NAc include inputs from the (pre)frontal cortex, amygdala, and hippocampus. Thus, limbic information received by the NAc can be projected to neurocircuits contributing to motivated behavior via pallido-thalamic and thalamocortical projections (Koob 1992); (see Fig. 1). The integrity of these specific pathways is crucial to provide an adequate response to internal and external stimuli and to govern attention and intentions related to a particular stimulus. Referring to rodent brain structures, the NAc consists of two distinguishable regions: the core and the shell, which are innervated by DA neurons arising from the VTA (Di Chiara 2002; Uhart and Wand 2008). Transferred to the human brain this refers to the lateral-rostral (putative core) and medial-caudal (putative shell) subdivisions of the NAc as the core region of the ventral striatum (Baliki et al. 2013). While the ventral striatum appears to be involved in motivated behavior and the attribution of incentive salience to novel, reward-associated cues, the dorsal striatum plays a major role in habit formation (Robinson and Berridge 1993). Interestingly, when comparing

passive vs. active alcohol administration (external vs. self-administration) in rodents, both produced a similar increase in dopamine in both NAc subdivisions. In contrast, passive sucrose administration elicited an increase in dopamine in both NAc components, while sucrose self-administration stimulated dopamine release exclusively in the shell (Bassareo et al. 2017). The authors hypothesize that during instrumental responding (i.e., self-administration) for sucrose, major adaptive mechanisms are activated to prevent the expression of changes (e.g., increase of NAc core DA) inappropriate for correct goal-directed action, which is not true for ethanol administration.

1.1 Acute Alcohol Effects on Dopaminergic Neurotransmission

During alcohol consumption, alcohol passes through the esophagus into the stomach. There, about 20% of the consumed alcohol is absorbed by the gastric mucosa and delivered directly into the bloodstream. The remaining 80% enter blood circulation through the small intestine mucosa membrane. Through this particular pathway, ethanol (EtOH) is distributed throughout the human body within seconds and overcomes the blood–brain barrier due to EtOH liposoluble properties (Lindenmeyer 2001). In the brain, several neurotransmitter systems interact in a complex manner (Fig. 1): It has been shown that both the opioidergic and the DA neurotransmitter systems are involved in the rewarding effects caused by EtOH. It has been originally hypothesized by Wise (1982) that drug and alcohol-induced DA release mediates the hedonic feeling associated with drug-induced reward (Di Chiara 2002; Wise 1982, 1996). However, this hypothesis has not been supported via pharmacological blockade of DA transmission. The results of DA blockage studies in both animals and humans resulted in (motivational) apathy rather than anhedonia. Therefore, DA has been attributed a role in response-eliciting, but not in hedonic properties (“wanting” instead of “liking”) (Boileau et al. 2003; Di Chiara 2002; Heinz et al. 1998, 2009; Samaha et al. 2021).

Robinson and Berridge (1993) suggested that “liking” refers to the experience of pleasure, which is controlled by opioidergic and also potentially endocannabinoid and gamma-aminobutyric acid (GABA)-benzodiazepine neurotransmitter systems. Here, Berridge and Kringelbach (2015) suggest a “common currency” reward network, since many diverse rewards activate a shared or overlapping brain system: food, music, sex/interpersonal proximity, and addictive drugs. One hedonic hotspot (causally enhancing “liking” reactions) for opioidergic enhancement was located in the NAc (Berridge and Kringelbach 2008, 2015; Berridge et al. 2009; Pecina and Berridge 2005; Robinson and Berridge 1993). Beyond opioidergic signals, endocannabinoidergic stimulation in an overlapping subregion of NAc medial shell similarly enhanced “liking” reactions to sucrose, while not altering “disliking” of a bitter solution (Mahler et al. 2007). This anatomical overlap between opioid and

endocannabinoid hedonic hotspots in NAc suggests that the same brain region might mediate both neurotransmitter forms of pleasure enhancement. Animal and human studies showed that alcohol stimulates endorphins, which act on mu-opiate receptors in the NAc and also stimulate DA release in the same brain area via indirect effects on GABAergic neurons (de Waele et al. 1994; Ramchandani et al. 2011; Spanagel et al. 1992). In detoxified alcohol-dependent patients, an increase of mu-opiate receptors can be found in the ventral striatum and medial prefrontal cortex (PFC), which was correlated to alcohol craving (Heinz et al. 2005a).

The other component of reward, “*wanting*” or “*craving*,” has been associated with the attribution of incentive salience to the drug of abuse and to drug-associated stimuli – importantly to be differentiated from conscious wanting or “desires” (Berridge and Kringlebach 2015). This results in a type of incentive motivation that promotes direct approach toward reward-related stimuli and consumption of rewards and does not require elaborate cognitive expectations (Berridge et al. 2009; Berridge and Kringlebach 2015). *Wanting* is assumed to be correlated with (phasic) cue-dependent DA release in the ventral striatum. Here, the work of Schultz et al. (1997) is of fundamental importance, which elucidated the role of DA neurons in mediating reward processing and reward-dependent learning. In a crucial experiment, monkeys received oral administration of an unexpected salient reward, i.e., fruit juice, which elicited immediate DA-bursts in VTA dopaminergic neurons (Schultz et al. 1997). Schultz et al. (1997) showed that these phasic activations are not specific to different types of rewarding stimuli; DA neurons react similarly to different kinds of appetitive stimuli and are also activated by novel stimuli that elicit orientating behavior. Phasic changes in the DA discharge can also be seen when reward is predicted via a Pavlovian conditioned stimulus (CS): bursts of dopaminergic firing followed directly after the presentation of a CS, which predicted upcoming reward. It has been proposed that this CS DA firing is related to associative reward-learning as well as action bias associated with incentive salience (McClure et al. 2003). On the other hand, neural DA responses fail to appear at the moment of a fully predicted reward-experience because they appear only if a prediction error occurs; i.e., if the received reward is larger than expected. If a predicted reward is not received, DA neurons firing is reduced (Schultz et al. 1997). Therefore, the DA neurotransmitter system functions as a signaling network registering the occurrence of salient stimuli and the unexpected absence of reward, i.e., the so-called prediction errors (Schultz 2016). However, DA in the NAc does not only code the salience, it also reflects the value of a potential reinforcer (Lak et al. 2016; Tobler et al. 2005). It has been suggested that reward-associated, stimulus-dependent DA release may be specifically vulnerable to sensitization, i.e. a stronger neuronal and behavioral response upon re-exposure to the pharmacological effects of repeated administration of dopaminergic drugs (Heinz et al. 2004a; Robinson and Berridge 1993). Interestingly, comparing social drinkers with alcohol-dependent patients, Yoder et al. (2016) showed that intravenous alcohol ingestion increased ventral striatal DA release in the alcohol-dependent group only. This might be a manifestation of the higher reinforcing value of alcohol in a population with alcohol addiction. Altogether DA enhancing and endorphin-stimulating effects of acute

alcohol intake can promote both the described hedonic response and a motivational response and may facilitate learning of motivational reactions to drugs and drug-associated stimuli.

In drug-susceptible individuals, neural sensitization of incentive salience by drugs of abuse like alcohol may result in compulsive “wanting,” which leads to consecutive drug intake. This can happen regardless of whether or not the drugs are “liked,” and thus contribute to the development of addiction (Berridge et al. 2009). Nevertheless, DA involvement in incentive salience also affects processing of aversive stimuli. In the NAc, DA and glutamate interactions have been associated with fearful experiences common in both appetitive and fearful behaviors. That points to multiple functional modes of these substrates, depending on specific external and internal factors (Berridge et al. 2009). Specifically, de Jong et al. (2019) showed that a certain subtype of mesolimbic dopamine neurons is involved in the encoding of aversion-predicting stimuli. They observed that in rodents, DA terminals in ventral NAc medial shell are excited by aversive stimuli, while DA terminals in all other NAc subregions are inhibited by aversive stimuli. Indeed, with distinct functionality, there is accumulating evidence for the heterogeneity of VTA DA neurons (Lammel et al. 2012; for a review, see Juarez and Han 2016). Multidisciplinary experiments in mice have indicated distinct feedback loops within the mesolimbic DA system (Yang et al. 2018). Medium spiny neurons in the medial NAc with D1 receptors inhibit activation of two subtypes of DA neurons in different parts of the VTA via GABA_A and GABA_B receptor classes. In contrast, D1 neuron populations in the lateral NAc project to VTA GABA neurons, which disinhibit (indirectly via local GABAergic neurons) DA neurons that synapse onto lateral NAc neurons. In light of the crucial role of disinhibition of VTA GABA neurons on DA neurons coding reward-related firing, only activation of this lateral NAc feedback loop reinforced self-stimulation in the experimental animals.

Complementary effects of EtOH have been documented in the past: while DA (and noradrenergic) mechanisms, along with the endogenous opioid systems of the brain, seem to be implicated in the rewarding effects of EtOH via activation of positive reinforcement pathways, the 5-HT system seems to be associated with the mediation of negative reinforcement (Heinz et al. 2001; Nevo and Hamon 1995; Valenzuela 1997) and 5-HT dysfunction is also associated with anxiety and depression in alcoholism (Heinz et al. 1998).

1.2 Excitatory and Depressant Acute Alcohol Effects on Dopamine and Related Neurotransmitter Systems and Behavior

1.2.1 Excitatory Effects of Alcohol

EtOH has different pharmacological effects on the central nervous system (CNS). In humans, an excitatory effect occurs before the depressant properties ensue with

further ingestion of alcohol. It was shown with low doses of alcohol, that one can observe physiological excitation, which is correlated with improved performance on motor, cognitive, and information-processing tests (Pohorecky 1977).

Findings from animal self-stimulation studies using doses of EtOH between 0.2 g and 2 g/kg suggest an activation of DA neurons and other catecholamines (Carlson and Lydic 1976; Ollat et al. 1988; Pohorecky 1977). Investigations using more specific synthetic DA agonists and antagonists have revealed that DA D₁ receptor (DRD₁) and DA D₂/D₃ receptors (DRD₂/DRD₃) are implicated in the increased EtOH-induced locomotor activity at lower doses (Cohen et al. 1997).

Several studies indicate increased striatal DA release following ethanol administration in humans (Aalto et al. 2015; Urban et al. 2010; Boileau et al. 2003). This effect was limited to male participants in one study and may indicate gender-specific effects of alcohol on DA neurotransmission (Urban et al. 2010). In contrast to studies that use two separate PET scan sessions to compare acute ethanol with a bolus infusion, Aalto et al. (2015) employed a single-scan design to assess the transient effects of ethanol infusions. Comparing baseline and ethanol intervention, a significant decrease in [11C]raclopride binding in the ventral striatum was found. The binding potential in limbic regions correlated with the onset of subjective effects as well as pleasurable feelings.

In an early experiment to assess the conscious experience of EtOH-stimulating effects, Williams (1966) asked volunteers to rate anxiety and depression at pre-arranged cocktail parties. It was observed that negative affective states decreased significantly with low levels of EtOH consumption (Williams 1966). Other behavioral studies reported increased talkativeness, feelings of elation and happiness, euphoria, relaxation and stress-reducing, anxiolytic effects as a result of alcohol intake (Ekman et al. 1963, 1964; Gilman et al. 2008).

Additional studies found that subjects expect alcohol to increase their sociability. After consuming EtOH, individuals reported positive feelings like being “alert,” “quick-witted,” and “attentive.” The amount of alcohol intake correlated positively with the alcohol expectancy factor termed “sociability” (Duka et al. 1998). Further, sociability-related alcohol expectancies were associated with sociability-related self-concept ratings when participants were exposed to alcohol primes (i.e., pictures or words associated with alcohol), but not when participants were exposed to neutral primes (Hicks et al. 2009). Individuals who experience greater stimulant-like effects from an acute alcohol dose reported greater drug-liking and elation, as well as greater behavioral preference for EtOH (over placebo) compared to individuals who experience mostly sedative-like effects of EtOH (de Wit et al. 1987, 1989).

In a study by Holdstock et al. (2000), healthy subjects consumed either a beverage with ethanol (0.2, 0.4, or 0.8 g/kg) or a placebo in a randomized and double-blinded conditioned manner for a total of four laboratory sessions. Subjects who were classified as habitual, moderate, or heavy EtOH users (consumption of ≥ 8 drinks/week with frequent binge episodes) displayed greater stimulant-like effects of alcohol compared to light drinkers. This is consistent with the idea of Newlin and Thomson (1990, 1999) who suggested that individuals who experience greater stimulant-like effects during the ascending limb and reduced sedative-like effects

on the descending limb of blood alcohol concentration (BAC) curve may be at greater risk for an increased alcohol intake and alcohol-associated problems (Holdstock et al. 2000; Newlin and Thomson 1990, 1999). Accordingly, alcohol-dependent individuals given a low dose of alcohol reported more stimulant effects than social drinkers, and individuals with a positive family history of alcoholism reported a greater initial response to alcohol challenge compared to subjects with a negative family history of alcohol addiction (Crabbe et al. 2010). The issue of (ethanol) reward in addiction and how to measure drug reward sensitivity (e.g., effects of drugs) in humans and animals has been critically reviewed (e.g., by Green et al. 2019; Plawecki et al. 2019; Stephens et al. 2010). From a methodological point of view, Plawecki and colleagues showed that the route of alcohol administration (intravenous alcohol infusion vs ingested dose of alcohol) only has a minimal effect on subjective responses to alcohol when breath alcohol concentration profiles are similar (Plawecki et al. 2019). Green et al. showed that alcohol craving (assessed in an intravenous alcohol challenge) was more predictive for the subsequent self-administration than measures of subjective alcohol-induced stimulation (measured via Biphasic Alcohol Effects Scale) per se (Green et al. 2019). A major feature of the allostatic dysregulation theory is a shift from reward-seeking to a negative affective state during protracted alcohol withdrawal, which has, however, been modeled best in rats thus far (Bickel et al. 2019; Koob 2014).

Stimulating effects of EtOH are thought to have a direct effect on DA neurons (Carlsson et al. 1974) and may primarily contribute to the motivation for further drug intake. The hedonic effects of alcohol, on the other hand, have been associated with the activation of mu-opiate receptors and can be blocked by naltrexone (Volpicelli et al. 1995).

The stimulating effect of EtOH appears to be modulated by the interaction of DA and 5-HT neurotransmission. 5-HT function is affected by alcohol and influences the mesolimbic DA reward system (Heinz et al. 2001, 2004a; LeMarquand et al. 1994a, b; van Erp and Miczek 2007). For example, acute EtOH can facilitate 5-HT reuptake in the hippocampus and decrease 5-HT_{1A} receptor functioning in the cortex (LeMarquand et al. 1994a). First studies with 5-HT uptake inhibitors, i.e., zimeldine, citalopram, viqualine, and fluoxetine, suggested some reduction of alcohol consumption in male subjects who are classified as moderate social drinkers (Gorelick 1989; LeMarquand et al. 1994b). However, these observed effects were of transient nature (see review by Kiefer and Mann 2005) and data from studies of selective serotonin reuptake inhibitors (SSRIs) in alcohol dependence are altogether not convincing: a meta-analysis by Garbutt et al. (1999) does not support SSRIs in the treatment of alcohol dependence. Regarding comorbidity of AUD and depression, presence of depressive disorders only worsens alcohol-related outcomes if it persists over longer time periods (Hartka et al. 1991). Even though there is some evidence that SSRIs might have a positive effects on affective symptoms and hence on the course of AUD (e.g., Kranzler et al. 2012; Pettinati et al. 2010), effect sizes of medication are small (Nunes and Levin 2004) and withdrawal symptoms can occur when ceasing SSRI intake (Henssler et al. 2019). With respect to disposition, the genetic architecture of AUD and major depressive disorder appears to be intertwined

in complex ways (Foo et al. 2018), and stress-dependent alterations of serotonergic neurotransmission were associated with both negative mood states and aggressive behavior in patients with alcohol use disorders (Heinz et al. 2011).

5-HT dysfunction was also associated with a low response to alcohol intake, which predicts the development of alcohol use disorders (Heinz et al. 2001; Hinckers et al. 2006; Schuckit and Smith 2000). Furthermore, chronic alcohol intake may exert neurotoxic effects on the 5-HT system. Depending on an individual's vulnerability, these neurotoxic effects may result in loss of central 5-HT function and give rise to negative mood states, such as anxiety and depression (Heinz et al. 1998).

As the World Health Organization (2007) stated, alcohol, compared to all other psychoactive substances, is arguably the most potent agent for eliciting aggression and reducing behavioral control (WHO 2007). A meta-analysis by Bushman and Cooper (1990) revealed that acute alcohol consumption does indeed facilitate aggressive behavior (Bushman and Cooper 1990; Hoaken and Stewart 2003; Rossow and Bye 2013). Most animal models combine early stress experiences, which can profoundly alter monoaminergic neurotransmission, with neurobiological investigations (Heinz et al. 2011). 5-HT modulates aggressive behavior via its effects on negative mood states in interaction with other neurotransmitters, of which corticolimbic DA continues to be of interest for its critical role in integrating motivational and motor functions (Heinz et al. 2001, 2003, 2011; Knutson et al. 1998; Robbins et al. 1989). It was shown by Ase et al. (2000) that the main 5-HT influence on accumbal DA neurons originates in the dorsal raphe nucleus (Ase et al. 2000), which has also been implicated in the regulation of alcohol self-administration (Yoshimoto and McBride 1992). As a result of these observations, animal experiments investigated the activity of accumbal DA and 5-HT during the phases of initiation, execution, and termination of alcohol drinking and observed interactions between DA activation and aggressive behavior (van Erp and Miczek 2007). DA is released during aggressive behavior and the NAc circuitry has been implicated in some forms of aggression (Heinz et al. 2011; Golden and Shaham 2018).

In human behavioral experiments, such as the Taylor Aggression Paradigm, where electric shocks are received from and administered to a fictitious opponent during a competitive task, acute alcohol intoxication in male social drinkers increases aggressive behavior at a BAC of 0.08% (Giancola and Zeichner 1997). Hereby it is assumed that an amygdala-mediated differentiation between threatening and non-threatening stimuli is disrupted during acute alcohol intoxication. Thus, the amygdala and other related neuronal networks may be less likely to correctly identify threatening stimuli. This may trigger an increase in approach and aggression in some individuals (Gilman et al. 2008). It was suggested that negative mood states can be facilitated by early stress and trauma exposure and contribute to aggressive behavior by facilitating limbic (amygdala) processing of aversive and threatening stimuli in serotonin-reduced neuronal states (Heinz et al. 2001).

1.2.2 Depressant Effects of Alcohol

Besides the excitatory effect of alcohol, EtOH can also act pharmacologically as a depressant of neuronal activity. As the dose of alcohol increases, *sedative effects* should become greater than stimulatory effects (Martin et al. 1993). Thus, when blood alcohol levels are declining (i.e., the descending limb of intoxication), alcohol's effects are largely sedative and unpleasant (Ray et al. 2009). These unpleasant feelings can be subjectively experienced as a hangover, exhaustion, and depression, or may even cause vomiting (Nagoshi and Wilson 1989).

There is a broad individual variability in the phenomenology of EtOH response (de Wit et al. 1989; Duka et al. 1998; Holdstock et al. 2000), and, stronger subjective experiences of the sedative and unpleasant effects of alcohol have been associated with decreased alcohol consumption (Ray et al. 2009; Schuckit and Smith 1996), leading to the low level of response hypothesis (LLR) that indicates that individuals that are less sensitive to the effects of alcohol are at greater risk for developing alcohol abuse problems (Schuckit and Smith 2000). However, as discussed above and taking into account Newlin and Thomson (1990, 1999), this theory can be complemented by the view that risk for alcohol dependence is linked to both a decrease in the sensitivity toward sedative effects but increased sensitivity toward positive and stimulating effects of alcohol (see review by Crabbe et al. 2010). In line with this, a large study, comparing heavy and light drinkers, found that in heavy drinkers, alcohol produced greater stimulant and rewarding reactions and lower sedative and cortisol responses, which were linked to binge drinking during a 2-year follow-up period (King et al. 2011).

In an early non-human behavioral experiment by Carlson and Lydic (1976), higher doses of EtOH suppressed the medial forebrain bundle reward system, which is known to function mainly via dopaminergic neurotransmission (Carlson and Lydic 1976). Besides inhibiting DA neurotransmission, alcohol also interacts with GABAergic, glutamatergic, and opioidergic neurotransmitter systems, which may all contribute to the sedative effects of EtOH (Cohen et al. 1997).

The depressant actions of EtOH on the CNS have indeed been related to facilitation of GABA neurotransmission via alcohol effects on the benzodiazepine/GABA receptor complex (Hunt 1983; Ticku 1989; Wang et al. 2000). Here, the muscle relaxant baclofen – a selective GABA-B receptor agonist – has gained some attention as a potential treatment option (Beraha et al. 2016; Garbutt et al. 2021; Müller et al. 2015; Pierce et al. 2018; Reynaud et al. 2017). Preclinical studies suggested an indirect modulation of the dopaminergic neurotransmission within the mesolimbic reward system as baclofen's mode of action (Bowery et al. 1987; Fadda et al. 2003). An early preclinical study showed that baclofen infusion into the VTA reduced drug-induced dopamine release within nucleus accumbens as well as drug self-administration (Xi and Stein 1999). The authors thus concluded that dopaminergic activity in the VTA could at least be partially inhibited by GABA-B receptor activation. In human studies, there is first evidence that baclofen is able to reduce alcohol-related neural cue reactivity, especially in high-dose application (Beck et al.

2018; Logge et al. 2021). Furthermore, Lovinger et al. (1989) demonstrated alcohol's dose-dependent inhibition of neuronal activation induced by the glutamate agonist *N*-methyl-D-aspartate (NMDA) in hippocampal neurons. In this context, Augier and colleagues used an alcohol-reward-choice paradigm in rodents to assess the motivation to obtain alcohol. Interestingly, the expression of the GABA transporter GAT-3 was selectively decreased within the amygdala of alcohol-choosing rats and a knockdown of this transcript even reversed choice behavior of rats that originally preferred a sweet solution over alcohol (Augier et al. 2018). These findings gave interesting directions for human research: GAT-3 expression was reduced in the amygdala of patients with alcohol dependence (Augier et al. 2018), and identifying the individual GABAergic constitutions might also be an important biomarker for identifying baclofen responders (Heilig et al. 2019; Spanagel 2018). Further studies supported the hypothesis that EtOH disrupts glutamatergic neurotransmission by decreasing cationic conductance through the NMDA receptor and thus inhibits NMDA receptor responses (Nevo and Hamon 1995; Tsai et al. 1995).

In addition, there is an EtOH-induced effect of analgesia, which is mediated by the opioidergic system. This effect was demonstrated in an early animal study, which investigated the ability of EtOH to stimulate opiate receptors; administration of EtOH (2–3.5 g/kg) in rats acutely induced an analgesic effect (Jørgensen and Hole 1981). Moreover, Neddenriep and colleagues showed that ethanol has analgesic-like properties also in chronic inflammatory and neuropathic pain models in mice (Neddenriep et al. 2019). In early *in vivo* work, Volkow and associates (1990) observed in a PET study of human subjects that EtOH inhibits cortical and cerebellar glucose metabolism, supporting similar findings in animal studies. These inhibiting effects of alcohol on regional brain metabolism were shown to be larger in alcohol-dependent patients than in healthy subjects after alcohol administration. The authors assumed that this decrease of energy metabolism is due to the EtOH action itself (Volkow et al. 1990). Lately, Bazov and colleagues have focused on the potential genetic basis of dysphoric state during acute and protracted alcohol withdrawal: using post-mortem NAc tissue of human alcohol-dependent individuals, they found that expression of DRD₁ and DRD₂ was correlated with expression of prodynorphin and κ-opioid receptor (OPRK1), indicating high levels of transcriptional interactions between these gene clusters (Bazov et al. 2018). These results thus emphasize co-expression patterns of opioid and dopaminergic genes putatively leading to the negative affective states during withdrawal in human alcohol-dependent individuals. In the field of negative affect during the course of addiction, the theory of hyperkatifeia has to be considered as well. Hyperkatifeia is defined as a greater intensity of negative emotional states during withdrawal, which can provide an additional source of motivation for chronic drug seeking via negative reinforcement (i.e., behavior to remove this aversive state) (Koob 2021). Neurobiological correlates of hyperkatifeia implicate the extended amygdala within a complex system of neuroadaptations in dopamine, opioid, GABA/glutamate systems as well as stress-related circuits (with neurotransmitter and hormones such as norepinephrine, glucocorticoid, and dynorphin). Understanding the basis of negative reinforcement in addiction might represent promising targets for pharmacological treatments (Koob 2021).

1.2.3 Acute Alcohol Effects on Cognition

At BAC levels lower than the legal intoxication limit, i.e., 0.02–0.03%, mental function impairments in attention and vigilance can be detected (Koelega 1995). A meta-analysis on studies using electroencephalography (EEG) demonstrated that alcohol intoxication significantly attenuated neurophysiological indices of stimulus processing linked to attention, automatic auditory processing, and performance monitoring, but not executive control (Fairbairn et al. 2021). These effects were dose-dependent, reaching significance at doses as low as 0.026% BAC (Fairbairn et al. 2021). In addition, alcohol affects cognitive processes such as judgment: Moderate doses of alcohol (0.5–0.8 g/kg) have been shown to lead to an overoptimistic assessment of a person's own ability (Tiplady et al. 2004), and to reduced perceptions of risk, thus contributing to risk-taking behavior by altering expectations about negative consequences (Fromme et al. 1997). A very recent randomized placebo-controlled study (RCT) by Karlsson and colleagues focused on the acute effects of moderate levels of alcohol on (personal and social) decision-making in healthy social drinkers. Interestingly, they observed a robust effect of alcohol on increasing utilitarian choices (e.g., hypothetically sacrificing a single individual for the sake of many), moral judgment and altruistic behavior (donating money), but no effects on measures of risk taking or impulsivity (Karlsson et al. 2022). Altogether, these studies support effects of moderate to heavy alcohol consumption on cognitive processes such as judgment, reasoning, and decision-making (Brumback et al. 2007).

Converging evidence also demonstrates that moderate to high doses of alcohol (0.4–0.8 g/kg) impair core components of executive functions, including working memory (WM) and response inhibition (Day et al. 2015; Bjork and Gilman 2014). Sensitivity to the impairing effects of alcohol is relative to the complexity of the response inhibition task. For example, while acute alcohol intoxication at a high dose (mean BAC 1.2%) impaired overall performance, participants performed especially worse in the demanding condition where they could not rely on automated stimulus-response associations (Stock et al. 2016). Using EEG, the authors further observed a specific effect of alcohol intoxication on neurophysiological components linked to motor inhibition and response evaluation (NoGo-P3), which are assumed to depend on DA signaling in mesocorticolimbic systems (Beste et al. 2010). DA projections to the PFC regulate WM function (Egan et al. 2001; Goldman-Rakic 1995) and prefrontal DA innervations modulate fronto-subcortical circuits, which regulate striatal DA release (Heinz 2000). Primate conditioning experiments by Williams and Goldman-Rakic (1995) directly showed that firing of PFC neurons sustains WM information. Thereby, the activity of these PFC neurons depends on optimal DA stimulation, which is reflected in an “inverted U-shaped curve” of DA effects on PFC WM functions (Williams and Goldman-Rakic 1995). As human studies indicated, the administration of D₂ agonists also improved WM performance, whereas the blockage of D₂ diminished WM functions (Luciana et al. 1992; Williams and Goldman-Rakic 1995).

PFC dysfunction can contribute to behavioral disinhibition and compulsive drug intake (Lubman et al. 2004). Several relevant prospective functional magnetic resonance imaging (fMRI) studies showed that PFC dysfunction is associated with the subsequent relapse risk in addicted patients: Grüsser et al. (2004) and Beck et al. (2012) observed that increased activation of the cingulate and adjacent medial PFC elicited by alcohol-associated cues predicted relapse in alcohol-dependent patients. Paulus et al. (2005) described that a decreased activation of the PFC during decision-making was associated with the subsequent relapse risk in methamphetamine-dependent subjects. However, to date the role of DA neurotransmission in these functional alterations remains to be explored.

1.2.4 Acute Alcohol Effects on Emotion Processing

Mood changes have been observed as a result of alcohol's stimulating and depressant effects. High to moderate doses of alcohol have been shown to impair emotion recognition in social drinkers, especially for negative facial expressions like sadness, fear, or anger (Eastwood et al. 2020; Honan et al. 2018; Khouja et al. 2019), while relatively low doses (0.25–0.3 g/kg) enhanced recognition of happy faces, which might contribute to the prosocial effects of alcohol consumption (Dolder et al. 2017; Kano et al. 2003). This association might be mediated by gender, as a recent field study found acute intoxication (measured as BAC) to impair facial emotion recognition accuracy in males only (Melkonian et al. 2021). In the context of emotion processing, Herman and Duka emphasize the interaction between the emotional state and alcohol consumption (Herman and Duka 2019): Acute alcohol consumption results in improved positive and decreased negative emotional states, thus consumption might be used as a coping strategy when experiencing negative emotions. Moreover, highly arousing emotional states are associated with increased alcohol consumption in social as well as problem drinkers, particularly in more impulsive individuals.

In an fMRI-study, Gilman et al. (2008) investigated the brain response to alcohol intoxication and emotional stimuli. The authors observed that intravenous alcohol infusion with a maximal BAC of 0.08% reduced brain activation toward fearful compared to neutral faces in brain regions involved in emotional processing, i.e. amygdala, insula, or parahippocampal gyrus. Reduced amygdala involvement when processing threatening but not happy faces has been also reported after oral alcohol administration (Sripada et al. 2011), along with an overall reduction of amygdala-OFC connectivity during emotion processing (Gorka et al. 2013). Gilman et al. (2012) showed that intravenous alcohol administration to a BAC of 0.08% attenuated amygdala activation toward fearful faces only in light but not heavy drinkers. This latter group also reported reduced subjective alcohol effects and, in contrast to the light drinkers, did not show significant activation of the NAc in response to alcohol administration, potentially reflecting tolerance development.

In sum, these studies indicate that acute alcohol consumption blunts neural activation in limbic regions normally implicated in emotion processing by

decreasing the difference in activation between threatening and non-threatening stimuli, which can contribute to both the anxiolytic properties of alcohol and to risky decision-making during intoxication.

1.3 Effects of Chronic Alcohol Intake on Dopamine Neurotransmission

Why do some people use addictive drugs on an occasional non-addictive basis, while others suffer from an addictive pattern of use?

Genetic factors have been suggested to play an important role, accounting for up to 50% of the variance in people with clinically defined alcohol or drug addiction (Gardner 2005; Uhl et al. 1993), while estimated SNP (Single Nucleotide Polymorphism)-based heritability ranges from 5 to 10.0% (Zhou et al. 2020). One hypothesis suggests that a “functional” DA deficiency in the brain reward system derives from a genetically determined hypofunction of *DRD₂* gene [e.g., Blum et al. 1996]. This hypothesis was supported by human neuroimaging findings showing reduced *DRD₂* levels in brain reward loci of persons with drug addiction (Ashok et al. 2017; Volkow et al. 1996, 1997, 2001), and from findings of low levels of *DRD₂* in human brain reward loci, which predict rewarding versus non-rewarding subjective responses to psychostimulants (Volkow et al. 1999). Volkow et al. (2006) hypothesized that low *DRD₂* availability is a partially heritable trait, which facilitates excessive alcohol and drug intake, while high *DRD₂* levels appear to be protective against alcoholism. Further evidence for a hypofunction of DA neurotransmission as a vulnerability factor was provided when observing that dopamine response in an amphetamine challenge was reduced in an adolescent genetic risk population (Casey et al. 2014), although, contrary to Volkow et al. (2006), no differences between basal *DRD_{2/3}* receptor availability were found in this sample. Furthermore, while reduced *DRD₂* sensitivity predicted relapse in alcohol-dependent patients (Heinz et al. 1996), this *DRD₂* down-regulation appeared to be a counter-adaptive down-regulation following *chronic alcohol intake*, which was reversed during early abstinence and was not correlated with *DRD₂* genotype (Heinz et al. 1995). Additional studies performed to directly test the hypothesis that *DRD₂* genotype is associated with alcohol dependence yielded mixed results, and it was suggested that genetic variation in *DRD₂* expression does not predispose to alcoholism per se (Kienast and Heinz 2006).

In a recent translational diffusion tensor imaging (DTI) study De Santis et al. observed an increased mean diffusivity in brain gray matter of chronically drinking rats and humans, which persisted into early abstinence (De Santis et al. 2020). This finding highlights the value of DTI applied to gray matter, in addition to white matter, as a source for imaging biomarkers, and confirms similarities between rodent and human models. The authors further used diffusion equations for dopamine neurotransmission to theoretically test the impact of experimentally measured

changes in the extracellular space (ECS) in rats on the extracellular dopamine concentration. Results indicate that a putatively facilitated diffusivity of dopamine due to altered ECS could progressively enhance their signaling properties and thus addictive potency.

1.3.1 Neuroadaptive Mechanisms

If alcohol intake induces DA release, chronic consumption should induce a compensatory *DA receptor down-regulation*, which can persist even after alcohol intake is stopped. Indeed, in detoxified alcohol-dependent patients, brain imaging studies with PET and endocrinological challenge studies revealed a reduction of sensitivity and availability of central DRD₂-receptors, which was correlated with lifetime alcohol intake and the subsequent relapse risk (Heinz et al. 1996). Confirmatory evidence for this adaptation comes from a recent meta-analysis by Kamp et al. (2019) on the dopaminergic system in alcohol-dependent subjects, demonstrating an association between chronic alcohol intake and reduced striatal DRD₂-receptors availability.

Following detoxification, when the stimulating effects of alcohol on DA neurotransmission are interrupted, PET studies measuring F-DOPA showed that alcohol craving was specifically correlated with a low *DA synthesis capacity* and with reduced DRD₂ availability in the ventral striatum including the NAc (Heinz et al. 2004b, 2005b); (see Fig. 2). During detoxification and early abstinence, DA dysfunction is further exacerbated by reduced intra-synaptic DA release, as shown in rodent experiments where extracellular DA concentrations decreased rapidly during detoxification (Diana 2011; Rossetti et al. 1992). A PET study confirmed that DA release following amphetamine administration was significantly reduced in detoxified alcohol-dependents, indicating that presynaptic DA storage capacity is reduced during early abstinence (Martinez et al. 2005). Together, these studies indicate that after detoxification, overall DA neurotransmission in the ventral and central striatum of alcohol-dependent patients is reduced (rather than increased or sensitized, as might be expected from the theory of Robinson and Berridge (1993)). While it has been hypothesized that these neuroplastic changes persist even during protracted abstinence (e.g., Diana 2011; Koob and Le Moal 2005), there is evidence for rather fast recovery of dopaminergic neurotransmission during abstinence. With respect to DA receptor sensitivity, Heinz et al. (1995) observed early effects of abstinence on the dopaminergic system, i.e. increases in receptor function, already after 1–7 days, especially in subsequent abstainers. In subsequent relapsers, adjustment of dopaminergic signaling was delayed, putatively reflecting the heightened relapse risk of treatment non-responders. A study by Hirth et al. even suggest a *hyperdopaminergic* state after protracted abstinence (Hirth et al. 2016): in post-mortem brain tissue of alcohol-dependent patients, a strong down-regulation of the DRD₁ receptor- and DA transporter (DAT)-binding sites was seen, but a rather unaffected DRD₂ receptor binding. To capture the course of abstinence, data was derived from alcohol-dependent rats. Again, there were no differences in DRD₂ receptor binding during

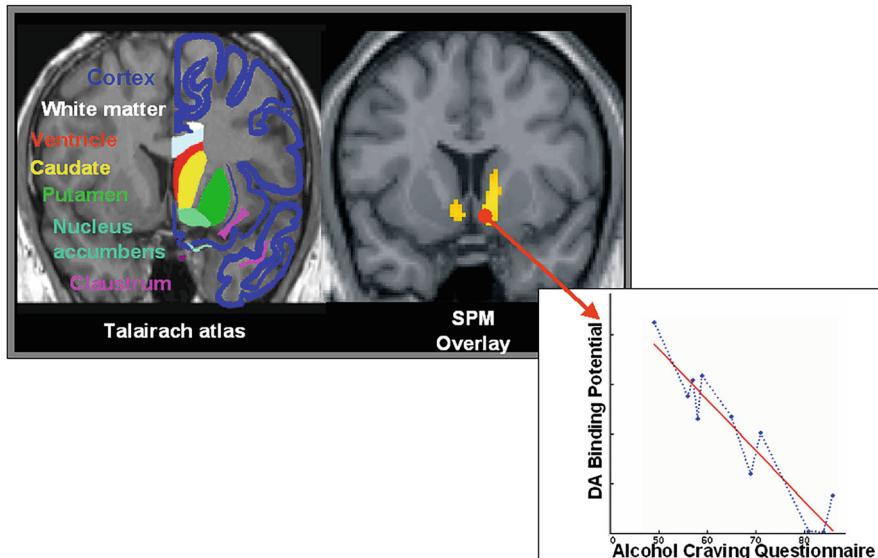


Fig. 2 Negative correlation between alcohol craving and DRD₂-availability in the bilateral nucleus accumbens/ventral striatum in a group of abstinent alcohol-dependent patients but not in healthy control subjects (modified according to Heinz et al. 2004b). The image at the upper right is a coronal view of the results of a PET correlation analysis of DRD₂ availability and alcohol craving measured with the alcohol craving questionnaire. The image at the upper left indicates that these areas correspond well to the ventral striatum/nucleus accumbens. The scatterplot at the bottom shows the correlation between DRD₂ availability (binding potential) in the right ventral striatum/nucleus accumbens and acute alcohol craving. DA dopamine, DRD₂ dopamine D₂ receptor, PET positron emission tomography, SPM statistical parametric mapping

withdrawal and prolonged abstinence, but instead a dynamic regulation of DRD₁ receptors, dopamine transporters and dopamine release properties yielding a *hyperfopaminergic* state during protracted abstinence. The authors suggested that at different time points, both, hypo- and hyperdopaminergic states are associated with an increased relapse vulnerability. Hansson and colleagues reviewed animal and human studies and emphasize changes in dopaminergic signaling over time, which were associated with concomitant alterations in mu-opioid receptor availability, suggesting a highly dynamic regulation of the reward system during abstinence (Hansson et al. 2019). In addition to dynamic changes in abstinence, a recent animal study suggests the role of gender (Salinas et al. 2021). After long-term alcohol exposure, male macaques showed decreased DA signaling in the putamen, while another group that was subjected to intermittent abstinence periods of 1 month, showed reduced DA release in the caudate. Long-term drinking non-abstinent female macaques however showed no decreased dopaminergic signaling in the putamen but only in caudate. Additionally, only male animals displayed a reduction in DRD₂ and DRD₃ auto-receptors function irrespective of abstinence status.

Importantly, DRD₂ down-regulation in the ventral striatum may interfere with the above described DA-dependent error detection signal (Schultz et al. 1997). Schultz et al. (1997) suggested that phasic alterations in DA release are not only required to learn new stimulus-reward associations but are also necessary to “unlearn” (extinguish) established associations. According to Schultz, a phasic dip of DA release occurs whenever a conditioned stimulus is not followed by the anticipated reward. Under this condition, the down-regulation of DA synthesis and storage and DRD₂ availability in the ventral striatum of detoxified alcohol dependent patients can interfere with this DA-dependent signaling of an error in reward expectation. Therefore, it may be difficult for alcohol dependent patients to divert their attention away from conditioned cues, which no longer signal subsequent delivery of any alcohol reward. The cues themselves may still elicit an orienting response even in the absence of DA firing due to cue-induced glutamate-dependent long-term potentiation (LTP) within a ventral hippocampus-ventral striatal pathway, which has been associated with perseverative behavior (Goto and Grace 2005). Thus, DA dysfunction following detoxification may specifically interfere with a phasic DA-dependent error signal dysfunction, which otherwise would indicate that alcohol-associated cues are no longer followed by reward. This may explain why patients continue to consume alcohol even though they no longer gain any rewarding experiences. Moreover, in light of the developmental changes of the mesocorticolimbic dopamine system during adolescence (Spear 2018), exposure to ethanol might induce abnormal plasticity, which could alter reward-related behavior. Indeed, intermittent ethanol treatment during adolescence induced increased basal dopamine levels compared to adolescent rats treated with saline. Compared to saline-treated adult rats, rats with adolescent alcohol exposure showed increased alcohol consumption in adulthood (Pascual et al. 2009). Epigenetic effects of repeated ethanol exposure during adolescence included the down-regulation of DRD₂ and NMDAR2B receptors and altered histone acetylation in the limbic system and prefrontal cortex (Pascual et al. 2009). In similar fashion, adolescent ethanol exposure induced cellular and dopaminergic alterations in the adult prelimbic cortex due to reduced expression of DA-related proteins, including catechol-O-methyltransferase (COMT) (Trantham-Davidson et al. 2017).

1.3.2 Morphological Alterations

Although functional and structural brain impairment is partially reversible after several weeks of abstinence (Crews et al. 2005; Hansson et al. 2010; Nixon 2006; Rosenbloom et al. 2003), the type and degree of damage varies across individuals (Oscar-Berman and Marinkovic 2007).

The most prominent damage in the frontal lobes is *cerebral atrophy*. Other morphological effects are *ventricular enlargement* and widening of the cerebral sulci of alcohol-dependent patients in relation to increasing age (Pfefferbaum et al. 1996; Sullivan 2000).

The majority of the evidence from neuropathological and neuroimaging investigations supports an increased vulnerability *model of “premature aging”* due to alcohol’s neurotoxic effects (Oscar-Berman and Marinkovic 2003): when comparing older to younger alcohol-dependent patients, certain brain structures show greater than expected reduction in size (or blood flow), e.g., in the cerebral cortex (Di Sclafani et al. 1995; Harris et al. 1999; Pfefferbaum et al. 1997), in the hippocampus (Laakso et al. 2000; Sullivan et al. 1995), in the corpus callosum (Pfefferbaum et al. 1996, 2006; Schulte et al. 2005) and in the cerebellum (Harris et al. 1999; Sullivan 2000). A more recent study by Guggenmos et al. (2017) supported this line of research applying machine learning techniques to structural brain data of alcohol-dependent individuals. While no brain aging was detected in the youngest alcohol-dependent subjects, it was observed that alcohol-related brain aging systematically increased with advancing age, even when controlling for lifetime alcohol consumption and general health status. At the microstructural level, *diffusion tensor imaging (DTI)* measures of neuronal fibers in the corpus callosum have provided evidence for a detrimental interaction between a person’s recent history of alcohol dependence and their age (Pfefferbaum et al. 2006); moreover, microstructural damage related to alcohol dependence was observed in cerebral areas that appeared to be intact when looking at structural MRI analyses (Zahr and Pfefferbaum 2017). De Santis and colleagues describe DTI as a powerful diagnostic tool to monitor alcohol-induced brain damage and to characterize the progression of the observed changes during early abstinence (De Santis et al. 2019a). In a recent study, De Santis et al. showed comparable DTI alterations in alcohol-dependent patients and rats with long-term alcohol consumption especially within the corpus callosum and the fornix/fimbria (De Santis et al. 2019b). Interestingly, in both species, a progression of DTI alterations into early abstinence (2–6 weeks) suggested an underlying process that appears to evolve soon after cessation of alcohol use. In a rodent model, Somkuwar and colleagues observed that forced abstinence from moderate to severe alcohol use was associated with gray matter abnormalities via microstructural (myelin) deficits as well as according deficits in cognitive function and executive behavior (Somkuwar et al. 2021). Such (micro) structural alterations could provide an alternative explanation for DRD₂ down-regulation: would DRD₂ receptors simply be reduced because of striatal atrophy, which leads to partial volume effects and thus decreases the signal from radioligand binding to DRD₂? This is certainly a possibility, but to date this type of striatal atrophy has not been described; also, measurements of mu-opiate receptors in the same brain area (ventral striatum) were increased rather than decreased in detoxified alcohol-dependent patients (Heinz et al. 2005a), suggesting that down-regulation of DRD₂ and up-regulation of mu-opiate receptors in the ventral striatum reflect specific neuroadaptive processes rather than simply resulting from striatal atrophy. This finding was replicated by Weerts et al. (2011).

The study of Heinz et al. (2005a) excluded carriers of the G-allele of the mu-opiate receptor (OPRM1) genotype, which was associated with increased affinity for endorphins and a stronger response to naltrexone, an opioid receptor blocker. A genotype-dependent, higher affinity for endogenous ligands (here endorphins) can

increase competition for receptor binding with radioligands such as carfentanil and thus decrease *in vivo* measures of (free) receptor availability *in vivo*. Indeed, a study by Hermann and colleagues (2017) included OPRM1 G-carriers and observed a genotype x mu-opioid receptor availability interaction on the relapse risk: particularly G-allele carriers showed an association between lower striatal mu-opioid receptor availability and an increased relapse risk. Post-mortem data, albeit difficult to compare due to rapid changes in endorphin concentrations (Zhu and Desiderio 1993), suggested reduced mRNA levels for the mu-opioid receptor in the striatum (Hermann et al. 2017). The authors concluded that opioid receptor availability *in vivo* is influenced by both endogenous endorphin concentrations and receptor affinity, which in turn interact with the effects of naltrexone on the relapse risk (Hermann et al. 2017).

1.3.3 Changes in Cue-Induced Neuronal Activation

Alterations in incentive salience attribution to alcohol-associated stimuli can be assessed with the so-called cue-reactivity paradigms (Drummond 2000; Ekhtiari et al. 2022). Animal experiments revealed that besides the drug itself, also alcohol- and drug-associated stimuli activate the DA reward circuitry including the ventral striatum (Dayas et al. 2007; Di Chiara 2002; Shalev et al. 2000). Brain-imaging studies have assessed the neuronal network responding to drugs of abuse, and its association with the prospective *relapse risk* and demonstrated replicability (Bach et al. 2020, 2021, 2022; Beck et al. 2012; Braus et al. 2001; Drummond 2000; George et al. 2001; Grüsser et al. 2004). In the context of these cue-reactivity paradigms, it is practicable to examine conditioned reaction on conceptually different levels (Carter and Tiffany 1999): (1) a subjective level where anxiety, joy, or craving can be evoked, (2) a physiological level measuring heart rate, skin conductance, or functional brain activation, and (3) a behavioral level, where the amount of alcohol intake or the latency until relapse can be observed (Wräse et al. 2006). In drug-dependent patients, it has been observed that drug-associated cues often elicit a physiological response similar to appetitive stimuli, although this does not automatically reflect conscious feelings of attraction or pleasure, and Lubman et al. (2009) showed that heroin users displayed reduced responsiveness to natural reinforcers across a broad range of psychophysiological measures.

Cue-induced functional brain activation can be indirectly assessed by measuring changes in cerebral blood flow with PET, by single photon emission computed tomography (SPECT) or by measuring the blood oxygen level dependent (BOLD) response with fMRI. Although these studies showed substantial variance in response toward the presentation of drug-associated stimuli, there are core regions which were activated in most studies in both patients and animal models (Kühn and Gallinat 2011; Martin-Fardon and Weiss 2013; Noori et al. 2016); (for core regions, see Table 1 and Fig. 3). Findings concerning the association between cue-induced activity in these brain areas and subjective craving for EtOH are not consistent. In some studies, severity of craving was associated with functional brain activation in

Table 1 Core regions activated by alcohol-associated stimuli during fMRI cue-reactivity paradigms

Brain structure	Function	Exemplary studies showing differences in activation between participants with AD and HC
Anterior cingulate cortex (ACC) Adjacent medial prefrontal cortex (MPFC)	Attentional and memory processes Encoding of motivational value of stimuli	Huang et al. (2018), Dager et al. (2014), Beck et al. (2012), Grüsser et al. (2004)
Orbitofrontal cortex (OFC)	Evaluation of reward and emotional value of stimuli	Myrick et al. (2004)
Dorsolateral prefrontal cortex (DLPFC)	Executive behavioral control, e.g. craving at rest Control of behavioral adaptations during learning processes	Bach et al. (2021), Schacht et al. (2013)
Basolateral amygdala	Specification of emotional salience of stimuli initiation of approach and avoidance behavior	Jorde (2014), Claus et al. (2011)
Ventral striatum (incl. NAc)	Motivational aspects of salient stimuli and association with motor responses	Reinhard et al. (2015), Beck et al. (2018), Sjoerds et al. (2014)
Dorsal striatum	Consolidation of stimulus-reaction patterns Habit formation	Filbey (2008), Grüsser et al. (2004)
Insula	Interoception and internal homeostasis	Bach et al. (2015), Vollstädt-Klein et al. (2011)

fMRI functional magnetic resonance imaging, AD alcohol dependence, HC healthy controls, NAc nucleus accumbens

the ventral striatum, OFC and ACC (Myrick et al. 2004), dorsal striatum (Modell and Mountz 1995), or in the subcallosal gyrus (Tapert et al. 2004). A quantitative meta-analysis of cue-induced brain responses associated with self-reported craving described three core regions for alcohol-associated stimuli: the ACC, ventral striatum, and right pallidum (Kühn and Gallinat 2011). Other studies, however, observed no significant correlation between alcohol craving and brain activation (Grüsser et al. 2004; Heinz et al. 2004b). These inconsistencies could be due to differences in self-reflection and verbalization by participants and the diverse nature of the stimuli used in the studies: alcohol-related words (Tapert et al. 2004), alcohol-related pictures, either with (Myrick et al. 2004) or without (Grüsser et al. 2004) a sip of alcohol (“priming dose”). Moreover, patient recruitment state was not similar: in some studies, patients did not undergo detoxification and were able to consume larger amounts of alcohol, at least to a later time point (Myrick et al. 2004), while other patients were detoxified and participated in an inpatient treatment program, where relapse could cause termination of treatment (Braus et al. 2001; Grüsser et al. 2004; Heinz et al. 2004b, 2007; Wrage et al. 2002, 2007).

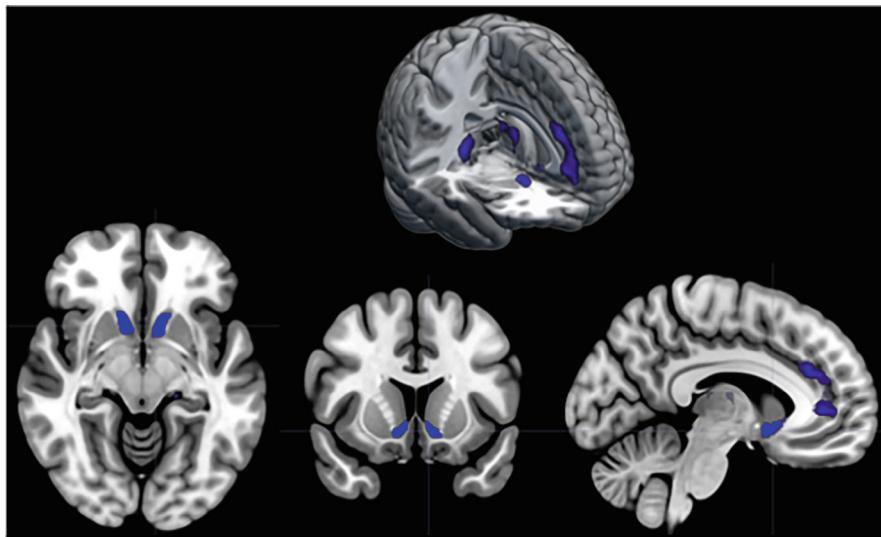


Fig. 3 Activation of the brain reward system assessed with fMRI during a cue–reactivity paradigm assessing the processing of alcohol-associated pictures in alcohol-dependent patients. The upper figure presents 3D-rendered BOLD responses in the bilateral ventral striatum, thalamus, and anterior cingulate cortex for the contrast alcohol-related pictures versus neutral IAPS pictures. The lower panel shows the same contrast superimposed upon an axial, coronal, and sagittal plane averaged T1 structural image (MNI152). *BOLD* blood oxygen level dependent response, *fMRI* functional magnetic resonance imaging, *IAPS* International Affective Picture System, *T1* T1-weighted magnetic resonance sequence

While a multitude of studies assessed brain activation during the presentation of alcohol-associated stimuli, only very few studies investigated to what extent brain activation elicited by alcohol or affective cues predicts an increased subsequent relapse risk. In a pilot study by Braus et al. (2001), alcohol cues elicited increased activation of visual association centers and the ventral striatum in detoxified alcohol dependent patients compared to healthy subjects. Patients with a history of multiple relapses displayed stronger cue-induced activation of the ventral striatum than patients who had abstained from alcohol for longer periods of time. Grüsser et al. (2004) replicated these findings in a prospective study: subsequently relapsing patients showed an increased BOLD response elicited by alcohol-associated stimuli in the ACC and adjacent medial PFC and in the central (dorsal) striatum. Similarly, Beck et al. (2012) observed an increased cue-induced brain response in medial PFC in a group of subsequent relapsers compared to abstainers and healthy controls, which interestingly became even more prominent, when correcting for local gray matter volume, i.e. when correcting for atrophy effects. Moreover, Bach et al. demonstrated replicability of increased neural cue reactivity and associations with relapse (Bach et al. 2020, 2021, 2022). The observations of Grüsser et al. are in line with animal experiments, in which cue-induced relapse after cocaine consumption was prevented by blockade of DA and glutamatergic AMPA receptors in the dorsal

rather than the ventral striatum (Vanderschuren et al. 2005). It has been suggested that the dorsal striatum is important for habit learning, i.e., for the learning of automated responses, and may thus contribute to the compulsive character of dependent behavior. In drug-addicted subjects, cue-induced craving preferentially elicits DA release in dorsal striatal structures (Volkow et al. 2006; Wong et al. 2006), reflecting the transition from ventral striatal, reward-driven behavior to dorsal striatal, stimulus–response habit formation (Berke and Hyman 2000). In line with this transition hypothesis, Vollstadt-Klein et al. (2010) observed an increased cue-induced brain response in heavy drinkers compared to light drinkers in the dorsal striatum, while light drinkers showed an increase in the ventral striatum and in prefrontal regions. Robbins and Everitt (2002) suggested that although the initial reinforcing effects of drugs of abuse may activate the ventral striatum, in the course of drug consumption, the transition to habitual drug-seeking behaviors is reflected in a predominant role of the dorsal striatum in cue-responses. According to clinical experience, many patients describe their relapse in terms of such automated actions and do not remember experiencing any typical craving before the relapse occurred (Tiffany 1990).

If there is indeed DA dysfunction in detoxified alcohol-dependent individuals, which interferes with phasic changes in DA neurotransmission and reflects an error of reward prediction, patients should have difficulties to attribute salience to newly learned stimuli. This hypothesis was experimentally confirmed: while in detoxified alcohol-dependent patients the ventral and central striatum displayed increased neuronal activation during the presentation of alcohol-related stimuli (Braus et al. 2001; George et al. 2001; Kareken et al. 2004; Modell and Mountz 1995; Myrick et al. 2004; Wrage et al. 2007), brain activation in the striatum was reduced when the same patients were confronted with newly learned cues, which indicated possible monetary reward (Wrage et al. 2007). Moreover, diminished activation of the ventral striatum was associated with the severity of alcohol craving. Decreased brain activation to newly learned, reward-indicating stimuli may thus interfere with the patients' motivation to experience new, potentially rewarding situations (for a meta-analysis, see Luijten et al. 2017). Indeed, a reduced learning rate in alcohol-dependent patients correlated with a dysfunctional connectivity between ventral striatal error signaling and dorsolateral prefrontal cortical activation (Park et al. 2010). These findings are in accordance with the hypothesis that alcohol and other drugs of abuse “hijack” a dysfunctional reward system, which tends to respond too strongly to drug-associated cues while failing to process adequately natural reinforcers (Grace et al. 2007; Volkow et al. 2004; Wrage et al. 2007).

1.3.4 Changes in Conditioning and Reward-Based Learning

A core process underlying the aforementioned cue-reactivity processes in addiction is the so-called Pavlovian-To-Instrumental-Transfer (PIT), a mechanism by which Pavlovian conditioned stimuli receive the propensity to elicit conditioned responses and to impact ongoing instrumental behavior, even if the instrumental behavior was

acquired independently of Pavlovian conditioning (Cartoni et al. 2016). In PIT, positively valued Pavlovian cues promote instrumental approach, while negatively valued Pavlovian cues promote avoidance (Huys et al. 2011). Here, the distinction is of importance between outcome-specific PIT (i.e., a particular reward-predicting cue selectively elevates instrumental responses that are associated with the same unique reward) and general PIT (i.e., a reward- or loss-predicting cue generally modifies instrumental responses toward any outcome) (Cartoni et al. 2016). In drug addiction, Pavlovian conditioned cues can thus bias instrumental behavior toward drug seeking and intake (e.g., Corbit and Janak 2007; LeBlanc et al. 2012; Ostlund et al. 2014). For example, in alcohol-dependent individuals, Garbusow et al. observed a stronger general PIT effect elicited by positive non-drug associated cues as well as a heightened functional PIT-related brain response in the NAc in prospective relapsers compared to patients who remained abstinent in the 3-month follow-up period (Garbusow et al. 2014, 2016). This phenomenon of increased PIT effects has also been observed in preclinical animal models of addiction (Cartoni et al. 2016). Interestingly, regarding PIT effects related to alcohol-associated stimuli, a reduced instrumental response was observed, that was, however, only evident in prospective abstainers, suggesting a protective and potentially acquired mechanism, i.e. an inhibition of approach behavior in the presence of alcohol cues which was not found in controls or prospective relapsers (Schad et al. 2019).

Moreover, there is first evidence for an interplay between PIT phenomena and decision-making processes: an increased PIT effect was associated with a general tendency to rely on habitual rather than complex goal-directed decision-making in healthy volunteers (Sebold et al. 2017). Prospective relapsers further displayed reduced mPFC activation during goal-directed decision-making; moreover, high alcohol expectancies were associated with low goal-directed control in relapsers, while the opposite was observed in abstainers and healthy subjects (Sebold et al. 2017).

On a neural level, PIT research concentrated on the dopaminergically innervated NAc, with lesion studies indicating NAc core to be specifically involved in general PIT and NAc shell in specific PIT processes (Corbit and Balleine 2011). An early animal study by Dickinson et al. (2000) observed that administration of a dopamine receptor antagonist diminished general transfer effects without affecting instrumental incentive learning per se. In line with that, Wyvell and Berridge showed that injections of amphetamine (as a dopamine agonist) into NAc increased general transfer in animals (Wyvell and Berridge 2000, 2001; Peciña and Berridge 2013). Regarding the role of dopamine in specific PIT effects, Laurent et al. (2014) showed that a DRD₁ receptor antagonist abolished specific transfer when infused into the shell (not into core), while a DRD₂ receptor antagonist did not have any effect on specific transfer when infused into either core or shell.

1.3.5 Long-Term Changes on Emotion Processing and Cognition

Since a seminal study by Philippot et al. (1999) demonstrated that alcohol-dependent patients experience deficits in the encoding of facial emotional expressions,

profound deficits in social cognition including facial emotion recognition has been meta-analytically confirmed in AUD (Bora and Zorlu 2017; Castellano et al. 2015), especially for negative affects like disgust, anger, and contempt (Bora and Zorlu 2017; Maurage et al. 2021; Rupp et al. 2017; Uekermann and Daum 2008). Stronger facial emotion recognition deficits have been linked to longer duration of alcohol use (Bora and Zorlu 2017) and greater lifetime alcohol intake (Charlet et al. 2014b), suggesting that these deficits could result from the neurotoxic effects associated with chronic alcohol consumption. Indeed, Trick et al. (2014) showed that the deficit of alcohol-dependent patients to accurately recognize fearful expressions was associated with reduced gray matter volume in frontal areas including inferior frontal cortex (IFC), and that gray matter volume in IFC was inversely related to the number of detoxifications. Rupp et al. (2017) further showed an association between facial emotion recognition performance and treatment outcome. Specifically, misinterpretation of disgust, anger, and neutral facial expressions at treatment onset was predictive of higher relapse and/or dropout rates, highlighting the clinical significance of social cognition impairments in AUD. So far, it is still unclear whether these deficits can recover with abstinence. One longitudinal study suggested facial expression recognition performance can improve within 3-month of abstinence (Erol et al. 2017), whereas another study found impaired facial emotion regulation to persist over a 2-month follow-up period (Rupp et al. 2021).

AUD patients also exhibited blunted brain activation during emotional stimulus processing (Salloum et al. 2007; Sawyer et al. 2019; Charlet et al. 2014b). However, explicitly investigating gender differences, Sawyer et al. (2019) found this was only true for men with AUD, while for women this brain activation pattern was quite more diverse. Charlet et al. (2014b) further observed increased rostral ACC activation during aversive face processing in AUD patients compared to controls that correlated significantly with longer abstinence and less subsequent binge drinking, in patients indicating a potential resilience factor. In healthy participants, dopamine storage capacity in the amygdala, measured with F-DOPA PET, has been linked to functional amygdala and dorsal ACC activity during emotion processing (Kienast et al. 2008). In contrast, in AUD patients this modulatory influence of DA storage capacity seems to be disrupted (Kienast et al. 2013). Moreover, patients displayed reduced functional connectivity between amygdala and dACC during aversive emotion processing, which was further linked to higher levels of trait anxiety (Kienast et al. 2013).

Two human studies simultaneously investigated brain activation elicited by both drug-associated cues and non-drug reinforcers such as sexual graphics or monetary reward in drug-addicted patients. One study revealed reduced brain activation elicited by sexual graphics in cocaine-dependent patients, while brain activation elicited by drug-associated cues was increased (Garavan et al. 2000). Comparing detoxified alcohol-dependent patients with healthy control subjects, another study observed that alcohol-dependent patients displayed increased activation of the ventral striatum during the presentation of affectively positive stimuli (Heinz et al. 2007). This ventral striatal activation appeared to have protective properties because

it was inversely correlated with the number of subsequent drinking days and the amount of alcohol intake in the 6-month follow-up phase (Heinz et al. 2007).

Regarding long-term changes in cognition, chronic alcohol consumption has been consistently associated with impairments in core executive functions like working memory, attention, response inhibition, or cognitive flexibility, although there is considerable heterogeneity within patients (Stavro et al. 2013; Le Berre et al. 2017). Charlet et al. (2014a) found increased functional activation (despite equal task performance) during high cognitive WM load in rostral and ventrolateral prefrontal cortex in prospective abstainers only, putatively indicating compensatory mechanisms that may contribute to resilience. Patients with AUD further displayed deficits in more complex cognitive processes like decision-making under uncertainty and risk (Brevers et al. 2014) or goal-directed behavior in response to changing environments (Sebold et al. 2014; Reiter et al. 2016). On a neural level, learning signals related to more goal-directed behavior in the mPFC were reduced in patients with AUD (Sjoerds et al. 2013; Reiter et al. 2016) and have been associated with later relapse (Sebold et al. 2017).

1.4 The Effect of Stress and Alcohol on the Dopaminergic System

Stress exposure is known to be one of the core mechanisms contributing to relapse in addiction (Bossert et al. 2013; Shalev et al. 2000; Sinha and Li 2007), while at the same time increased drug intake seems to alter the physiological stress system (Heinz et al. 1995; Moss et al. 1995, Chaplin et al. 2015). One characteristic of this interplay is that alcohol and stress might have similar effects on neurochemical systems, particularly on the dopaminergic system: Saal et al. (2003) demonstrated that in vivo administration of drugs of abuse including alcohol as well as acute stress both increased strength at excitatory synapses on midbrain dopamine neurons. In line with this, exposure to stress as well as drugs has been shown to commonly affect GABAergic synapses and therefore increase VTA DA neuron firing (Niehaus et al. 2010). Stress has further been associated with alterations, i.e. reduction in dopamine DRD₂/DRD₃ receptor availability (Campus et al. 2017; Sim et al. 2013) and there is first evidence that stress exposure might only increase alcohol consumption in individuals with low DRD₂ receptor availability (Delis et al. 2015). In a human study, Sebold et al. (2019) assessed the effect of chronic life stress exposure on striatal DRD₂ receptor availability in detoxified alcohol-dependent patients. They observed a strong positive association between striatal DRD₂/DRD₃ availability and stress in patients, but not in healthy controls. These findings suggest that dopamine receptor sensitivity and availability is modulated not only by genetic factors and in vivo dopamine release, but also acute and chronic stress exposure.

1.5 The Dopamine System in a Comprehensive Account of Addiction Development

A comprehensive model of the development and maintenance of addictive behavior was described by Lüscher et al. (2020). The authors distinguished between the so-called “compulsive” drug seeking and drug taking. A behavior is called compulsive in these animal models if it is carried out in spite of immediate aversive consequences. Compulsive drug seeking can be separated from compulsive drug taking, e.g. if pressing a lever to obtain a drug reward is spatially and temporally separated from obtaining this reward, so punishing the seeking response does not directly affect (later) drug taking and vice versa.

The authors confirm the notion that drugs of abuse release dopamine in the ventral striatum including the nucleus accumbens, which thus reinforces drug intake. However, they emphasize that in addition to these well-known dopamine effects, projections from the orbitofrontal and medial prefrontal cortex to the dorsomedial striatum (in primates equivalent to the nucleus caudatus) have to be activated. Drug seeking and drug consumption are goal-directed in these early stages of the development of addiction, and value-related computations in the orbitofrontal and medial prefrontal cortex can play a decisive role in such goal-directed control. Lüscher et al. (2020) suggest that activation of the ventral striatum including the nucleus accumbens is not necessary for goal-directed behavior control. Instead, the ventral striatum plays a key role in stimulus-triggered behavior and mediates effects of drug-associated stimuli in interaction with the basolateral amygdala.

When drug seeking becomes more habitual, spiraling loops link the ventral with more dorsal parts of the striatum, thus drug seeking becomes increasingly associated with dorsolateral striatal activation (in primates equivalent to the putamen), which received important input from the motor cortex. At this more advanced state of drug addiction, drug cue-associated effects depend upon input from the central rather than the basolateral amygdala and its projections to the substantia nigra pars compacta.

Finally, compulsive drug intake occurs irrespective of immediate punishment. According to Lüscher et al. (2020), this last stage of the development of drug addiction only occurs when prefrontal control of the dorsolateral striatum is lost.

While the so far described development largely reflects work of Robbins and Everitt, Lüscher also adds observations from direct optogenetic self-stimulation of dopaminergic neurons in rodents (Pascoli et al. 2018).

In these optogenetic experiments, the first steps in the development of addictive self-stimulation are quite similar to previously observed effects of chronic drug intake: the authors emphasize the role of projections from the medial prefrontal cortex and the ventral hippocampus to GABAergic neurons with DRD₁ receptors in the nucleus accumbens. Again, cue effects can be mediated by projections from the basolateral amygdala to GABAergic neurons with DRD₂ receptors in the nucleus accumbens.

However, there is a difference in the identified neurobiological correlates of compulsive drug intake. While Robbins and Everitt emphasize loss of top-down

cortico-striatal control in compulsive stages of addiction, Pascoli et al. (2018) observed an increased rather than reduced interaction between the orbitofrontal cortex and the dorsomedial striatum in exactly those animals that “compulsively” continue dopaminergic self-stimulation in spite of immediate punishment (i.e., in spite of aversive consequences of every third drug-seeking response).

In summary, a more traditional approach suggests that compulsive drug intake is associated with a loss of control of the prefrontal cortex over drug-seeking habits mediated by the dorsal striatum (putamen), while optogenetic findings suggest a “gain-of-function” and hence an increase of the interaction between the orbitofrontal cortex and the dorsomedial striatum (nucleus caudatus). A possible way to harmonize these explanatory models is to suggest that the increased, “gain-of-function” interaction between the orbitofrontal cortex and the dorsomedial striatum occurs before a later loss of function of top-down control (Lüscher et al. 2020). However, a recent paper confirms previous findings regarding serotonin neurotransmission in the prefrontal cortex in addiction development (Heinz et al. 2011; Heinz 2017) and suggests that a low prefrontal serotonin concentration contributes to the transition to compulsive drug intake, because there is a lack of presynaptic serotonin 5-HT_{1B} receptor mediated inhibition of orbitofrontal projections to the dorsal striatum (Li et al. 2021). So again, an increased rather than decreased orbitofrontal–dorsal striatal interaction is implicated in compulsive drug intake.

Even more important may be a fundamental criticism of animal models of “compulsive” drug intake. First, aversive consequences of drug intake in humans are usually delayed, not immediate (e.g., somatic diseases associated with drug consumption or impaired job performance leading to professional disadvantages, etc.) (Charlet and Heinz 2017). Secondly, obsessive thoughts differ phenomenologically from “obsessive” drug craving and, like compulsions in obsessive-compulsive disorders (OCD), can only briefly be suppressed, while drug craving and seeking is usually much more flexible (unless accompanied by strong aversive withdrawal symptoms) (Schoofs and Heinz 2012). Thirdly, there is a substantial neurobiological difference: in OCD, glucose utilization in the prefrontal cortex is increased (Baxter 1990; Nordahl 1989), while it was found to be decreased in addiction (Volkow et al. 1993, 1994). Furthermore, there are important differences in dopamine neurotransmitter systems between rodents and primates (Bradberry 2007). Altogether, animal models offer in-depth understanding of molecular mechanisms and neurobiological systems involved in drug seeking and taking. However, findings have to be replicated or modified in human studies. Humans reflect on their behavior, talk about it, and can modify it accordingly, which is the foundation of all psychosocial interventions. While drug effects can bias neural systems relevant for decision-making and may thus make it particularly difficult to “kick a habit,” treatment of addiction will only improve when animal findings are translated into human studies and persons with addictive behavior are respected as human beings with decision-making capacities who are offered comprehensive therapy including social support, empowerment, self-organized groups and – if required – specialized pharmacological and psychotherapy.

2 Summary

Altogether, animal experiments and human studies suggest that (1) DA function is prominent both when acquiring excessive alcohol intake and during chronic alcohol consumption. (2) Alcohol-induced DA release contributes to alcohol craving, while hedonic pleasure is mediated by other neurotransmitter systems, e.g., opioidergic neurotransmission. (3) Dopamine DRD₂ receptor down-regulation and low DA synthesis rates are at least partly neuroadaptive, compensatory mechanisms following chronic alcohol intake and correlate with reduced neuronal activation during reward expectancy, which is coupled with motivational and learning deficits. (4) DA dysfunction persists after detoxification for a limited amount of time (days to weeks) and can interfere with salience attribution to non-drug stimuli, while neuronal responses to alcohol cues remain elevated and predict the subsequent relapse risk. (5) An up-regulation of mu-opiate receptors in the ventral striatum contributes to chronic alcohol intake and craving. Dopamine–glutamate and dopamine–endorphin interactions remain to be further explored to optimize treatment strategies in alcoholism.

Besides growing knowledge on positive reinforcement in the development of addictive disorders, the field of hyperkatifeia describes the important aspect of (negative) motivators for relapse. Assessing relevant neurobiological markers here might inform additional therapeutic strategies for preventing increased negative mood states in abstinence motivating to continuous consumption. Other important future direction in addiction research is the investigation of changing dopaminergic signaling during acute and protracted abstinence as well as the translational consideration of the exact interplay between complex neurotransmitters systems, with animal models informing human research and vice versa.

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Molecular Imaging Studies of Alcohol Use Disorder



Patrick Bach, Philippe de Timary, Gerhard Gründer, and Paul Cumming

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Abstract Alcohol use disorder (AUD) is a serious public health problem in many countries, bringing a gamut of health risks and impairments to individuals and a great burden to society. Despite the prevalence of a disease model of AUD, the

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current pharmacopeia does not present reliable treatments for AUD; approved treatments are confined to a narrow spectrum of medications engaging inhibitory γ -aminobutyric acid (GABA) neurotransmission and possibly excitatory N-methyl-D-aspartate (NMDA) receptors, and opioid receptor antagonists. Molecular imaging with positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can open a window into the living brain and has provided diverse insights into the pathology of AUD. In this narrative review, we summarize the state of molecular imaging findings on the pharmacological action of ethanol and the neuropathological changes associated with AUD. Laboratory and preclinical imaging results highlight the interactions between ethanol and GABA A-type receptors (GABA_{AR}), but the interpretation of such results is complicated by subtype specificity. An abundance of studies with the glucose metabolism tracer fluorodeoxyglucose (FDG) concur in showing cerebral hypometabolism after ethanol challenge, but there is relatively little data on long-term changes in AUD. Alcohol toxicity evokes neuroinflammation, which can be tracked using PET with ligands for the microglial marker translocator protein (TSPO). Several PET studies show reversible increases in TSPO binding in AUD individuals, and preclinical results suggest that opioid-antagonists can rescue from these inflammatory responses. There are numerous PET/SPECT studies showing changes in dopaminergic markers, generally consistent with an impairment in dopamine synthesis and release among AUD patients, as seen in a number of other addictions; this may reflect the composite of an underlying deficiency in reward mechanisms that predisposes to AUD, in conjunction with acquired alterations in dopamine signaling. There is little evidence for altered serotonin markers in AUD, but studies with opioid receptor ligands suggest a specific up-regulation of the μ -opioid receptor subtype. Considerable heterogeneity in drinking patterns, gender differences, and the variable contributions of genetics and pre-existing vulnerability traits present great challenges for charting the landscape of molecular imaging in AUD.

Keywords Alcohol use disorder (AUD) · FDG · Molecular imaging · Neuroinflammation · PET · Receptors · SPECT

Abbreviations

2DG	2-[¹⁴ C]deoxyglucose
AUD	Alcohol use disorder
BP _{ND}	Binding potential (non-displaceable)
D1R	Dopamine D ₁ receptor
D2R	Dopamine D ₂ receptor
DALYS	Disability-adjusted life years
DAT	Dopamine transporter
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and statistical manual of mental disorders fifth revision

EMA	European Medicines Agency
FDA	Food and Drug Administration
FDG	[¹⁸ F]fluorodeoxyglucose
GABA	γ -Aminobutyric acid
GABA _{AR}	GABA A-type receptors
NMDA	N-methyl-D-aspartate
PET	Positron emission tomography
SPECT	Single-photon emission computed tomography
TSPO	Translocator protein
VS	Ventral striatum
WCST	Wisconsin Card Sorting Test

1 Introduction

The prevalence of alcohol use exceeds 70% among adults in some countries (Degenhardt et al. 2018). The adage *dosis sola facit venenum*, attributed to Paracelsus, holds especially true for alcohol. Drinking a glass or two of wine may induce a socially acceptable disinhibition and increased verbosity, along with a blood ethanol concentration of 5–10 mM. However, a tenfold higher dose is likely to induce loss of consciousness in individuals who have not acquired tolerance, whereas a 20-fold higher dose may cause coma and death. As such, ethanol has a relatively low potency and low safety range. Excessive alcohol use is one of the leading causes for death and disability worldwide, accounting for up to 6% of deaths worldwide and approximately 5% of the global disease burden, with alcohol use being the seventh leading risk factor for death and disability-adjusted life years (DALYs) (Degenhardt et al. 2018). For all-cause mortality, there is a positive and curvilinear association with the level of alcohol consumption, with the minimum mortality risk occurring at around 100 g per week (Degenhardt et al. 2018). High concentrations of ethanol and its primary metabolite acetaldehyde induce oxidative stress and deoxyribonucleic acid (DNA) damage in cultured neurons (Lee et al. 2005) and are teratogenic for fetal mice (Webster et al. 1983). Excessive alcohol use links to over 60 acute and chronic diseases (Rehm et al. 2003). Indeed, alcohol consumption has a roughly linearly association with risk of stroke, coronary disease (excluding myocardial infarction), heart failure, fatal hypertensive disease, and fatal aortic aneurysm; those with very heavy alcohol consumption (>100 g/day for males or 60 g/day for females) have a life expectancy that is shortened by decades (Rehm et al. 2003). Chronic alcohol use has also been associated with cognitive impairments, covering a spectrum of disorders including alcohol-related dementia and the Wernicke-Korsakoff syndrome (Hayes et al. 2016).

Alcohol use disorder (AUD), which replaces the earlier terms alcohol dependence and alcoholism, refers to a condition in which drinking evokes symptoms that impair mental and physical health. According to the current classification system, the

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (<https://doi.org/10.1176/appi.books.9780890425596>), these symptoms include: a strong desire to drink alcohol; unsuccessful efforts to cut down or limit alcohol use; evidence of tolerance, such that increased doses of alcohol are required in order to achieve effects originally produced by lower doses; continued alcohol use despite social or interpersonal problems or clear evidence of overtly harmful physical consequences (e.g., liver cirrhosis); alcohol use in situations in which it is physically hazardous; occurrence of withdrawal symptoms when substance use has ceased or been reduced, as evidenced by a characteristic withdrawal syndrome typically including sweating, nausea, tachycardia, hypertension, tremor, but also severe events such as seizures, psychotic symptoms, and delirium tremens (National Clinical Guideline 2010).

Globally around 107 million people suffer from AUD, of whom 70% are men (James et al. 2018). Although men show higher rates of alcohol use and binge drinking, women are more susceptible than are men to deleterious health effects of AUD (Holman et al. 1996; Keyes et al. 2019). Longitudinal data from the USA also show a steeper increase in alcohol-related deaths in females, compared to males between the years 1999 and 2017 (White et al. 2020). Indeed, death rates for women with AUD are 50–100% higher than for men, reflecting alcohol-related accidents, heart disease, stroke, and liver diseases (Mokdad et al. 2004). Part of the gender differences in alcohol-related health consequences may reflect differences in alcohol metabolism and body fluid compartments (Lieber 2000).

Historically, Cloninger and colleagues (Cloninger et al. 1981) proposed a binary typology of individuals with alcoholism, with Type I alcoholism occurring in both sexes, causing few social and legal problems and either mild or severe AUD symptoms. In contrast, Type II alcoholism was said to occur predominantly in men, with earlier age at onset and causing higher rates of social and legal problems, rating high on novelty seeking temperament (Cloninger et al. 1981). Initial findings of an association with certain genetic markers, especially involving dopaminergic neurotransmission, have been reassessed due to the generally weak reproducibility of such studies (Dao et al. 2021; Jung et al. 2019). Current diagnostic systems (DSM-5, see above) have conceptualized AUD as a dimensional construct, classified as mild, moderate, or severe, according to the number of criteria met by an individual. As such, AUD is a chronic relapsing condition characterized by repeated heavy alcohol consumption despite negative consequences. While studies indicated that 5–45% of untreated individuals with AUD may achieve some improvement or remission, meta-analyses show that the average short-term abstinence rate in non-treated individuals (e.g., waiting lists) is only about 20%, versus 40% in treated individuals (Moyer and Finney 2002). Thus, there is scope for improving the general efficacy of AUD treatment. We suppose that the search for more effective treatments could benefit from an improved understanding of the individual neurobiological factors associated with AUD.

2 Treatment of AUD

In general, treatment for AUD encompasses social, psychological, and pharmacotherapeutic strategies (Kiefer and Mann 2005). Pharmacotherapeutic strategies for the acute phase of alcohol withdrawal of patients presenting with a physical dependence generally involve an adapted dose of benzodiazepines and vitamin supplementation (Kosten and O'Connor 2003) followed by long-term therapy. The sedative compounds clomethiazole and the benzodiazepines, as allosteric activators of inhibitory γ -aminobutyric acid (GABA)-A receptors (GABA_AR), have anxiolytic and anticonvulsant actions, thus decreasing the intensity of withdrawal symptoms and protecting against the life-threatening seizures that can occur during acute detoxification. Currently, the European Medicines Agency (EMA) or the Food and Drug Administration (FDA) has approved three types of medication for long-term treatment of AUD. Of these, the aldehyde dehydrogenase inhibitor, disulfiram has been available since the 1940s. Disulfiram produces an aversive reaction to alcohol consumption by irreversibly inhibiting aldehyde dehydrogenase, leading to the accumulation in blood of the primary ethanol metabolite acetaldehyde, which results in flushing, sweating, nausea, and tachycardia. As such, disulfiram mimics the trait of alcohol intolerance seen in some Asian populations due to a functional polymorphism of the aldehyde dehydrogenase enzyme (Goedde and Agarwal 1987).

The other two approved medications for treating AUD are naltrexone and acamprosate. Naltrexone is an opioid-antagonist with high affinity for μ -opioid-receptors and a lesser affinity for κ - and δ -opioid receptors (Altshuler et al. 1980; Lee et al. 1988). Alcohol consumption stimulates the release of opioid peptides and μ -receptor activation, which modulates alcohol-induced dopamine release and consequent reward signaling within the nucleus accumbens and mesocorticolimbic system (Hansson et al. 2019; Mitchell et al. 2012). Alternatively, the ethanol metabolite (*R*)-salsolinol may act as an agonist at central μ -opioid-receptors, thereby contributing to behavioral sensitization and excessive alcohol intake (Deitrich et al. 2006; Quintanilla et al. 2014, 2016). For example, microinjections of salsolinol into the rat posterior ventral tegmental area increase dopamine release in the nucleus accumbens shell (Deehan Jr et al. 2013). This presents a mechanism whereby the opioid receptor antagonist naloxone could attenuate ethanol-induced increases in dopamine release in the nucleus accumbens, which theoretically should remove the incentive to consume ethanol (Gonzales and Weiss 1998). Acamprosate, a homotaurine analog, is classically considered an NMDA receptor antagonist and positive allosteric modulator of GABA_A receptors (Spanagel et al. 2005; Umhau et al. 2010), thereby attenuating alcohol craving. Studies that are more recent failed to replicate effects of acamprosate on N-methyl-D-aspartate (NMDA) receptors or metabotropic glutamate receptors (Spanagel et al. 2014). Hence, the pharmacological mechanisms whereby acamprosate exerts its effects remain to be fully established.

There is emerging clinical and preclinical support for the efficacy of still unapproved medications for the treatment of AUD, notably the anti-glutamatergic compound topiramate (Blodgett et al. 2014). Other medications showing a certain

efficacy include the 5HT₃ antagonist ondansetron (Johnson et al. 2000), the nicotinic partial agonist varenicline (Litten et al. 2013), and the GABA-B agonist baclofen (Bschor et al. 2018). For a comprehensive review of novel agents for the pharmacological treatment of alcohol use disorder, see Burnette et al. (2022). Antidepressants showed small to medium effects of depressive symptoms in patients with comorbid AUD and depression, but showed very limited effects on alcohol use (for systematic reviews, see Agabio et al. (2018); Foulds et al. (2015)). Overall, the available pharmacological treatments are supportive in the acute withdrawal phase, but of modest benefit in sustaining long-term abstinence. This implies that establishing better the molecular mechanisms underlying AUD symptomatology and addictive behavior might guide the development of improved pharmacological interventions. In this regard, molecular neuroimaging using Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) enables the probing of acute and long-term changes in the brain due to ethanol consumption.

3 GABAergic Effects of Ethanol

Some researchers have attributed the effects of ethanol and other alcohols on neuronal function to their high solubility in the plasma membrane lipid bilayer, and consequent changes in the biophysical properties of membranes (Murail et al. 2012; Patra et al. 2006), along with non-specific effects at various other targets (Eckardt et al. 1998; Harris et al. 2008; Spanagel 2009). More in keeping with classical pharmacology, ethanol and other alcohols are allosteric modulators of GABA_A receptors, thus potentiating the inhibitory chloride currents stimulated by endogenous GABA (Nestoros 1980), much in the manner of benzodiazepines. The GABA_A receptor is a heteropentameric ligand-gated ion channel that occurs in a wide diversity of subunit compositions; not all forms are equally sensitive to interactions with ethanol, but various GABA_A receptor subtypes have sensitivity for alcohol (Mihic et al. 1997; Sundstrom-Poromaa et al. 2002). In particular, the negative modulation of GABA_{AR}s by the imidazobenzodiazepine partial inverse agonist Ro15-4513 antagonizes the behavioral effects of low to moderate doses of alcohol (Suzdak et al. 1988), apparently by occupation of the benzodiazepine binding site on the α 5-subunit of the GABA_{AR} (Sundstrom-Poromaa et al. 2002), which are notably abundant in the hippocampus.

The chemical structure of Ro15-4513 lends itself for preparation as a tracer for PET using the positron-emitting radionuclide Carbon-11 (physical half-life 20 min). Indeed, [¹¹C]Ro 15-4513 showed high uptake in brain of Cynomolgus monkeys, which was displaceable by treatment with flumazenil in cerebral cortex and basal ganglia (although not in cerebellum) (Halldin et al. 1992). Similarly, PET recordings with [¹¹C]Ro15-4513 showed relatively high accumulation in frontal cortex, temporal cortex, and hippocampus (Inoue et al. 1992b). Relative to a metabolite-corrected arterial input function, the total distribution volume of [¹¹C]Ro15-4513

in human brain ranged from 3.5 ml g⁻¹ in cerebellum to 9 ml g⁻¹ in anterior cingulate cortex. Rat studies showed no displacement of [¹¹C]Ro15-4513 by the GABA_{AR} α 1 subunit selective hypnotic medication zolpidem (Lingford-Hughes et al. 2002). Further studies in non-human primates confirmed the relative selectivity of [¹¹C]Ro15-4513 binding for the α 5-subunit of the GABA_{AR} in limbic cortical regions (Maeda et al. 2003). A PET study in abstinent men with AUD showed a significant decrease in [¹¹C]Ro15-4513 binding in nucleus accumbens, parahippocampal gyri, right hippocampus, and amygdala compared with a healthy control group (Lingford-Hughes et al. 2012). Furthermore, the individual extent of decreased hippocampal binding correlated with impaired performance in a verbal memory task in the patients. While the abstinence period of 6 weeks excludes any acute effect of competition from alcohol, these reductions may reflect toxicity in limbic structures, or adaptive down-regulation of GABA_{ARs} in response to chronic ethanol exposure. One might thus expect a normalization of GABA_{AR} binding after long-term abstinence.

Membrane binding studies in vitro with [³H]Ro15-4513 showed that a line of alcohol-sensitive rats had a higher affinity (lower K_D) but no change in B_{max} relative to the alcohol-insensitive strain, in conjunction with greater sensitivity of the binding in cerebellum to displacement by diazepam (Uusi-Oukari and Korpi 1990). That result is hard to interpret, but may be consistent with a shift in the population distribution of GABA_{AR} subtypes in relation to ethanol sensitivity. However, autoradiography with [³H]Ro15-4513 showed no difference in the GABA_{AR} availability in a strain of alcohol-preferring rats, nor did the proportions of zolpidem and diazepam-sensitive binding sites differ (Wong et al. 1996).

There seems to have been no study testing the effect of an acute ethanol challenge on [¹¹C]Ro15-4513 binding in living brain, either in experimental animals or in humans. The antagonist ligand [¹⁸F]flumazenil is used more often than [¹¹C]Ro15-4513 for PET studies of GABA_{AR}. Acute ingestion of ethanol at an intoxicating dose was without effect on [¹⁸F]flumazenil cerebral uptake in a small group of healthy volunteers (Farde et al. 1994). In that same report, [¹⁸F]flumazenil PET estimates of the saturation binding parameters (B_{max} and K_D) did not differ significantly between healthy controls and men with AUD. Thus, the available PET tracers seem unfit to establish the acute and chronic effects of ethanol on GABA_{AR} availability, possibly due to their inadequate selectivity for the receptor subunits involved in AUD.

4 Brain Energy Metabolism

The specific action of ethanol as an allosteric activator of inhibitory GABA_{ARs} might predict a general inhibition of brain metabolism. The rate of cerebral glucose metabolism is measured autoradiographically from the progressive metabolic trapping of the glucose analogue 2-[¹⁴C]deoxyglucose (2DG) in the brain or by PET using [¹⁸F]fluorodeoxyglucose (FDG). In one 2DG study, rats administered ethanol

in their drinking water for 3 days showed a tendency toward increased 2DG uptake in the brain, whereas longer term administration evoked a global depression of metabolism (Nobrega et al. 1987). More consistent with expectations, intraperitoneal administration of ethanol evoked acute widespread reductions in cerebral 2DG uptake in alcohol-preferring rats (Strother et al. 2005). However, other studies report a dose-dependent effect, whereby 0.25 g/kg ethanol increased 2DG uptake in mesocorticolimbic and nigrostriatal circuit components, but administration of 1.0 and 2.0 g/kg ethanol evoked more circumscribed increases, primarily in the mesocorticolimbic circuit (Williams-Hemby and Porrino 1997a). We suppose that this may reflect the biphasic behavioral effects of alcohol, where a low dose can have a more distinctly stimulant profile. Furthermore, the same authors showed that treatment with a dopamine antagonist tended to block the mesocorticolimbic and nigrostriatal increases in 2DG uptake evoked by the intragastric ethanol at the 0.25 g/kg dose, but with lesser effect on the higher doses (Williams-Hemby and Porrino 1997b). Thus, the cerebrometabolic effects of low-dose ethanol may arise due to altered dopamine signaling, rather than global inhibitory effects of GABA_AR activation on neuronal activity.

Other rat studies employing chronic ethanol exposure showed increased 2DG uptake in sensorimotor cortex, globus pallidus, thalamus, and cerebellum during an acute phase of alcohol withdrawal, suggesting a disinhibition of neuronal activity in these regions, which might underlie the propensity for withdrawal symptoms, *delirium tremens*, and seizures during acute detoxification (Campbell et al. 1982). In further rat studies, post withdrawal increases in 2DG uptake persisted in certain limbic structures weeks after withdrawal; these long-term changes may conceivably relate to toxicity and the risk for relapse (Eckardt et al. 1986; Smith et al. 2001). However, others reported widespread decreases in 2DG uptake during withdrawal, a difference that the authors attributed to the minimal restraint and lesser stress in their study (Clemmesen et al. 1988). However, rats trained to drink ethanol voluntarily showed decreased 2DG uptake in the hippocampal complex, habenula, anterior ventral thalamus, and mammillary bodies upon ethanol challenge, but increased uptake in the nucleus accumbens and locus coeruleus (Williams-Hemby et al. 1996). Conversely, water challenge in the alcohol-habituated rats evoked widespread increases in 2DG uptake, consistent with the disinhibition reported in other studies. Overall, the various rat 2DG studies show either decreased or increased metabolism after ethanol, depending on the dose and route of administration. However, studies in an acute withdrawal paradigm have more consistently shown increased cerebral metabolism, presumably due to disinhibition. FDG microPET imaging showed that ethanol challenge to naïve Wistar rats reduced whole-brain FDG uptake, especially in parietal cortex and cerebellum, whereas rats with ethanol exposure for 3 months showed a lesser decline, and FDG uptake in rats with 12 months exposure was unaffected by the challenge (Gispert et al. 2017). In the same rat study, the ethanol challenge increased FDG uptake in specific regions (ventral striatum and entorhinal cortex), and effect not showing signs of tolerance after long-term drinking.

In a rare human PET study with [¹¹C]glucose, which is arguably superior to FDG as a tracer for the glucose metabolic rate, there was 20–30% lower glucose metabolism in various cortical and subcortical regions in a group of nine detoxified alcoholics compared with healthy controls (Wik et al. 1988). Results of FDG-PET studies generally concur with preclinical findings using the 2DG autoradiographic method. In one human study, a low dose of ethanol evoked variable effects on FDG uptake in healthy volunteers, whereas a higher dose decreased global metabolic rate in the same subjects (de Wit et al. 1990). However, there were no clear relationships between the mood-altering effects of alcohol and altered brain metabolism. In a subsequent study in 20 healthy volunteers, a dose of 0.25 g/kg decreased global CMR_{Glc} by 10%, whereas 0.5 g/kg evoked a 23% global decrease (Volkow et al. 2006). The lower dose mainly affected the cerebral cortex, whereas the higher dose also reduced metabolism in cerebellum, mesencephalon, basal ganglia, and thalamus; these effects of rather low doses were not associated with significant impairment in performance of a cognitive test battery. An FDG-PET study in detoxified AUD subjects compared with healthy controls did not indicate any group difference in the hypometabolism evoked by a challenge with lorazepam (Volkow et al. 1997); this led the authors to conclude that the metabolic deficit seen in the baseline scans could not be attributable to GABAergic mechanisms per se. Further investigations by the same group showed that the ethanol-induced reductions in FDG uptake were offset by increases in the uptake of the alternate energy substrate [¹¹C]acetate (Volkow et al. 2013a); thus, ethanol may provoke a shift away from the usual absolute dependence of brain tissue on glucose metabolism in favor of acetate or perhaps ketone bodies. It was shown that patients with AUD show higher brain acetate metabolism and lower brain glucose metabolism compared with controls and that this shift from glucose to acetate metabolism in AUD persists beyond the acute intoxication state (Volkow et al. 2017). The authors suggested that this might result in a paradoxical energy-deficit state in the brain during alcohol detoxification, when acetate levels in plasma decrease, which in turn might drive withdrawal symptoms. In line with this hypothesis, recent data from a small pilot trial also indicated that individuals following a ketogenic diet during withdrawal from alcohol experienced reduced withdrawal symptoms and craving intensity (Wiers et al. 2021).

Alcoholism occurs more frequently in men than in women and the preponderance of molecular imaging studies of AUD has included exclusively male patients. An FDG-PET study in detoxified female AUD patients did not indicate any substantial reduction in metabolic rate, which argues against claims of greater toxicity of alcohol for the female brain (Wang et al. 1998).

There are relatively few reports on cerebrometabolic changes associated with chronic and severe AUD. An FDG-PET study of a 40-year-old individual with Wernicke-Korsakoff syndrome showed bilateral thalamic and severe bilateral temporal-parietal hypometabolism (Fellgiebel et al. 2003). After thiamine treatment and confirmed alcohol abstinence for 9 months, there was substantial recovery of clinical state along with FDG uptake in cortical regions. However, there was no recovery of FDG uptake in the thalamus during this remission. A study in 12 Wernicke-Korsakoff patients showed atrophy of the thalamus and mammillary

bodies, along with some loss of frontal lobe volume, all consistent with Papez circuit degeneration (Reed et al. 2003). FDG-PET in the same individuals showed relative declines in metabolism in white matter and in subcortical gray matter of the diencephalon. An FDG-PET case study in a patient with alcoholism-related hallucinosis showed normal uptake in the temporal lobes, but 14% reduced uptake in the left thalamus (Soyka et al. 2000). A test of the selective GABA transporter 1 inhibitor tiagabine in healthy controls did not interfere in the cerebrometabolic effects of alcohol challenge as measured by FDG-PET (Fehr et al. 2007).

5 Metabotropic Glutamate Receptors

As distinct from the ionotropic glutamate receptors, which are ligand-gated ion channels, there is an important family of at least five glutamate receptor types, which mediate their effects via coupling to intracellular second messenger systems. As such, they are known as the metabotropic glutamate receptors (mGluR). We have recently reviewed the literature on molecular imaging of this important class of receptors, as well as the NMDA-type ionotropic receptors (Kim et al. 2020). A recent FDG-PET study examined the effect on cerebral glucose metabolism in alcohol-dependent rats with infralimbic cortex-specific knockdown of the type 2 metabotropic glutamate receptor (mGluR2) after pre-treatment with the mGluR2/3 agonist LY379268 or vehicle (Meinhardt et al. 2021). Results showed that, compared to vehicle treatment, the mGluR2/3 agonist LY379268 challenge led to decreased FDG trapping in the infralimbic cortex of control animals under resting state conditions, while there was no such effect of LY379268 in the mGluR2 deficient, alcohol-dependent rats. The authors interpreted these results to indicate that alcohol-dependent animals deficient in mGluR2 could not modulate their glucose utilization in the infralimbic cortex upon pharmacological receptor activation.

Initial PET studies of the type five-metabotropic glutamate receptor (mGluR5) used the ligand [¹⁸F]FPEB, which is now finding increasing competition from the alternate tracer [¹¹C]ABP688. A recent dual tracer study tested the effects of an acute challenge with alcohol on the cerebral availabilities of mGluR5 to [¹⁸F]FPEB PET (Leurquin-Sterk et al. 2018), while also measuring in the same moderate drinkers the effects on dopamine receptor availability to [¹⁸F]fallypride, as shall be discussed in greater detail below. They reported that baseline availability of binding sites for [¹⁸F]FPEB in the prefrontal cortex, temporal lobe, caudate nucleus, and thalamus correlated with “liking” of the effect of alcohol, as did declining [¹⁸F]fallypride in similar regions, suggesting a link between cortical dopamine release, mGluR5 availability, and reinforcing properties of alcohol. This notion was lent support by a preclinical finding that higher baseline binding of [¹⁸F]FPEB in the rat nucleus accumbens predicted future predilection to consume ethanol (de Laat et al. 2019); prolonged ethanol exposure generally decreased the mGluR5 availability in rat brain. Further clinical PET research with [¹⁸F]FPEB indicated that prolonged abstinence (2–6 months) was associated with recovery of the initially low mGluR5 availability in

brain, along with a decline in the intensity of craving (Ceccarini et al. 2020). This is encouraging with respect to the reversibility of acquired brain changes in AUD.

An [¹¹C]ABP688 PET study of 14 male AUD patients showed a significant 10% higher binding in various cortical regions as compared to healthy controls, and an inverse relation between amygdala binding with craving scores in the AUG group (Akkus et al. 2018); this study made careful matching of non-smoking subjects, as tobacco consumption has strong independent effects on mGluR5 availability. Another [¹¹C]ABP688 PET study in a group of 12 AUD patients with prolonged abstinence showed only small decreases in mGluR5 binding in some cortical regions as compared to controls (Joo et al. 2021). An additional functional connectivity analysis using a seed placed in the inferior parietal cortex of the abstinent AUD patients showed abnormal connectivity with distal regions such as the occipital pole and dorsal visual cortex. While difficult to interpret, the result may call for more studies aiming to link AUD-related molecular imaging with functional connectivity; changes in receptor abundance may prove to weak surrogates for more behaviorally and cognitively relevant changes in network activity of the brain.

6 Neuroinflammation

There is considerable evidence for involvement of peripheral and central inflammation in the development of the AUD. Heavy alcohol consumption induces neuroinflammation either via a direct effect on microglial reactivity (De Santis et al. 2019, 2020; Fernandez-Lizarbe et al. 2008; Zou and Crews 2010) or by excitotoxicity due to GABA/glutamate imbalance (Mon et al. 2012) and resultant oxidative stress (Almansa et al. 2009). AUD patients also present with important signs of peripheral inflammation (Leclercq et al. 2012) that are partially attributable to increases in gut permeability, to alterations in the composition of the gut microbiota (Leclercq et al. 2014), and possibly to complex peripheral metabolomics changes in the body (Leclercq et al. 2020). There is extensive evidence that inflammation and neuroinflammation contribute to aspects of addictive behaviors in animal models (Robinson et al. 2014).

The translocator protein (TSPO) binding site (formerly known as the peripheral benzodiazepine receptor) is a cholesterol transporter located in the mitochondrial membrane of microglia, which are the resident macrophages of the brain. Radio-tracers for the TSPO binding site can reveal microglial activation in response to neurotoxic insults, although there is some ambiguity about the cellular localization of TSPO, complicated by the caveat that most TSPO PET tracers distinguish a functional polymorphism of TSPO in human populations (Cumming et al. 2018). For example, this phenomenon explained the allelic dependence of [¹⁸F]-FEPPA binding in human PET studies (Mizrahi et al. 2012), and the general requirement for genotyping of individuals, given the roughly equal abundances of binding and non-binding alleles in human populations. Roughly 10% of individuals are homozygotic for the non-binding allele, and thus show negative results with most TSPO PET tracers other than prototypic ligand, [¹¹C]PK11195.

Preclinical data indicated an increase in TSPO in alcohol-dependent rats (Tamborska and Marangos 1986). In particular, there were 20–50% increases in the binding of [³H]Ro-5-4864 to cortical and cerebellar membranes, which persisted for 3 days after withdrawal, but had largely normalized at 4–7 days. There were no accompanying changes in GABA_AR sites labelled with [³H]-ethyl-β-carboline-3-carboxylate. In another rat study, chronic exposure to ethanol vapor increased the autoradiographic binding of the prototypic TSPO ligand [³H]PK11195 in thalamus and hippocampus, with trend level increases for another TSPO ligand, [³H]PBR28, compared to control rats (Tyler et al. 2019). However, corresponding [¹¹C]PBR28 PET studies did not reveal increased TSPO binding *in vivo*, which led the authors to question the validity of that tracer for detecting microglial activation in the alcohol-dependent model. Three young baboons underwent serial TSPO PET with [¹⁸F]DPA714 PET at baseline, during a binge-drinking paradigm, and after prolonged withdrawal (Harris et al. 1996). The total distribution volume in brain at steady-state (V_T ; ml g⁻¹) was nearly doubled during alcohol exposure relative to baseline and remained 50% increased after several months of withdrawal, suggesting persistence of microglial activation in that model.

Despite the disparate results in rat models, results of the non-human primate study cited above might still predict at least a transient increase in TSPO binding sites in alcohol-dependent human subjects. However, in a TSPO PET study with [¹¹C]PBR28, there was a 20% reduction in the V_T in hippocampus of a group of detoxified AUD individuals (Kalk et al. 2017). The magnitude of V_T correlated positively with verbal memory performance in the combined group of AUD and healthy controls, but not in the AUD group in isolation. Another [¹¹C]PBR28 PET experiment in groups of 15 AUD and control subjects showed 10% lower V_T in brain of the AUD groups at 1–4 days after the last drink (Hillmer et al. 2017); exploratory analysis showed a negative correlation between severity of alcohol dependence and [¹¹C]PBR28 in striatum and hippocampus. Another [¹¹C]PBR28 PET study ($n = 19$) comparing participants with AUD and a similar sized group of healthy controls did not show any group differences in V_T , except when considering only the mixed affinity subgroup (i.e., TSPO rs6971 heterozygotes) of AUD patients, who proved to show a reduction in binding (Kim et al. 2018). Furthermore, cholesterol levels in the combined group correlated inversely with [¹¹C]PBR28 binding in the brain, suggesting a functional relationship between the TSPO phenotype and inflammatory responses. Rats treated with ethanol for 2 weeks in a binge-drinking model showed twofold increases in TSPO binding to [¹⁸F]DPA714 PET, but this neuroinflammatory response was substantially relieved by treatment with the opioid-antagonist nalmefene (Tournier et al. 2021).

7 Dopamine

We have seen above that antipsychotic medication could block some of the cerebrometabolic effects of a low dose of ethanol, suggesting a mechanism via effects on dopaminergic signaling. We can measure the integrity of nigrostriatal

dopamine innervations with SPECT and PET tracers for various markers for biochemical constituents of the dopamine terminals, namely synaptic vesicles, dopamine reuptake sites, and the pathway for dopamine synthesis (Doudet et al. 2006). The latter pathway is probed by [¹⁸F]FDOPA, an exogenous levodopa analogue that is metabolically trapped in neuron terminals containing the enzyme DOPA decarboxylase, thus giving an index of the local capacity for dopamine synthesis. In an [¹⁸F]FDOPA PET study of ten AUD patients designated a Type I according to Cloninger, the group mean analysis indicated a 28% elevation in [¹⁸F]FDOPA trapping in the left putamen, and a 36% elevation in the right caudate (Tiihonen et al. 1998). These increases correlated inversely with performance in the Wisconsin Card Sorting Test (WCST). The finding of increased dopamine synthesis capacity goes against the conventional expectation of reduced dopaminergic transmission in patients with substance dependence. Indeed, the striatal [¹⁸F]FDOPA influx was completely within the normal range in another study of AUD patients (Heinz et al. 2005b), although individual results correlated inversely with the degree of craving reported during abstinence. Yet another [¹⁸F]FDOPA PET study showed normal influx in a group of 12 detoxified AUD patients. However, advanced kinetic analysis of the steady-state trapping of [¹⁸F]FDOPA metabolites (V_D ; ml g⁻¹) showed that the patient group, unlike healthy controls, showed no significant correlation between V_D in left amygdala and activation in left anterior cingulate cortex in response to aversive visual stimuli (Kienast et al. 2013). Further advanced kinetic analysis of the same data set showed that the net cerebral influx of [¹⁸F]FDOPA was completely normal in the AUD group. However, the magnitude of V_D in the left caudate head was reduced by 43% relative to the controls, consistent with a 58% increase in the turnover rate of trapped [¹⁸F]fluorodopamine (k_{loss} , min⁻¹) (Kumakura et al. 2013). Furthermore, the extent of craving reported at the time of PET scanning correlated with the individual magnitude of k_{loss} in the ventral striatum. Thus, advanced kinetic analysis of [¹⁸F]FDOPA PET suggests intact dopamine synthesis capacity in AUD patients, but a state of elevated dopamine turnover, at least in the condition of withdrawal.

SPECT studies with dopamine transporter (DAT) ligands can establish degeneration of the nigrostriatal dopamine system in Parkinson's disease. A [¹²³I]- β -CIT study comparing 21 impulsive violent AUD patients, 10 non-violent AUD cases, and 21 age-matched controls showed increased spatial heterogeneity in the right striatum of the violent AUD group, along with absence of the normal left-to-right asymmetry in DAT (Kuikka et al. 1998). The authors interpreted this to indicate a subtle disturbance in the development of the nigrostriatal pathway in patients with AUD prone to violence. Another such SPECT study from the same group showed relatively reduced striatal DAT binding in the non-violent AUD group, versus a slight increase in the violent group, relative to healthy controls (Tiihonen et al. 1995). Others showed reduced DAT binding in the striatum of 28 AUD subjects during withdrawal and a significant restoration with prolonged sobriety (Laine et al. 1999). In that study, there was a significant correlation between reduced DAT binding and scores on a depression rating scale, irrespective of the state of withdrawal. Another study reported a positive correlation between the novelty seeking

personality trait and striatal [^{123}I]- β -CIT binding in a group of AUD patients (Laine et al. 2001). A [$^{99\text{m}}\text{Tc}$]-TRODAT SPECT study in AUD patients showed reduced DAT availability in striatum, which was more pronounced in proportion to the duration of alcohol abuse; this reduction in DAT availability was associated with impaired performance in the WCST (Yen et al. 2016).

In a [^{123}I]PE2I SPECT study of a group of nine AUD patients, striatal DAT availability was significantly decreased relative to the control group (Repo et al. 1999), which was seemingly confirmed in a postmortem whole hemisphere autoradiographic study with [^{123}I]PE2I (Tupala et al. 2001). Another postmortem study with [^{125}I]PE2I showed a lack of the usual correlation between age and DAT availability in AUD patients designated as Type I alcoholics, whereas there was the usual decline with age in the control material and Type II patient sample (Tupala et al. 2003). The authors speculated that the Type I group might have had a disease-related change in DAT obscuring the usual 5–10% decline per decade of healthy aging. In studies conducted *in vivo* using cerebral microdialysis or brain slice voltammetry, there was no sign of any differences in the alcohol-evoked dopamine release in wild-type and DAT-KO mice, indicating that effects on the dopamine system are unlikely to entail a direct interaction between ethanol and DAT (Mathews et al. 2006).

Upon release from presynaptic terminals, dopamine acts at receptors expressed on striatal medium spiny neurons and cortical pyramidal cells belonging to two pharmacological classes: dopamine D₁-like receptors (D₁R) and D₂-like receptors (D₂R). Preclinical evidence indicates that ethanol along with pentobarbital and flunitrazepam decreases the binding of the D₁R antagonist [^3H]Sch23390 in mouse striatum in a dose-dependent manner, without altering the binding in cerebral cortex (Inoue et al. 1992a). The pharmacological basis of the interaction is not immediately apparent.

In contrast to the sparse D₁R PET literature, there is an extensive literature on effects of alcohol and AUD on the D₂R, which has highest expression in the extended striatum, and much lower expression in cerebral cortex. Whole hemisphere autoradiography with [^{125}I]epidepride revealed decreased D₂R in cortex of Type I patients with AUD, versus a trend toward increased binding in Type II patients (Tupala et al. 2004). The kinetic analysis of uptake of the D₂R ligand [^{11}C]raclopride is amenable to quantitation as the steady-state binding potential (BP_{ND}; proportional to B_{\max}/K_D) relative to uptake in cerebellum, a non-binding reference region. Notably, the magnitude of [^{11}C]raclopride BP_{ND} is influenced by competition from endogenous dopamine, such that increased dopamine release reduces the magnitude of BP_{ND} in living brain. Voxel-wise analysis of [^{11}C]raclopride BP_{ND} in healthy volunteers did not show any acute effects of intravenous alcohol administration, although individual declines in striatal BP_{ND} did correlate with the subjective responses (Yoder et al. 2007); this implies a considerable degree of variability in the dopaminergic response to a standard dose of alcohol in healthy volunteers. Furthermore, the same research group showed that alcohol infusion after neutral cues evoked a decrease in striatal [^{11}C]raclopride binding in healthy controls, consistent with unconditioned dopamine release, whereas olfactory cues not

followed by alcohol seemingly reduced dopamine release, consistent with a negative/positive reward prediction error model for dopamine (Yoder et al. 2009). On the other hand, others found that consuming an alcohol-free beer flavored beverage reduced ventral striatal [¹¹C]raclopride binding in a heterogeneous group of healthy males to an extent that was more pronounced in those subjects with close relatives suffering from AUD (Oberlin et al. 2013). Subsequent work showed that intravenous ethanol administration reduced [¹¹C]raclopride binding specifically in the left ventral striatum of heavy drinkers, whereas consumption of beer flavored drinks evoked dopamine release in the right ventral striatal; conjoint ethanol administration and beer flavored drink consumption evoked a bilateral dopamine release, suggesting the composite of conditioned and unconditioned effects (Oberlin et al. 2015). The cue-related decrease in [¹¹C]raclopride BP_{ND} in the right ventral striatum in habitual beer drinkers was associated with BOLD signal responses in the bilateral orbitofrontal cortex, consistent with a role for that region in decision making (Oberlin et al. 2016). Further [¹¹C]raclopride PET studies implicated polymorphism A118G in the mu-opioid-receptor gene as a major determinant of striatal dopamine responses to alcohol. Results showed that the striatal dopamine response to alcohol was restricted to carriers of the minor 118G allele (Ramchandani et al. 2011), which might contribute importantly to individual vulnerability to loss of control of alcohol intake.

Whereas in conventional practice, [¹¹C]raclopride administration is as a single bolus, the bolus plus continuous infusion experimental design obtains a persistent steady-state of binding during the PET session. This allows acquisition of PET recordings in the baseline and challenge conditions in a single study. Applying this method in healthy volunteers, D₂R availability at baseline in the left nucleus accumbens correlated with the subjective experience of intoxication after an ethanol infusion (Yoder et al. 2005). This could imply that low basal occupancy of these receptors by dopamine in healthy individuals predicts a greater response to pharmacological challenge evoking a release of dopamine. In another bolus plus infusion study, intravenous ethanol administration evoked a decline in [¹¹C]raclopride binding in groups of AUD patients and controls with and without family history of AUD by 6–7% in the ventral striatum and 2–5% in the caudate and putamen (Kegeles et al. 2018). There was an interaction with order of treatments, such that the subjects with family history who first received the placebo showed a relatively greater effect of the placebo, which could indicate a greater effect of expectation of alcohol infusion in these individuals, presumably indicating a greater vulnerability to its effects on dopamine release.

Using the [¹¹C]raclopride bolus plus infusion paradigm, others showed that intravenous ethanol evoked a bilateral 13% decrease in BP_{ND} in the ventral striatum, with lesser decreases also seen in the caudate/putamen (Aalto et al. 2015). The pronounced effect seen in that study may reflect the high dose, which resulted in a mean blood ethanol level of 1.3 g/L. On the other hand, intravenous infusion of ethanol at a rate clamping the blood level to 0.8 g/L (the legal limit for driving in many countries) evoked a decline in [¹¹C]raclopride binding confined to the right ventral striatum of AUD patients, but was without significant effect in a matched

group of social drinkers (Yoder et al. 2016). As such, AUD may entail a kind of sensitization to the dopamine-releasing effects of ethanol, or perhaps a greater sensitivity to alcohol-related sensory cues, even in the context of an ethanol infusion.

Comparison of a group of AUD subjects with healthy individuals indicated a 20% lower [¹¹C]raclopride BP_{ND} throughout striatum at baseline (Martinez et al. 2005). This result is consistent with a broad literature showing reduced dopamine receptor availability in various addiction conditions, including psychostimulant dependence (Volkow et al. 2007), obesity (Volkow et al. 2008), and even internet addiction (Kim et al. 2011). Furthermore, AUD subjects showed blunting of the [¹¹C]raclopride BP_{ND} reduction after pharmacological challenge with amphetamine, with only 5% displacement in the limbic striatum as compared to 13% in the control group (Martinez et al. 2005). In a combined FDG/[¹¹C]raclopride PET study, others showed blunting of the methylphenidate-induced dopamine release in a group of AUD patients compared with healthy controls (Volkow et al. 2013b). Furthermore, in that study the cerebrometabolic inhibition in striatum to FDG-PET showed a concomitant reduction in its response to methylphenidate; control and patient groups both showed strong correlations between striatal dopamine release with reduced FDG uptake in the subthalamic nucleus, anterior cingulate, and medial orbitofrontal cortex, thus implicating a disabling of limbic circuits.

In another study, the baseline and amphetamine-evoked reductions in [¹¹C] raclopride BP_{ND} did not differ in non-dependent individuals with and without family history of AUD, nor were there differences in the amphetamine-evoked cortisol and growth hormone levels (Munro et al. 2006). This suggests that the dopaminergic manifestations of AUD are more likely to be an acquired trait than genetically determined. However, a comparable [¹¹C]raclopride study in rats showed greater response to ethanol administration in Wistar rats as compared to (naïve) alcohol-preferring rats, which would be more consistent with a pre-existing genetic state of desensitization to dopamine-releasing effects of alcohol in that model (Sullivan et al. 2011).

Whereas [¹¹C]raclopride BP_{ND} reveals striatal D₂R binding, the more affine tracer [¹⁸F]fallypride is also sensitive to the lower abundance extrastriatal binding, albeit with the requirement for more prolonged PET recordings. In a [¹⁸F]fallypride PET study of healthy controls, intravenous infusion of ethanol was without much effect on D₂R availability (Pfeifer et al. 2017); on the other hand, baseline [¹⁸F] fallypride binding in cortical regions correlated with a positive subjective experience. At baseline, a group of AUD patients showed a non-significant 8% reduction in striatal [¹⁸F]fallypride BP_{ND}, and significant 10–20% reductions in thalamus, hippocampus, and insular and temporal cortex as compared to a healthy control group, thus calling attention to extrastriatal dopamine signaling in AUD (Rominger et al. 2012) (Fig. 1). The age-related decline in [¹⁸F]fallypride binding was greater in the AUD group (7%/decade) than in the controls (4%/decade), but this loss was seemingly reversible; prolonged abstinence in some of the patients was associated with partial restoration of the striatal and thalamic binding (Fig. 2). Similarly, an [¹²³I] IBZM SPECT study showed that relatively higher striatal D₂R availability in detoxified inpatients predicted early relapse (Guardia et al. 2000); here, the higher

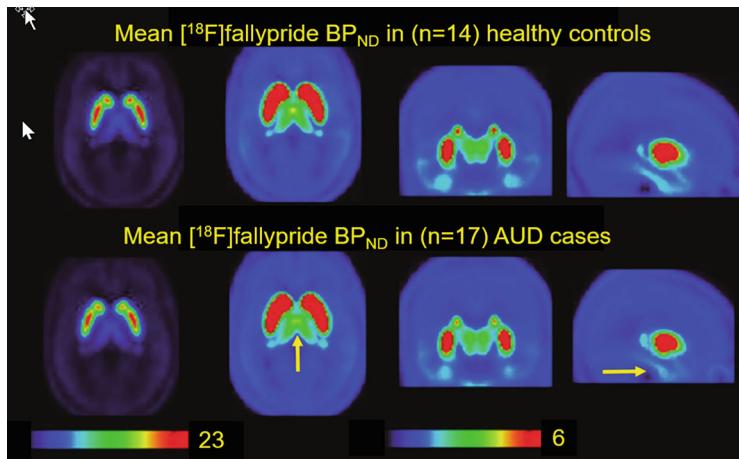


Fig. 1 Mean parametric maps of $[^{18}\text{F}]\text{fallypride}$ BP_{ND} in groups of male healthy controls and AUD patients. The left-hand side with color scale to BP_{ND} of 23 shows little sign of altered D_2R availability in striatum of the AUD group. Contraction of the color scale to BP_{ND} of 6 shows 20% reductions in the binding in thalamus and entorhinal cortex. Figure modified with permission from Rominger et al. (2012)

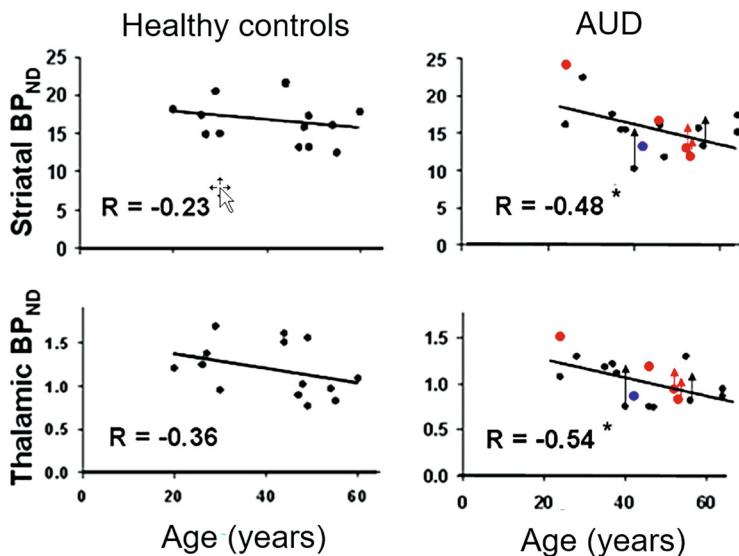


Fig. 2 Correlation of striatal and thalamic $[^{18}\text{F}]\text{fallypride}$ binding potential (BP_{ND}) with age in (left) healthy controls and (right) AUD patients. The blue dot indicates a relapse with unaltered alcohol consumption, whereas the red dots indicate harm reduction compared to baseline consumption. The vertical arrows indicate individuals with increased BP_{ND} at long-term follow-up. Modified with permission from Rominger et al. (2012)

D₂R availability may indicate a lesser tonic occupancy by dopamine, rather than a down-regulation of D₂R per se. This distinction touches on the formal ambiguity of baseline findings with benzamide D₂R ligands, resolution of which calls for complex saturation binding studies involving administration of PET tracers at high and low molar activity (Cumming 2011).

8 Serotonin

A PET study with the serotonin selective reuptake site (SERT) ligand [¹¹C]DASB failed to show any group differences in a comparison of 30 inpatients with AUD with 18 healthy controls, nor was there any relationship with aggressive and violent characteristics of the alcoholic group (Brown et al. 2007). This result stood in contrast with findings of an earlier [¹²³I] β -CIT SPECT study, notably a study in 23 male AUD patients reporting a 30% lower availability of brainstem serotonin transporters relative to age-matched healthy controls (Heinz et al. 1998). This discrepancy may reflect the lesser sensitivity of [¹²³I] β -CIT SPECT, which is nearly ambivalent with respect to its affinity for DAT and SERT, and has lower specific binding than the SERT-selective PET ligand [¹¹C]DASB. PET studies with the controversial serotonin synthesis tracer α -[¹¹C]-methyl-*L*-tryptophan (Cumming 2014) showed cortical regions with elevated or decreased tracer uptake in a group of non-depressed AUD patients relative to controls (Nishikawa et al. 2009).

A PET study with the serotonin 2_AR antagonist ligand [¹⁸F]altanserin did not show any relationship with alcohol (or tobacco) consumption in a large population of healthy volunteers (Erritzoe et al. 2009). The pre- and post-synaptic serotonin 5HT_{1A} receptors were studied in an [¹⁸F]MFWAY PET study in non-human primates using a chronic alcohol self-administration model (Hillmer et al. 2014). Relative to the baseline condition, there were widespread increases in the availability of 5HT_{1A} receptors after 3 months of self-administration, notably in the dorsal raphe nuclei, where they represent presynaptic autoreceptors on serotonin neurons. This result suggested that low autoreceptor availability could predict the acquisition of ethanol self-administration.

9 Opioid Receptors

The clinical efficacy of opioid-antagonists, such as naltrexone and naloxone, in the treatment of AUD has motivated a series of PET investigations of opioid receptors, recently benefiting from the emergence of tracers that are selective for the μ , δ , and κ -opioid receptor subtypes. However, the first phase of the research used non-selective ligands such as [¹¹C]diprenorphine. In one such study, the [¹¹C] diprenorphine V_T was marginally increased in a group of early abstinence AUD patients (Williams et al. 2009); however, there was a significant correlation between

increased binding in the anterior cingulate cortex with the severity of craving, which is a predictor of relapse. In another study, AUD patients had relatively increased binding in the ventral striatum and other brain regions of the μ -selective agonist ligand [^{11}C]carfentanyl, but no differences in the uptake of the δ -selective ligand [^{11}C]methylnaltrindole (Weerts et al. 2011). In another [^{11}C]carfentanyl study, μ -opioid receptor availability was elevated in the ventral striatum and nucleus accumbens in AUD patients compared to healthy controls; this increase persisted after 5 weeks of abstinence and correlated with intensity of alcohol craving, which is predictor for relapse (Heinz et al. 2005a). In AUD patients under treatment with naltrexone (FDA-recommended dose of 50 mg daily), there was nearly complete occupancy at μ -opioid receptors labelled with [^{11}C]carfentanyl, but only 21% occupancy at δ -sites labelled with [^{11}C]methylnaltrindole (Weerts et al. 2008). In an extension of those study, the naltrexone-evoked increases in plasma cortisol levels showed a negative correlation with [^{11}C]methylnaltrindole in ventral striatum and other limbic brain regions of healthy subjects, whereas AUD subjects showed no such relationship (Wand et al. 2013). Similarly, there was a significant correlation between plasma cortisol response and baseline [^{11}C]carfentanyl binding in brain of healthy subjects, but no such relationship in the AUD group (Wand et al. 2012). The reason for these dissociations between brain receptor levels and cortisol release after naloxone challenge remains uncertain. A subsequent [^{11}C]carfentanyl PET study in alcohol-dependent patients compared the effects of naltrexone versus placebo treatment on relapse risk, and examined whether such effects are moderated by the A118G μ -opioid-receptor polymorphism (Hermann et al. 2017). They indeed found a significant interaction between the μ -opioid-receptor polymorphism, [^{11}C] carfentanyl binding in the ventral striatum, and relapse risk. More specifically, in carriers of the less common G-allele, lower striatal [^{11}C]carfentanyl binding was associated with a higher relapse risk, an effect that was especially pronounced in the group treated with naltrexone. The authors concluded that the low [^{11}C]carfentanyl binding in the ventral striatum might indicate a low tonic opioid signaling at μ -opioid-receptors, thus explaining the ineffectiveness of naltrexone treatment in this subgroup.

Occupancy by naltrexone at κ -opioid receptors labelled with [^{11}C]-LY2795050 by a dose of 100 mg naltrexone, which exceeds the FDA-recommended daily dose of 50 mg, correlated negatively with the reduction in alcohol consumption and correlated positively with craving in a mixed gender group of AUD patients treated with naltrexone (de Laat et al. 2020). The authors attributed these results to the competing effects of naltrexone at μ - and δ -opioid receptors. In another [^{11}C]-LY2795050 PET study, AUD patients had significantly reduced κ -opioid receptors in amygdala and pallidum compared to healthy controls and absence of the normal age-related decline in κ -opioid binding sites (Vijay et al. 2018). Naloxone-precipitated opioid withdrawal evoked increased [^{11}C]raclopride displacement in the dorsal striatum of opioid-dependent males (Shokri-Kojori et al. 2021) suggesting a link between opioid receptors and dopamine release in substance abuse. Moreover, the magnitude of this effect correlated with the aversive experience evoked by opioid receptor blockade.

10 Discussion and Conclusions

In reviewing the molecular imaging of AUD, we have focused on the effects of challenge with ethanol on brain metabolism and receptor availability, and the corresponding long-term changes encountered during withdrawal in AUD patients. Molecular neuroimaging studies have contributed to elucidating the mechanisms of alcohol on brain neurochemistry, receptor systems, reward processing, and the neurobiological basis of AUD symptomatology. Their results demonstrate widespread dysregulation in dopaminergic, opioid, serotonergic, and GABAergic systems in AUD. The presented results indicate that these changes are dynamic and dependent on the severity of the addiction, the time since last alcohol use and the individual history of alcohol exposure. This dynamicity might also explain the divergent results of molecular neuroimaging studies. In addition, individual patient characteristics, such as gender and smoking status, which have not been investigated systematically in molecular neuroimaging studies yet, but were repeatedly associated with different alcohol use patterns and treatment trajectories, might explain variability in presented study results.

Effects of ethanol on the GABAergic system mediate ethanol's acute sedating and anxiolytic effects. The reduction in GABA_AR availability observed in animal and human PET studies suggests a down-regulation of these receptors or changes in receptor affinity, which might in part explain differences in ethanol sensitivity and development of tolerance toward ethanol's effects. However, the interpretation of such results is made complicated by subtype specificity of the available tracers. With regard to withdrawal states, the available preclinical and clinical data – mainly derived from spectroscopic and microdialysis studies – have indicated that disturbed balance between GABAergic and glutamatergic systems results in a hyper-glutamatergic state, which drives withdrawal symptoms (Hermann et al. 2012; Roberto and Varodayan 2017). Currently, the lack of NMDA receptor tracers limits the capacity of molecular neuroimaging studies to document specific changes in the glutamatergic neurotransmission system.

The available molecular neuroimaging PET and SPECT studies consistently show changes in dopamine D₁R and D₂R availability, as well as changes in DAT availability in patients with AUD. Results from animal and human data converge in demonstrating significant ethanol-induced displacement of dopamine-tracer BP_{NDS} in striatal regions, which are associated with a subjective ethanol-induced "high" and thus support a key role for dopamine in mediating the rewarding properties of alcohol. Presented data are compatible with the occurrence of a dynamic change from a hypodopaminergic state during early withdrawal to a hyperdopaminergic state during longer abstinence. This seems consistent with the findings of a recent meta-analysis of human and animal data (Hirth et al. 2016), also matching with the theoretical conceptual neurobiological framework of addictive disorders proposed by Koob and Volkow. Dynamic changes occur in dopaminergic neurotransmission proceeding from acute intoxication and binge stages, through the withdrawal and negative affect stage, to the preoccupation and anticipation stage of dependence.

Hypodopaminergic and hyperdopaminergic states might both represent dysfunction of the reward processing system that drives alcohol use and relapse in patients with AUD. As the functional state of the dopaminergic system has been associated with increased craving in individuals with AUD, the potential dynamic regulation of the dopamine system in AUD should have consequences for pharmacological treatments. Depending on the current state of the dopaminergic system, direct pharmacological interventions with agonists or antagonists of D₁R or D₂R would yield variable behavioral effects. Perhaps in line with this hypothesis, clinical studies investigating direct dopamine receptor antagonists did not yield consistent effects (Hutchison et al. 2006; Schmidt et al. 2002; Wiesbeck et al. 2001). New approaches that consider receptor internalization and desensitization might help to elucidate the complex dynamics of the dopaminergic system in AUD.

Molecular neuroimaging studies have significantly contributed to our understanding of the role of the opioid systems in AUD and the neurobiological effects of pharmacological treatment with opioid-antagonists, such as naltrexone. The available data from studies that used selective tracers for the μ , δ , and κ -opioid receptor subtypes indicate a higher μ -opioid receptor availability in the ventral striatum, nucleus accumbens, and anterior cingulate cortex in patients with AUD and a significant positive association between μ -opioid receptor availability and alcohol craving, which predicted subsequent relapse. In contrast, data indicated a decrease in κ -opioid receptors in amygdala and pallidum in individuals. Regarding the effects of opioid-antagonists, study data showed that FDA-recommended doses of 50 mg naltrexone produced a near complete inhibition of the μ -opioid receptor in recently abstinent patients with AUD, while there was a lower inhibition and greater variability of δ -opioid receptor blockade, which may contribute to individual differences in treatment outcomes to naltrexone. In addition, higher doses of naltrexone (100 mg per day) yielded a κ -opioid receptor occupancy above 90%, which was associated with higher craving and fewer reductions in alcohol use. This might indicate that especially the actions of naltrexone at μ -opioid receptors (and to a lesser extent at δ -opioid receptors) might confer its beneficial effects on relapse risk and drinking outcomes, while κ -opioid receptor blockade, as seen with higher doses, might be associated with lesser efficacy. This biphasic effect could also provide a framework for explaining the observations that lower doses of naltrexone can have greater clinical efficacy in patients with AUD.

The limited molecular neuroimaging data on the serotonergic system in AUD indicate changes in serotonin transporter availability and availability of 5HT_{1A} receptors in the brainstem. From a clinical perspective, the serotonergic system is of interest, due to the high comorbidity of AUD and depressive disorders. In addition, treatment with antidepressants has had inconsistent effects on depressive symptoms and drinking behavior in clinical trials, which draws attention to the likely importance of individual differences in the serotonergic systems of patients with AUD (Agabio et al. 2018). Furthermore, ionotropic 5-HT₃ receptors may represent a viable pharmacological treatment target in AUD, due to their role in regulating dopamine release in the mesolimbic system (Kilpatrick et al. 1996). In line with that finding, a preliminary clinical trial indicated a significant effect of the 5-HT₃

receptor antagonist ondansetron on alcohol use in patients with AUD (Johnson et al. 2000). Here molecular neuroimaging studies that target the serotonergic system might contribute to a better understanding of the variable treatment effects observed in patients with comorbid AUD and depression. After a long moratorium against clinical research with ibogaine and classical hallucinogens, we are seeing new interest in their potential for relieving AUD (Barsuglia et al. 2018; Cameron et al. 2021).

Regarding the detrimental effects of alcohol on brain metabolism and brain structure, molecular neuroimaging studies provided proof for a dose-dependent effect of ethanol on cerebral metabolism, with higher doses of ethanol resulting in widespread hypometabolism. In addition, studies indicated an ethanol-induced TSPO-dependent activation of microglia in the brain and following neuroinflammatory responses as a potential mediator of ethanol's detrimental effects on cerebral metabolism and brain structure. By probing acute and chronic changes in cerebral metabolism and neurotransmission, we may come to establish better the nature of dependence and the correlates of abstinence and relapse, perhaps delivering a more individualized medicine that can support improved outcomes for those living with AUD.

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The Continuing Challenges of Studying Parallel Behaviours in Humans and Animal Models



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Abstract The use of animal models continues to be essential for carrying out research into clinical phenomena, including addiction. However, the complexity of the clinical condition inevitably means that even the best animal models are inadequate, and this may go some way to account for the apparent failures of discoveries from animal models, including the identification of potential novel therapies, to translate to the clinic. We argue here that it is overambitious and misguided in the first place to attempt to model complex, multifaceted human disorders such as addiction in animals, and especially in rodents, and that all too frequently “validity” of such models is limited to superficial similarities, referred to as “face validity”, that reflect quite different underlying phenomena and biological processes from the

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clinical situation. Instead, a more profitable approach is to identify (a) well-defined intermediate human behavioural phenotypes that reflect defined, limited aspects of, or contributors to, the human clinical disorder, and (b) to develop animal models that are homologous with those discrete human behavioural phenotypes in terms of psychological processes, and underlying neurobiological mechanisms. Examples of past and continuing weaknesses and suggestions for more limited approaches that may allow better homology between the test animal and human condition are made.

Keywords Addiction · Alcohol use disorder (AUD) · Biomarkers · Face validity · Reward

1 Introduction

It is an ongoing challenge for biomedical researchers to develop adequate models and methods to study human conditions and disorders using non-human animals, so that questions that for ethical or technical reasons are not readily approached in humans can be addressed experimentally. This includes the field of addiction psychology and neuroscience, and in the context of the present article research on alcohol abuse and addiction, where there is an urgent need for better understanding of the causes and consequences of drug and alcohol abuse, in order to inform the development of pharmacological and behavioural interventions that may be effective at preventing and/or treating addictions. And yet, despite decades of research and investment of considerable sums of money, we seem to have only a glimmer of hope for a rational, empirical- and theory-based approach to the treatment of drug addiction, Alcohol Use Disorder (AUD) and their sequelae. The aim of this article is to ask why, given the wealth and ingenuity of research, this is the case? And what might we do differently to promote future success?

To be sure, drug and alcohol abuse and addiction science has made much headway over the past decades; we now have a good idea of the principal targets for most drugs of abuse (though alcohol remains a problem child), we have a panoply of theoretical approaches to account for different aspects of addiction, and perhaps different kinds of addiction (Badiani et al. 2011), and we have identified and studied the (dys)functioning of several brain areas implicated in the psychological mechanisms by these theories. And although we have only a partial understanding of the workings within and especially between those brain areas, and how their function changes during the addiction process, important progress is being made at the systems, cellular and genomic levels. And yet we appear to be no closer today to effective treatments for addictions than we were 20–30 years ago. For example, our ever-more-sophisticated knowledge of the role of the neuromodulator dopamine and its various receptor targets in motivational processing has not led to the development of useful therapies based on the actions of this or closely related neurotransmitter

systems. Likewise, detailed understanding of how glutamatergic processes play a critical and complex role in the neuroplastic changes implicated in the development of addictions has not been followed by therapies targeting these processes. Rather, the most useful pharmacological agents are aimed still, not at modifying the neurobiological and/or psychological processes underlying addiction, but at “simply” providing substitutes for the drugs whose addiction they are used to “treat”; albeit with very important social and medical harm reducing benefits. Methadone has been used in this way for many years, not to *treat* opioid addiction (methadone *is* an opioid), but to *divert* the user away from the more harmful forms of use that are common to heroin and/or fentanyl. Drugs that modify emotional processes (e.g. SSRIs) can be given to sufferers from Alcohol Use Disorder (AUD) principally with the aim of mitigating deficits in those processes; though depending on the theory of addiction one ascribes to, it may be seen to treat addiction’s underlying causes in a more direct way (Koob and Le Moal 1997). Similarly, ongoing efforts in the UK to develop a substitute for alcohol that does not induce liver damage (e.g. Alcosynth by David Nutt) are founded on a set of pragmatic and humanistic principles and strategies designed to minimize the harmful consequences of alcohol use and alcoholism. These efforts to reduce the harms of alcohol or drug addiction may be seen to reflect a sense of hopelessness about the possibility of *actually* developing effective research-informed treatments. And neurobiology and pharmacology are not the only failures in this scenario: Despite the wealth of evidence and theoretical understanding of the importance of drug-associated cues and contexts in initiating and modulating drug-seeking and craving, therapeutic strategies aimed at weakening their emotional and motivating impact –rooted in behaviouristic principles as empirically robust and replicable as any in the field of psychology or behavioural neuroscience – have proven only moderately (if at all) effective in treating addiction and relapse vulnerability (Drummond 1995; Mellentin et al. 2017).

These frustrating facts point to a fundamental weakness in our current understanding of the psychological and neurobiological bases of addiction and AUD, raising challenging questions about our research approaches. Because so many of the concepts and ideas on which our therapeutic proposals have been based are derived from animal models, might we have to conclude that the lack of success in developing treatments is because such models are not only inadequate or incomplete (all models are necessarily incomplete as they seek to simplify and isolate from the real world), but are unreliable or even misleading. Indeed, critics may opine that pre-clinical scientists in the addiction area have promised much (especially in the opening and closing paragraphs of our publications and grant applications) but delivered little of practical value. But why should that be?

A contributing factor might be that animal researchers have simply been too ambitious in what they are trying to achieve; non-human animals such as rats or mice, outside the lab do not develop AUD; and seldom use alcohol and so any approach that attempts to model these uniquely human conditions in non-human animals is folly from the outset. It is (in part) this human-uniqueness concern, combined with the lack of practical, translated outcomes, that has motivated some

to propose “that animal models of addiction have not served us well in understanding and treating addiction in humans”, describing the field of preclinical research using non-human animals as “a huge waste of resources” (Field and Kersbergen 2020). Indeed, on its face this position seems hard the challenge though we might be unsettled by the breadth of its implication, that both prongs of the critique logically extend to many if not most human diseases, in particularly mental health diseases. Is not depression, schizophrenia, anxiety disorder, eating disorders, and so on, not also uniquely human, if only because they are diagnosed in humans, by humans, using human language and understanding? And also in relation to these conditions, the science seems to have accomplished little else other than provide post-hoc models to better understand why drugs already used and known to be effective clinically, do what they do.

Whatever the case, our approach here is more forward-looking, focusing less on the question of whether and more on the questions of how and why. Specifically, might there be a sensible, but perhaps less ambitious way forward that identifies aspects of behaviour or underlying (psychological and/or neurobiological) processes that are fundamental to the addiction process (biomarkers, or intermediate behavioural phenotypes (Duka et al. 2011a)), to establish human experimental laboratory models and procedures that probe those biological or behavioural processes, or phenotypes, and that map well to select aspects of addiction; and to *then* establish animal models that are homologous with (not simply analogous to) these human models.

We note that the relationship between these steps is a logical, not a temporal one; and it may well be that the discovery of an aberrant behaviour in the laboratory animal precedes the establishment of a human laboratory procedure, modelling a specific aspect thought critical in the addiction process. Whatever the temporal sequence of events, there are two logical steps in the process: First, the behaviour under study must reflect a functional aspect of the addiction process that is recognized (empirically and/or theoretically) as contributing to addictive aetiology and/or behaviour; and second, the animal model needs to be homologous with the human laboratory model. A corollary of the approach is that animal researchers worry less about modelling superficial similarities (analogies) between the behaviour in the lab and the clinical reality (i.e. modelling for face validity; more on this later), and rather focus on studying behaviours and phenomena that are theoretically and empirically robustly related to the addictive process. Though there lies part of the rub; we do not yet have a universally accepted theory, or even a broad conceptual framework, of addiction and it may well be that no single theory can be adequate to account for such a complex and multifactorial phenomenon. Indeed, this topic has been and was recently again debated, in part in the context of evidence that some of the basic underlying neurobiological effects dissociate for different drugs (Badiani et al. 2011; Piazza and Deroche-Gammonet 2014). We can be sure these debates will continue for the foreseeable future with both camps equally convinced by different (and sometimes the same) data. Whatever the case, it behooves the researcher to develop and place their own behavioural model within as robust a theoretical framework as

possible; something that, in our view, preclinical researchers in the addiction field, but also in other mental health areas, too seldom attempt.

2 Theoretical Context

From the foregoing, it should be clear that the interpretation of animal experiments, or any experiment, is theory dependent. As noted by the sociologist Homans, “there is nothing more lost than a loose fact” (Homans 1950) and we would extend this notion to “there is nothing more lost than a loose model”. Models and methods that are held to be theory-free are unlikely to provide a close analogy, let alone homology, between the clinical reality and the human experimental or animal laboratory. We have seen an abundance of such theory-free models in recent years, including ones that preport to model clinical diagnostic criteria (which themselves have no basis in scientific theory; Deroche-Gammonet et al. 2004; Vanderschuren and Everitt 2004), and/or patterns of drug consumption (Ahmed and Koob 1998), or environmental or social “setting” (Badiani 2013), or the phenomenology of relapse following abstinence (Epstein et al. 2006). And while such analogous models may have the appearance of completeness and relevance to the outside world, it is our view that if they are to serve as useful models to explore the fundamental underlying substrates and mechanisms, animal and human experimental tests need to be based on theoretically sound principles that establish homology between the processes and mechanisms (psychological or neurobiological) probed by our laboratory tests and those underlying the clinical condition. Indeed, certain tests and procedures in the laboratory that seek to probe such homologous processes may look quite dissimilar on the surface. Our point is that the mere presence or absence of “face validity” is neither sufficient nor necessary to justify inclusion or exclusion of the animal or human experimental model in our empirical analyses of drug and alcohol-related behaviours. It is against this conceptual background that we discuss and evaluate the empirical study of alcohol abuse and addiction in the non-human animal and human experimental laboratory (Table 1).

3 Rewarding Effects of Alcohol

The conventional view of alcohol abuse and alcoholism is that alcohol is taken because it is in some way rewarding. However, the nature of the rewarding effect is far from clear and may differ substantially across individuals. In reality, reward value is understood to represent an aggregate measure relating not only to the acute (and past) experiences of “euphoria” and “feelings of high”, but also subjective experiences of relaxation, satisfaction and fulfilment, relief from tension and craving, etc. (Heinz et al. 2003; Hendler et al. 2013). Early reports from studies with alcohol and other abused drugs indicated that drug reward-value assessments can differ

Table 1 Some benefits and limitations of alcohol (and other drug) related models in human and non-human subjects

Model/procedure	Benefits	Limits
<i>Reward models</i>		
Drug self-administration	Oral or IV routes; human and non-human animal versions; good predictor of abuse liability (predictive validity); vast parametric toolbox; widely used	Multiple underlying drivers; low ecological validity for IV alcohol; technically demanding (especially in mice); in rodents, oral alcohol requires use of fading/substitution techniques
Subjective measures: Self-reports (SR); taste reactivity (TR); drug discrimination (DD)	SR easy to implement in humans (e.g. rating scales); rich, individualistic data; TR with alcohol in non-human animals; detailed neurobiological understanding; vast literature on DD in animals	SR unreliable in humans; TR technically demanding in non-human animals; only oral routes of administration; poor correlation with subjective reports. DD limited in humans; links to reward and abuse liability tenuous
Conditioned place preference (CPP)	Easy to develop and implement; monotonic dose-effect relations; testing under “sober” conditions	Many versions/forms and mechanisms poorly understood (e.g. CRf, Pavlovian approach, sign-tracking); limited human equivalence data
<i>Conditioning models</i>		
Conditioned reinforcement (CRf)	Underlying psychobiological mechanisms well studied in human and non-humans; mechanistic homology; model of relapse	Limited understanding of dose-effect relations; limited use with drug rewards; understanding derived from non-drug reward; in humans, requires contingency awareness
Pavlovian-instrumental transfer (PIT)	Theoretical relevance to (contextual) relapse; growing evidence from human studies; similar neurobiology human and non-human animals	Different forms/versions; technically demanding; limited evidence using drugs (no mouse versions); no evidence in humans using alcohol; in humans, requires contingency awareness
Cue-reactivity (attentional bias (AB); conditioned orienting (CO))	Good evidence of relevance to alcohol abuse and alcoholism; multiple established measures (e.g. eye-tracking/STROOP)	Limited data from non-human animals (conditioned orienting); no evidence using drug or alcohol rewards
Pavlovian approach & Sign/goal-tracking	Good understanding of underlying psychobiology; measurements of individual differences; widely studied	Many variables determine shape/distribution of response; limited (but growing) evidence from human studies; links to abuse liability unknown

(continued)

Table 1 (continued)

Model/procedure	Benefits	Limits
<i>Impulsivity models</i>		
5-CSRT & delay-discounting tasks	Protocols developed in human and non-human animals; fair consistency human and animal findings	Time and effort consuming training; sensitive to overtraining and variations in protocols; links to alcohol abuse is complex
<i>Intake/treatment models</i>		
Binge drinking & withdrawal	Modelling intake patterns; similar neurotoxic and behavioural outcomes in humans and animals	Critical variables unknown (speed, amount, etc.); large species differences in pharmacokinetics and neurobiology; no agreed definition of binge-intake; few models incorporate volitional aspects

substantially among individual subjects (Schuckit 1984, 1994), with some people feeling stimulated and therefore experiencing high reward value and others feeling sedated, experiencing low (or no) reward value. The extent, then, to which ethanol “reward” represents a useful concept for assessing alcohol’s addictive potential, and/or the success of potential treatments of alcohol abuse remains unclear.

To this point, Ray et al. (2009) proposed a 3-factor model, capturing the dimensions (1) stimulation and other pleasant effects, (2) sedative and other unpleasant effects, and (3) alleviation of tension and negative mood. The subjective evaluation may be characteristic for the individual and may represent a heritable trait (Viken et al. 2003), but it is also clear that the effect experienced depends upon dose and pharmacokinetic time course. Thus, the euphorogenic effects of alcohol are often associated with rising blood alcohol levels (e.g. Martin et al. 1993; Erblich et al. 2003) while declining levels are more likely accompanied by sedation (Earleywine 1994a, b; Erblich et al. 2003). And whilst those who choose to drink also experience greater alcohol-induced increases in positive mood and liking (and do not experience increased anger, anxiety, and sedation post-alcohol (Li et al. 2020)), it is also understood that certain individuals drink for the euphoric effects of alcohol, whilst others drink to alleviate anxious moods (Booth and Hasking 2009; Goldsmith et al. 2009). This variability in response, both between and within individuals poses a challenge for scientists seeking to model the rewarding effects of alcohol in non-human animals, e.g. in deciding which strain to use, as well as whether to model the effects of the rising or declining phases of blood alcohol levels.

Even more so when considering that measures of alcohol reward in humans typically depend upon subjective self-assessment (self-report) of mood states, something that has no translational equivalent in the animal laboratory. Within the human laboratory, several questionnaire-type tools have been developed, of which probably the best known is the Profile of Mood States (POMS: McNair et al. 1971). However, even within the human literature, the results obtained from different rating scales are

not entirely consistent (Ray et al. 2010), and there is long-standing evidence to show that human subjects more generally have poor conscious access to and/or cannot reliably report about their affective states (Nisbett and Wilson 1977). This basic problem is even more evident when we have to rely on retrospective self-reports when even brief delays between experience and reporting result in pronounced biases (Schwarz 2007). Where then does the animal researcher start to model human assessments of reward?

3.1 Self-Administration

Partly for the aforementioned reasons, human instrumental self-administration procedures have been used extensively as a proxy-measure of the rewarding qualities of addictive drugs. These procedures have been used with different drugs of abuse including morphine and cocaine, and there is a (though somewhat more limited) literature on human self-administration either using oral (Bigelow et al. 1975; Griffiths et al. 1975, 1976) or intravenous (IV) alcohol in the laboratory (Vaughan et al. 2019), including to evaluate subjective responses to alcohol as a more precise measure of alcohol sensitivity (Gilman et al. 2012; Zimmermann et al. 2013; Hendershot et al. 2016). It is worth noting that although IV infusion of ethanol may provide more precise insights into alcohol sensitivity than oral, it is technically complex and limited in ecological validity. Promisingly, animal models using oral ingestion, rather than IV infusion, are now more frequent as a means of self-administration (Cyders et al. 2020).

It is important to note that self-administration measures of reward value do not always correlate with subjective reports of liking, indicating that these measures do not reflect a single (or even a related) phenomenon (Comer et al. 2008). Indeed, these types of findings reinforce earlier reports that people will self-administer doses of morphine or cocaine that produce no reported subjective effects (Fischman 1989; Lamb et al. 1991). While incomplete, these data clearly suggest that human self-administration measures can reflect different and dissociable underlying processes from subjective self-reports of drug reward, and more precise insights are likely to result from combining assessments of subjective rating with self-administration. For that reason, it is worth considering whether self-administration procedures offer a preferred means of carrying out experiments in animals and humans to explore homologous processes across the species and to allow a more direct comparison of empirical outcomes.

Following the pioneering work of Hank Samson and colleagues, oral self-administration of ethanol is now well established in the rodent laboratory (Roehrs and Samson 1981, 1982; Grant and Samson 1985; Samson 1986; Tolliver et al. 1988). Rodents typically avoid consuming pure ethanol, but they can be trained using a sucrose-fading technique by first training an instrumental response for a sucrose solution, and adulterating this with increasing concentrations of ethanol, to eventually respond for and consume a sucrose-free alcohol solution (Samson

1986). And despite such fading or substitution methods potentially confounding interpretations of empirical findings (e.g. not knowing whether responding is maintained by ethanol and/or [the memory of] sucrose), such procedures have some features in common with the typical pattern of human alcohol use; use that often begins by taking sweetened cocktails (alcopops) or cider, before progressing to more “adult” drinks of purer alcohol that are unsweetened. Although rats have been most frequently used in this model, a limited number of studies have employed mice, to study genetic influences on alcohol reward (Stephens et al. 2005a, b), to test the efficacy of novel pharmacological approaches to treating alcohol abuse (Middaugh et al. 2000), and/or in order to take advantage of certain advanced neurobiological approaches such as circuit-specific optogenetic silencing or excitation, better suited for mice (Juarez et al. 2019).

However, despite the apparent similarity between oral self-administration in people and non-human animals, there are aspects of the procedures that make them rather different. In animal studies, we are dealing with alcohol naïve subjects, with an inherent dislike of the taste of ethanol, requiring extensive practice (and, e.g., use of the aforementioned sucrose-fading techniques) to overcome. In the human experimental laboratory, we inevitably train the instrumental response over a much shorter period of time (and often by instruction rather than self-discovery) in individuals who have already had considerable experience with the effects of alcohol (it would in most cases be unethical to use ethanol-naïve subjects), and the social drivers and contexts in which ethanol drinking may be accepted, encouraged, or disapproved. These factors underlying self-administration of alcohol in human and non-human experimental animals are sufficiently different to suggest that the behaviours, though superficially similar (analogous), may not be homologous. To this point, whilst human subjects are willing to perform an instrumental response with a fixed ratio $>1,000$ (Bigelow et al. 1975; Zimmermann et al. 2013), it is rare that laboratory animals (e.g. outbred rats) will perform at fixed ratios greater than even 10. Whether such discrepancies reflect species-differences or differences in alcohol experience (and so forth) between humans and rats in the laboratory is unclear. Nevertheless, it is an empirical question whether experimental manipulations that are effective in modulating ethanol self-administration in laboratory animals are likely to do so in humans. These issues are also discussed by Zimmermann et al. (2013). At a minimum, we hope (and most believe) there is sufficient in common between human and non-human animal self-administration phenomena to allow it to be used in “proof-of-concept” laboratory studies, to evaluate drug reward value as a potential biomarker for examining possible treatment effects.

3.2 Conditioned Place Preference

A commonly used task to study the “rewarding” effects of drugs (and hence their abuse potential) in rodent models (especially in mice) is the place conditioning (or conditioned place preference, CPP) procedure. In its basic form, this procedure

involves a (non-response-contingent) drug administration experience repeatedly paired with exposure to a distinctive environment, while on separate sessions, a physically different environment is paired with a placebo/vehicle treatment. At test, when given a choice, non-drugged rats or mice typically spend more time in the environment previously associated with treatment with a drug with abuse potential, an effect interpreted as the animal having acquired a “preference” for the drug-paired environment due to the rewarding qualities of the drug being studied (for reviews, see Tzschenkne 1998; Bardo and Bevins 2000; Cunningham et al. 2006; Stephens et al. 2010; McKendrick and Graziane 2020).

CPP has many benefits; it is relatively easy to perform and, in contrast to simple consumption studies, dose-effect curves are generally monotonic increasing, which is certainly true for ethanol in mice (Groblewski et al. 2008). However, perhaps because of its seemingly straightforward nature, there appear to be as many versions of the place preference method as there are laboratories using the task. Common differences include the number of environmental compartments (ranging from a single to 3 separate compartments), types of discriminative cues used (e.g. tactile, visual), visibility of the “drug environment” from the “non-drug environment”, numbers of drug-environment pairings, duration of the drug-environment pairing, the use of unbiased vs. biased designs, and so forth. Although for many drugs of abuse, such as opiates and psychomotor stimulants, positive effects in the CPP procedure are sufficiently robust to withstand some variation in procedures, for others (e.g. ethanol) positive effects depend on judicious selection of the appropriate procedures, and/or may differ across species (Cunningham et al. 1993); for additional review of these different methodologies, see Cunningham et al. (2011); McKendrick and Graziane (2020)).

As we and others have pointed out (Stephens et al. 2010; McKendrick and Graziane 2020), although seemingly simple conceptually, the CPP procedure is difficult to interpret in terms of its underlying psychological processes, and its naming using the heavily cognitive term “preference” is unfortunate, and perhaps misleading. A general problem with the procedure is that, with some praiseworthy exceptions, few researchers have attempted to systematically explore the psychological processes involved in drug- or non-drug CPP, and relatively little is known about how “preferences” for drug-paired stimuli develop and are maintained and expressed. Consequently, it is mostly unclear how and why seemingly subtle methodological and procedural differences may or may not affect performance on this task, and differences across laboratories, such as those mentioned earlier, could reflect the way in which some procedures bias the test to particular learning and memory strategies. Thus, while CPP is commonly used, e.g., to study gene-association with “reward” (e.g. Cunningham and Phillips 2003; Kliethermes et al. 2007), unless effort is spent on parsing putative component psychological (e.g. learning and memory) processes, the task is insufficiently well understood to allow robust conclusions. In rodents, for example, minor variations in the procedure are able to bias the test to assess processes as different as Pavlovian approach (sign-tracking), conditioned approach to positive incentives (Mead et al. 2005; Cunningham and Patel 2007), anxiolytic effects of the drug, and/or effects on associative

learning (McKendrick and Graziane 2020). Moreover, without such understanding, it becomes near impossible to establish tests in human subjects that probe the same psychological processes as those in rodent CPP measures, i.e., to establish homologous tests.

The complexity of the issue is illustrated, e.g., by findings that the C57BL/6J mouse, that in measures of consumption and choice shows preference for and high consumption of ethanol solutions relative to other strains, does not show elevated “preference” in tests of ethanol CPP (Cunningham 1995). One possibility is that the development of place “preference” in CPP reflects a balance of the aversive and rewarding effects of ethanol, so that variations in sensitivity to aversiveness interact and interfere with the expression and thus measurement of reward (Cunningham and Henderson 2000; Cunningham et al. 2003).

Looking beyond ethanol, several examples using other drugs of abuse further illustrate the issue. For instance, Cunningham et al. (1999) reported that differences between C57BL/6J and DBA2/J mice in cocaine CPP were dependent on the length of the session. In another example, deletion of the *grlal* gene encoding GluR1 subunits of glutamatergic AMPA receptors was reported both to abolish CPP for cocaine (Dong et al. 2004) and to have no effect (Mead et al. 2005), even though the latter report covered the dose used by Dong et al. Likewise, whilst Valjent et al. (2006) reported deficits in cocaine-induced place preference conditioning (and the development of sensitization) in EGR1 (or Zif286) knockout mice using a 3-chamber CPP procedure, Li et al. (2006) found no deficits in CPP (or sensitization) in using the same mice and identical procedures, except that a single chamber CPP setup was used. It is possible, of course, that these sorts of procedural or environmental differences between laboratories (including unspecified differences) interact with genotype to alter drug reward, perhaps by shifting the dose-effect curve for one strain, but not for the other. However, it is also possible that differences in the findings between two laboratories reflect subtleties in the place preference training and testing procedures that have nothing to do with reward. In the absence of better understanding of the underlying mechanisms involved in the acquisition and expression of CPP, one simply cannot know.

Studies using a procedure similar to CPP in humans remain rare but those that exist confirm the development of place preference to amphetamine or alcohol in human subjects in the behavioural pharmacology laboratory (Childs and De Wit 2009, 2013, 2016; Krishnan et al. 2023). In these experiments, individuals experienced either amphetamine or alcohol in one of two environments and were then asked to rate their “liking” for each of the environments using Likert-scales, as well as to indicate their preference for one of the environments. Liking was greater for the drug-associated room, and there was some evidence for a preference for the room that was paired with amphetamine or alcohol, over the other non-drug/alcohol-paired room. Important and interesting as these experiments are, they also raise tricky questions. In rodent CPP experiments, several researchers (Mead et al. 2005; Cunningham and Patel 2007; McKendrick and Graziane 2020) have proposed that preference for the previously drug-paired environment reflects a Pavlovian approach response – an automatic approach to cues associated with rewards and related to

sign-tracking (sometimes, inappropriately called autoshaping). But from the human version of the task (Childs and De Wit 2009, 2013, 2016) we might conclude such implicit learning mechanisms to be secondary as preference for the amphetamine- or alcohol-paired contexts was principally driven by explicit, conscious (positive and negative) subjective responses to the drug. Further research might clarify whether the psychological processes underlying this type of human place preference resemble those underlying the analogous behaviour in rodents.

4 Model of Conditioning in Addiction

At present, most theories that describe the development and maintenance of addictive behaviour agree on the important role of Pavlovian and instrumental conditioning (e.g. Wikler 1948; Robinson and Berridge 1993; Franken 2003; Everitt and Robbins 2005). Cues that are regularly associated with the consumption of a drug such as ethanol become conditioned stimuli (CS+) that are endowed with a broad range of emotional, cognitive, and motivational functions. These include the ability to elicit conditioned physiological, emotional, and incentive responses, and in addition in humans, subjective drug craving that are thought to impact instrumental drug-seeking behaviour.

Conditioning models of drug addiction are widely used in animal research and a large number of studies, including from our groups, demonstrate that cues associated with drug experience acquire incentive properties that can trigger and maintain drug seeking (e.g. Stewart et al. 1984; Everitt and Robbins 2005; Crombag et al. 2008; Tomie and Sharma 2013). Related studies have also been conducted with human volunteers in the laboratory using arbitrary or neutral cues (e.g. the colour of the drinking vessel) associated with drug experience (e.g. an alcoholic drink) to show that such cues acquire salience and produce attentional, emotional, and (other) conditioned behavioural responses (e.g. Hogarth and Duka 2006). In the case of human subjects, an important condition for these cued-responses to develop is a conscious awareness or expectancy of the reinforcer in the presence of the conditioned stimulus. For instance in the case of smoking and alcohol-related stimuli, only when expectancies of the reinforcer were explicitly activated, either by instruction (Field and Duka 2002) or by elaboration of the contingencies between the stimulus and reinforcement (Hogarth et al. 2005), did cues acquire the ability to alter attentional, emotional, and behavioural processes. These and other findings may appear to differentiate cue reactivity in human subjects from procedurally similar phenomena in animals; however, the distinction may be more apparent than real as we have no way of knowing whether animals also develop an explicit (conscious?) awareness of the relationship existing between the reinforcer and the cue predicting it. Moreover, there is now some evidence, including from our lab using an Emotional Blink Procedure and modified Flanker Task, showing that (at least) attentional capture effects by cues *can* develop outside of explicit conscious awareness (Leganes-Fonteneau et al. 2018, 2019); and we found some evidence for conditioned

hedonic effects, specifically cue-triggered feelings of pleasantness (Jeffs and Duka 2017). Findings like these further highlight the need for more research in human subjects into implicit processes involved in the development of addictions.

Whatever the case, it remains a topic of wider scholarly debate whether, and to what extent, awareness of the CS-US relationship is a necessary part of the process whereby CS-US associations are formed and/or expressed, as held by various expectancy theorists (Bolles 1972; Dickinson 1997; Mackintosh 1997). As noted, findings from most contemporary human studies on conditioning support this view and suggest that the presence of awareness of the CS-US contingencies precedes the presence of conditioned responses (Hogarth and Duka 2006), but we have seen examples ourselves to the contrary (see paragraph above).

Of course, it could also be that awareness and conditioning occur in parallel and/or that the awareness aspect simply reflects the subject “reflecting” on and narrating about his/her own conditioned behaviour. Indeed, a recent study in our lab showed that stimuli associated with alcohol-reward captured attention as an involuntary consequence of a goal-driven mechanism; and when participants held a search goal for alcohol-related targets, there was a consistent involuntary attentional bias to alcohol distractors (Brown et al. 2018).

One of the most used approaches to studying conditioning in the human laboratory involves measures of emotional reactivity to a conditioned stimulus, assessed by quantifying stimulus approach (attentional bias; see below), skin conductance responses, and/or subjective feelings of pleasure following stimulus presentation. Similarly, Pavlovian conditioning paradigms using emotional-reactivity measurements offer a tool for studying learning and memory processes involved in substance abuse and addiction (and more recently, for exploring underlying anatomical and neurochemical substrates), in the human laboratory.

There is a vast amount of behavioural evidence supporting the existence of attentional biases, which are closely correlated with Pavlovian approach responses (Buzsaki 1982), to drug-related stimuli in addiction-related disorders. These attentional biases become apparent during performance on attentional orienting tasks such as the MacLeod’s dot-probe task, when tracking eye-movements, and/or using (secondary) task-interference procedures (e.g. the Stroop task). This type of attentional bias has been demonstrated for alcohol (e.g. Stetter et al. 1995; Townshend and Duka 2001), nicotine (e.g. Herman 1974; Hogarth et al. 2003), cocaine (Rosse et al. 1997), or opioid-dependent subjects (Lubman et al. 2000). The relevance of some of these attentional measures to the experimental medicine study of addiction is suggested by observations that a greater attentional bias to drug-related cues is predictive of poorer treatment outcome (see also below). This relationship exists especially for attentional bias measured using the Stroop interference procedure for cues associated with alcohol (Cox et al. 2002), tobacco (Waters et al. 2003), heroin (Marissen et al. 2006), or cocaine (Carpenter et al. 2006). Thus, measures of attentional bias could provide surrogate measures of the effectiveness of potential therapeutic interventions. Moreover, a recent and useful review of the literature by Heitmann et al. (2018) on the effectiveness of attentional bias modification procedures (e.g. by explicitly training subjects to direct their attention away from drug-

or alcohol-related stimuli) appears to demonstrate positive effects on symptoms of addictive behaviour, at least in the case of alcohol (see also Wiers et al. 2023). However, as these authors themselves note, more and more rigorous research using clinical samples is needed to verify the effectiveness of such interventions. Whatever the case, attentional bias may be useful as a reliable measure to be used in human subject studies and could offer a true homology in terms of psychological equivalence, hopefully based on a common underlying neurobiology.

Although the methods described in the previous paragraph have little resemblance at a superficial level to the animal tests on CPP described in the previous section, in both cases, the underlying psychological processes are thought to depend (at least in large part) on approach behaviour mediated by Pavlovian learning mechanisms. Of course, in the case of CPP, the approach may be to a particular context, whereas in the human studies discrete cues are used and thus the underlying neural networks are likely to diverge to some extent. Partly for this reason, as outlined below, the use of behavioral models employing simple, discrete cues may be helpful for establishing homologous approaches between animals and humans (see below).

Before discussing these approaches, it is worth noting that, as far as we are aware, no potential pharmacological treatments have been tested using the attentional cue-reactivity paradigm, although cognitive-behavioural treatment approaches aimed at altering drug user's attentional bias to drug cues have proven successful to an extent (e.g. Field and Cox 2008; Heitmann et al. 2018). In addition, successful cognitive treatment based on 12-step individual and family psychotherapy increases patients' insight into their inability to control their alcohol craving, and at the same time leads to avoidance of drug cues, i.e. attentional bias to drug-related cues is suppressed (Townshend and Duka 2007). Thus, attentional bias as a measure of reactivity to conditioned stimuli may offer a useful biomarker for exploring the emotional, motivational, and cognitive consequences of conditioning drug cues, as well as of brain substrates underlying these. An example of such an approach using functional magnetic resonance imaging (fMRI) by (McCleron et al. 2007) demonstrated how responsiveness to smoking-related cues is associated with increased BOLD responses within the amygdala (see also, e.g., Brody et al. 2002) – an area traditionally implicated in Pavlovian learning and emotional regulation; and this increase was reduced in abstinent smokers who had undergone cue-exposure/extinction- treatment (see below). Likewise and more recently, Goldstein and colleagues (Parvaz et al. 2021) using a combination of electroencephalogram (EEG) to measure changes in prefrontal cortex activity, and eye-tracking as an index of attentional bias towards drug cues, were able to demonstrate how cognitive reappraisal training, associated with prefrontal control, decreased spontaneous attention bias to drug-related cues in (moderate using) cocaine-addicted individuals. It is worth repeating then that attentional bias is not only a useful proxy for laboratory studies on the rewarding effect (and by inference, abuse or addictive properties) of drugs and alcohol in human subjects, but may also offer an important therapeutic target; whether via behavioural/cognitive (e.g. reappraisal training) or pharmacological

(Passamonti et al. 2017) interventions to direct attention away from certain (drug and alcohol) cues and/or towards other less destructive ones.

5 Studying Drug-Related Conditioning in Human and Non-human Animals

5.1 *Conditioned Reinforcement*

Two aspects of associative learning or conditioning that may contribute to (different versions of) CPP in animal studies are conditioned (secondary) reinforcement (CR) and Pavlovian approach. Conditioned reinforcement refers to the ability of environmental cues associated with the US/reward to acquire reinforcing properties in their own right. Thus, it seems possible that approach to the environment associated with drug experience reflects “seeking” a conditioned reinforcer. Conditioned reinforcement is more conventionally and more satisfactorily assessed in an instrumental learning context in which animals are shown to acquire a novel instrumental response to gain access to the conditioned reinforcer, often a discrete stimulus (e.g. a light or tone) previously explicitly paired with the reward (Ferster and Skinner 1957; Robbins 1978). The brain regions involved in conditioned reinforcement are well explored and several studies have implicated the amygdala and orbitofrontal cortex (Holland and Gallagher 1999; Parkinson et al. 2000), as well as ventral striatum (Everitt et al. 1999). Because conditioned reinforcement represents a psychologically and neurobiologically well-characterized behaviour, it seems an excellent candidate for translational work between animals and humans. Helpfully, the procedure has previously been applied in human imaging studies, revealing the involvement of the same brain circuitries (Cox et al. 2005), so that there appears to be a convincing argument for homology between the phenomenon of conditioned reinforcement in rodents and humans; and thus for a useful candidate for comparative studies.

Having had a long-standing interest in understanding GABA function and reward, we previously conducted parallel human and mouse experiments using a homologous conditioned reinforcement task to understand the mechanisms by which variations in the gene, encoding the a2 GABA subunits increase risk for addictions (Duka et al. 2015). Healthy human volunteers carrying either a cocaine-addiction “risk” or “protective” GABRA2 single nucleotide polymorphism (SNPs) were tested for their subjective responses to methylphenidate, and methylphenidate’s ability to facilitate the conditioned reinforcing (CRf) effects of a visual cue (CS+) associated with monetary reward. In parallel, methylphenidate’s ability to facilitate responding for a visual CRf was studied in wildtype and a2 knockout mice. Human risk SNP carriers were insensitive to methylphenidate’s effects on mood and in facilitating CRf; similarly, mice with the gene deletion were insensitive to methylphenidate’s ability to increase responding for CRf; suggesting a potential mechanism whereby

low a2-subunit levels increase risk for addictions (and indicating that circuits employing GABAA-a2 subunit-containing receptors may protect against risk for addictions).

Several important questions remain open about CRf. With one notable exception (Smith et al. 1977), we know of no other published studies that have systematically varied the value of the (paired) unconditioned reward in order to quantify the effects on performance of the conditioned reinforcement task. This would be an important requirement for quantitative measures of conditioned reinforcement to be used to detect treatment effects on (alcohol) reward value. Additionally, and perhaps surprisingly, there is relatively little systematic work on the efficacy of drug rewards to support conditioned reinforcement (Panlilio and Schindler 1997; Di Ciano and Everitt 2004), in large part because explicit (passive) Pavlovian pairing of drug reward with a discrete (would be) cue is challenging (but see, e.g., LeCocq et al. 2022). Nonetheless, there is a plethora of reports purporting to model cue-induced relapse in non-humans that are often thought (not unreasonably) to reflect conditioned reinforcement processes and that are procedurally similar, at least at the testing stage (i.e. that measure subjects' willingness to press levers for a contingent drug-paired cue). Nonetheless, the CRf approach/procedure allows assessment of reward sensitivity for conventional (non-drug) rewards, providing at best only a close proxy-measure of drug reward as it remains unclear how the method behaves as a more direct assay of sensitivity to drug reward (but see Smith et al. (1977) for the development of CRf using ethanol as the primary reward.

5.2 *Pavlovian Approach*

As noted, the second psychological process potentially involved in (some forms of) CPP is Pavlovian approach learning, by which animals learn to approach environmental stimuli that are predictive of reward. This behaviour has more recently gained a great deal of attention in the shape of studies on a closely overlapping (if not identical) phenomenon called sign-tracking, whereby (some) animals actively engage with reward-associated cues (e.g. approaching and biting a cue light turned on, or pressing a lever inserted when a food reward is delivered) in a reinforcer-selective and species-specific manner (Brown and Jenkins 1968); even when the animal's sign-tracking behaviour has no consequences for reinforcer availability (no contingency exists between the response and reinforcement). Thus, in the context of CPP, the "preference" for an environment paired with drug reward might reflect (in part) approach to reward-predictive cues in the environment. To be clear, while CRf implies that the animal associates the positive incentive value to the reward-associated cues with performing a flexible or voluntary response; i.e. establishes a representation of goal-directedness of the response (Robbins 1978), Pavlovian approach or sign-tracking seems less flexible, and the shape of the conditioned response is determined in large part by the nature of the cue and US, and/or how these are paired, e.g., in time and space (Gallagher et al. 1990; Tomie

1996). Importantly, while both CRf and Pavlovian approach rely on subjects' acquiring an association between the US and CS, their expression appears to be mediated by experimentally dissociable neural systems (Parkinson et al. 2000). At least one study (Cunningham and Patel 2007) demonstrated Pavlovian approach to a cue associated with alcohol administration in a procedure modified from a standard CPP procedure, perhaps suggesting that CPP is a variant of Pavlovian approach. And, since sign-tracking has been demonstrated to occur in humans (Wilcove and Miller 1974), there may be opportunity for cross-species concilience using this approach.

Following its rediscovery by Robinson and colleagues (Uslaner et al. 2006), influenced by earlier work from Tomie (1996), Pavlovian approach has undergone somewhat of a reappraisal as a fruitful model to study underlying processes and mechanisms of substance abuse and addiction; and the number of studies has increased accordingly, resulting in a greatly improved understanding of its psychological and neurobiological underpinning. For instance, we know (predominantly from studies with rats) that typically only a proportion of subjects develop a sign-tracking (and not a goal-tracking) response, whereas another proportion develop a goal-tracking (but not sign-tracking) response; and a (typically) larger proportion of subjects (intermediates) alternate between the two responses (Flagel et al. 2009; Meyer et al. 2012). We know these proportions of sign and/or goal-trackers vary as a function of a host of dispositional (potentially genetic) and/or environmental/circumstantial variables, including strain, supplier, housing conditions, and so forth (Fitzpatrick et al. 2013). We also know that the explanation of differences between sign- and goal-trackers relates in part (and for some reason) to differential sensitivity to discrete, localized, punctate cues versus spatially and temporally more generalized, background, contextual ones, as evidenced by, e.g., goal-trackers being more susceptible to contextual renewal effects (Pitchers et al. 2017a, b).

Furthermore, at least in the case of alcohol reinforcers, whether a rat behaves as a sign-tracker or goal-tracker may be influenced by the precise relationship of the cue onset to reinforcer availability; if alcohol (i.e. reinforcer) availability is limited in time, then approach to the alcohol source may occur at cue onset (goal-tracking), whereas if the alcohol is available for a longer period following cue presentation, approach behaviour may tend to be directed initially towards the cue before approaching the alcohol source (Tomie et al. 2006, 2011; Tomie and Sharma 2013). Such observations, indicating some flexibility in response depending on particular subtleties in alcohol availability, suggest it may be difficult to translate rodent laboratory findings, even if confirmed in carefully controlled human experimental studies, directly to human behaviour in typical social or pathological drinking situations.

We also know, at the neurobiological mechanism level, that while sign trackers (but not goal-trackers) show distinctive cue and/or response-locked dopamine activity spikes in the nucleus accumbens (Flagel et al. 2011), these same rats also suffer from relatively blunted cognitive/attentional (cholinergic) control mechanisms in the prefrontal cortex (Pitchers et al. 2017a, b).

A more complete review of the literature is beyond the scope here, but it will be clear that the sign- versus goal-tracker model is potentially an important insight when it comes to preclinical addiction models; but it will be essential (and potentially fruitful) from a translational, model validation perspective that research in this area using human subjects is promoted and expanded. Such research is gradually emerging including using sophisticated approaches involving eye-tracking and functional brain imaging (Schad et al. 2020), though at present mostly using non-clinical samples. Moreover, we are far removed from establishing whether or to what extent sign (or goal) tracking performance, or the sign-tracking phenotype, bears any explanatory relevance to use, abuse, or addiction involving alcohol or other substances (see Flagel et al. 2021; Pohorala et al. 2021).

A phenomenon related to Pavlovian approach but less often studied. Especially within the context of alcohol or drug abuse is the (conditioned) orienting response to cues predictive of reward (Buzsaki 1982). In human subjects, this phenomenon has been exploited by studying the tendency of substance involved or addicted subjects to allocate attention to a stimulus associated with the drug, over another stimulus that has no association with the drug. These types of biases are readily measured using eye-tracking techniques to track and quantify the focus of attention, or with cognitive interference tasks, like STROOP during which allocation of attention to the emotional stimulus (e.g. reading a word with emotional meaning) takes up resources needed for explicit task demands (e.g. naming the colour in which the word is written). The relevance of this measure with respect to studying drug or alcohol abuse is indicated by findings that greater attentional bias to drug cues is associated with poorer treatment outcome, including in the case of alcohol (Cox et al. 2002) and other drugs of abuse such as tobacco (Waters et al. 2003), heroin (Marissen et al. 2006), and cocaine (Carpenter et al. 2006).

5.3 *Pavlovian-Instrumental Transfer (or PIT)*

A third, and neurobiologically dissociable, behavioural consequence/property of reward-associated cues is their ability to potentiate or energize ongoing instrumental responding, even in the absence of any contingency between their presentation and the response (as is the case with conditioned reinforcement). Thus, cues previously associated with reward through classical or Pavlovian training are able to facilitate instrumental responding for that or other rewards when presented passively and independent of the subject's behaviour; a phenomenon known as Pavlovian-instrumental transfer (PIT) (see O'Connor et al. 2010). Notably, depending on the particular Pavlovian training conditions, the cue may serve to facilitate responding for one particular reward (outcome-specific PIT), or a range of rewards (generalized form of PIT) and these two "forms" of PIT are again dissociable neurobiologically (e.g. Corbit and Balleine 2005). Although most work in the non-human animal laboratory has used food rewards to establish the cue-reward association, two reports indicate that cues previously associated with ethanol delivery are capable of

increasing instrumental responding for ethanol in a PIT-like manner, consistent with ethanol-related cues facilitating ethanol-seeking behaviour (Glasner et al. 2005; Corbit and Janak 2007). Nonetheless, with some notable exceptions (LeBlanc et al. 2012), PIT remains a phenomenon mostly studied and characterized using non-drug reinforcers; and whilst its role in drug abuse and addiction has been argued (Wyvill and Berridge 2001; Berridge and Robinson 2003), and especially in contextual influences in drug seeking and relapse susceptibility following remission (Crombag et al. 2008), supporting evidence for this is principally theoretical.

Interestingly, the magnitude of PIT is sensitive to behavioural sensitization (repeated drug administration) induced following Pavlovian training (Wyvill and Berridge 2001), indicating that the extent to which drug-associated cues facilitate further drug seeking may be increased by drug-exposure history; though inducing ethanol dependence following Pavlovian and instrumental training in itself does not further increase the facilitatory effects of ethanol-cues (Glasner et al. 2005). By contrast, in an experiment in which rats were chronically exposed to ethanol *prior* to Pavlovian and instrumental training, the facilitatory effect of a food-paired cue on operant responding for food reward (PIT) was significantly impaired (Ripley et al. 2004). Thus, while ethanol reward clearly supports the development of PIT, ethanol dependence may impair the subsequent development of PIT using different (non-drug) rewards, at least in rodents. Encouragingly, the PIT phenomenon has now been reproduced in the human laboratory (e.g. Paredes-Olay et al. 2002; Hogarth et al. 2007; Mahlberg et al. 2021). In line with data from the animal studies, PIT-related neural activity changes (fMRI BOLD) in the nucleus accumbens and amygdala (Talmi et al. 2008) and the latter was found to positively correlate with polygenic risk for alcohol consumption (Garbusow et al. 2019). But, to date, no human studies exist that have investigated PIT using ethanol (or other drug) rewards.

5.4 Potential of Conditioning Measures as Biomarkers

The possibility of establishing test procedures in rodents and humans that are theoretically homologous provides an enormous advantage in translating between animal and human models, and vice versa. Although work remains to be done, the conditioning models outlined in this section appear to fulfil, or are capable of fulfilling, the requirement for construct validity of an animal model. However, although the importance of drug-related cues in triggering or invigorating drug seeking is well established, it is less clear which, to what extent, and under which conditions each of the specific processes outlined contributes to drug or alcohol seeking, relapse, or use and abuse more widely in real life (but see Chen et al. 2023). Nevertheless, these approaches seem in our view to offer a potential for validity not approached by other, more general animal models of addiction.

6 Subjective Experiences

As noted, evaluation of ethanol's rewarding effects in humans often depends on subjective self-reports, and direct (or even indirect) measurements of subjective states in non-human animals are clearly challenging; how, if at all, might we relate animal to human studies in this area? Berridge and colleagues produced a robust body of behavioural neuroscientific work supporting the proposal that some subjective experiences, namely hedonic reactions to tastes introduced into the mouth, can be reliably measured and inferred from facial expressions preserved across mammalian species (Berridge and Grill 1983; Berridge 2000), offering a cross-species approach to studying subjective hedonic and aversive experiences. Though the taste-reactivity methodology is limited to orally administered flavoured substances, and so provides no straightforward application for studying subjective effects of drugs of abuse (typically administered through other routes), it could offer a window for assessing alcohol-related subjective experience in rodents. In support of this notion, alcohol was found to produce similar orofacial responses in rats as sucrose/quinine mixtures (Kiefer et al. 1990; Wukitsch and Cain 2021). Moreover, Kiefer et al. (1990) have used the taste-reactivity procedure to compare subjective hedonic responses by alcohol-preferring (P) and non-preferring (NP) rat strains, reporting that, following repeated experience with alcohol, P rats show an increase in appetitive (hedonic) taste-reactivity responses (and decreased aversive responses) to alcohol relative to NP rats (see also Wukitsch and Cain 2021). Thus, these types of findings suggest a possible methodology to obtain preclinical understanding of drug-related subjective experiences, at least for alcohol, that could then be compared to our understanding from the substantive body of studies on human subjective experiences related to drugs of abuse.

The more conventional means of studying "subjective" effects of abused drugs in non-human animals is by using drug discrimination procedures. In this methodology, the animal is required to use the experience of the drug's effect to provide a discriminative (interoceptive) cue (presumably, serving as an occasion setter) to make the appropriate instrumental (typically lever-pressing) response. Although the nature of the subjective experience that generalizes across or discriminates between drugs is unknown, it seems plausible that both humans and non-human species could utilize the same subjective experience(s) of the drug in order to "solve" the discrimination task (Kamien et al. 1993). Whilst there is a rich literature on discriminative stimulus effects in non-human animals (Grant 1999; Kostowski and Bienkowski 1999), there have been relatively few investigations into the nature of the alcohol or drug-induced interoceptive discriminative stimulus in humans. Human volunteers can perform such discriminations based on ingestion of low doses of ethanol and discriminate based on a feeling of "light-headedness" produced by the alcohol (Duka et al. 1998a, b, 1999) and this alcohol discriminative stimulus effect generalizes to benzodiazepines which are also reported to generate feelings of "light-headedness" (Jackson et al. 2003). Such reports are consistent with rodent reports that an ethanol discriminative stimulus generalizes to other sedative hypnotic agents such as benzodiazepines and barbiturates (Kostowski and Bienkowski 1999).

What this example also illustrates is that the human studies do not unequivocally link alcohol's discriminative properties to its rewarding effects so it is difficult to relate subjective reports, used in so many human studies, with discriminative performance. Nevertheless, under the right circumstance the subjective ratings of the stimulant effects of alcohol do predict the amount of alcohol subsequently consumed (Duka et al. 1998b). Thus, although subjective reports assay something that is several levels of neural processing away from behavioural measures, correlations between these domains can sometimes be established.

7 Alcohol and Measures of Impulsivity

A relatively more recent focus of addiction researchers in both the non-human animal and human labs has been on decision-making processes and the role of frontostriatal dysfunction in addiction (Jentsch and Taylor 1999). This focus stems, in part, from neurocognitive evidence that addicts often show persistent performance deficits on decision-making tasks reminiscent of focal damage to prefrontal (PFC), ventromedial PFC (Verdejo-Garcia and Bechara 2009), or orbitofrontal cortex (Rogers et al. 1999). Moreover, within the alcohol research field, a number of reports demonstrate a relationship between alcohol misuse and impulsivity (see Dick et al. 2010; Herman and Duka 2019 for a review) again pointing to disruption in neural circuitries involving PFC subregions. Important here is to recognize that the term impulsivity is used in human studies to describe several quite different behaviours (and presumably underlying psychological and neurobiological mechanisms), including "rash" acts arising from "sensation seeking, risk-taking, novelty-seeking, boldness, adventuresomeness, boredom susceptibility, unreliability, and unorderliness" (Depue and Collins 1999). A useful attempt was made by Whiteside and Lynam (2001) to map these complex concepts into five orthogonal (or only weakly related) traits (for more extensive discussion and references, see Dick et al. 2010). These traits encompass "positive" and "negative urgency" (acting rashly when experiencing, respectively, positive and negative mood), "lack of planning" (acting without forethought), "lack of perseverance" (failure to tolerate boredom, or to remain focussed in the face of distraction), and "sensation seeking", the tendency to seek novel or thrilling stimulation.

The 5 traits are derived essentially from personality inventories, and an important question is to what extent these traits can be operationalized in humans, and more critically, then in non-human animal models homologous with the human experimental procedures. Dick et al. (2010) already point to this fundamental difficulty in reconciling performance measures in laboratory tasks with personality traits, because the former reflect specific cognitive processes under particular experimental conditions, whereas the latter are stable traits and likely to be independent of particular tests; and are thus broader than specific cognitive functions. Likewise, Harriet De Wit et al. (2006), in a more general analysis trying to relate personality inventories with behavioural measures of impulsivity, suggest that self-report measures assessed

using such inventories are generally unrelated to task-based measures. Nonetheless, several experimenters have made attempts to link at least some specific laboratory measures to personality traits, including suggestions that “urgency” may be reflected in the ability to inhibit prepotent responses (Bechara and Van der Linden 2005) and lack of perseverance may relate to resistance to proactive interference; and their suggestions have found some empirical support (McCarthy et al. 2001; Gay et al. 2008).

Along similar lines, Harriet De Wit and colleagues (2006a; 2006b) proposed that the laboratory tasks used by them could be allocated to two categories or forms of impulsivity: a first which they labelled “impulsive disinhibition” and which included a “Stop-task” and a “Go/No-Go task”; and a second that included “Delay-Discounting” and the “Balloon Assessment of Risk Task” (BART) which they labelled “impulsive decision making”. The distinction made by De Wit et al. has also been described by others (Lane et al. 2003) and may map onto the categories “impulsive action” and “impulsive choice” used by others in the field.

Likewise, based on findings from non-human animals, Evenden (1999) made a similar point that impulsivity is a term with several meanings, including the inability to withhold a response (“impulsive disinhibition”), the relative intolerance to delays and/or uncertainties in reward, or the perseveration of a non-rewarded response (“impulsive decision making”). Although several tasks fall within these descriptors, two tasks have been especially popular; the 5-choice serial-reaction time task (5-CSRTT) (Robbins 2002; Sanchez-Roige et al. 2012) and the “delay-discounting” tasks (e.g. Richards et al. 1997); these tasks are thought to give a reasonable assessment of the two basic concepts of “impulsive action” and “impulsive choice”.

However, in human subjects the relationship between performance in the two tasks and alcohol abuse is complex. Alcohol given acutely has little effect on performance on a delay-discounting task (Richards et al. 1999; Dougherty et al. 2008; Adams et al. 2017), while only severely intoxicating amounts tend to induce discounting of delayed rewards at lower rates (Ortner et al. 2003). Reynolds et al. 2006a argue that such failures to find more robust effects may reflect particular design aspects of the task used, including the use of hypothetical question-based measures. And, indeed, studies using a task in which real delays were used (Experiential Discounting Task; EDT) report that acute doses of alcohol do induce “aversion” to delayed reward. Arguably, the EDT task is more closely related to the kind of delay-discounting procedures used in non-human animal models. That said, whilst there are studies demonstrating performance differences on EDT between alcohol-preferring and non-preferring strains of rats (Wilhelm and Mitchell 2008; Beckwith and Czachowski 2014, 2019), we are not aware of any reported effects of acute ethanol in rodent delay-discounting task performance (Wilhelm and Mitchell 2012).

In contrast to the somewhat mixed effects of acute alcohol on task performance, chronic use in the form of heavy drinking or alcoholism is in fact correlated with an intolerance to delays (e.g. Mitchell et al. 2005; Field et al. 2007; Adams et al. 2017). Thus, increased sensitivity to delay may contribute to loss of control over chronic drinking behaviour, with acute ethanol intoxication adding little further effect to this

kind of impulsivity. Moreover, Sanchez-Roige et al. (2014) reported that heavy alcohol drinkers (binge drinkers), compared to social non-binge drinkers, also showed more premature responses in a homologous 5-CSRTT designed for human subjects. Importantly, this pattern of behaviour was also found in alcohol-preferring C57BL/6J (B6) mice, albeit before alcohol exposure, compared to alcohol averse DBA2/J (D2) mice. In a further study of non-dependent social drinkers, individuals with a familial history of alcohol abuse were more prone to premature responses than those without; these findings taken together are consistent with the idea that impulsivity – in this case waiting motor impulsivity – is a potential predictor (i.e. biomarker) or even risk factor for alcohol use (Sanchez-Roige et al. 2016).

Findings consistent with some of these conclusions have also been reported in other rodent models: For example, and as already noted, rat strains selected for high alcohol drinking are more sensitive to reward delays than rats selected for low ethanol consumption (e.g. Wilhelm and Mitchell 2008; Beckwith and Czachowski 2019). Likewise, outbred mice selected for high-alcohol drinking showed as more impulsive on a delay-discounting task compared to low-alcohol preferring mice (Oberlin and Grahame 2009). And whilst the evidence that by itself chronic alcohol pre-exposure impacts delay-discounting performance is somewhat more complex and mixed (Beckwith and Czachowski 2019; Meinhardt et al. 2021), these observations point to excessive sensitivity to reward delays as a predisposing risk factor in chronic alcohol (ab)use (Bickel et al. 2012; cf. Gowin et al. 2019).

In the case of the 5-CSRT task, we have found that alcohol given acutely did not increase the numbers of premature (impulsive) responses in mice in the standard, that is, over-trained, form of the 5-CSRTT (Oliver et al. 2009), and a similar null-effect was observed by others using rats (Bizarro et al. 2003). Interestingly, when we provoked premature responding during probe trials by increasing the intertrial interval, we found that a dose of 1 g/kg ethanol did increase impulsivity scores. One interpretation then (and account for the null-effect) is that actions that are over-trained and/or otherwise are performed habitually can be relatively insensitive to effects of ethanol, while situations that require non-habitual action, e.g. where the subject is required to adjust or adapt its behaviour and respond accordingly to novel requirements, (impulsive-related) behavioural performance is sensitive to the effects of alcohol.

Efforts to establish a link between alcohol preference and impulsivity in rodent strains on the 5-CSRT task (which typically requires extensive training) have been rather less straightforward. For instance in an early study in mice, Patel et al. (2006) reported that the C57BL/6 strain (substrain not specified) was less impulsive than the DBA/2 strain (in a version of the task in which premature responding was not punished). This was and is an unexpected observation since mice of the C57BL/6J strains consume on average more alcohol compared to DBA/2 mice. Conversely, we reported that C57BL/6J mice were *more* impulsive than DBA2/J mice, at least when we used 5-CSRTT probe sessions that used extended intertrial intervals; and the degree of impulsivity correlated with subsequent alcohol consumption (Sanchez-Roige et al. 2014). Moreover, when Peña-Oliver and colleagues (2015) compared alcohol-preferring and non-preferring rats on a series of tasks including sign-

tracking and the 5-CSRTT, they reported no significant differences in performance on either of these tasks. However, it should be noted that in the Pena-Oliver study, 5-CSRTT was performed under fixed intertrial interval, whereas Sanchez-Roige et al. used a procedure in which the 5-CSRTT incorporated a variable intertrial interval to prevent the animals from using internal timing to decide when to respond. This variation appears to increase the deficit seen in the alcohol-preferring mice. To the best of our knowledge, the 5-CSRTT with the variable intertrial interval has not been used with alcohol preferring rats. For now then, performance on 5-CSRT tasks in rodents seems less able to inform us on, what seems to be, a well-established links between impulsivity and alcohol abuse. Moreover, some of the above discrepancies point to subtle variations in task requirements affecting performance and these need careful attention when comparing findings from human and non-human animal studies.

With regard to the increase in impulsive responding after ethanol treatment, our results are more in agreement with other reports using different paradigms of impulsivity in rats, including the delay-of-reinforcement paradigm, where ethanol increased impulsive behaviour (Poulos et al. 1998; Tomie et al. 1998; Evenden and Ryan 1999; Olmstead et al. 2006) (cf. Wilhelm and Mitchell 2012), suggesting that ethanol given acutely increases both impulsive choice and impulsive action. Similarly, in human studies, in measures of response inhibition, when the subject is required to withhold an already initiated response (e.g. stop-signal tasks), ethanol seems to increase impulsivity in moderate drinkers and in college students (Mulvihill et al. 1997; Dougherty et al. 1999, 2000; Field et al. 2010), though also these effects can at times be subtle (Liu et al. 2021).

Thus, in several laboratory tasks designed to tease apart specific aspects of impulsive behaviour, there appears to be good consistency between animal and human laboratory tasks, both in terms of measures or traits that predict high alcohol consumption and in the acute effects of alcohol. These are valuable findings as, on the one hand, they allow confident use of the animal tests to predict effects of treatment in humans, while on the other, they allow the use of experimental manipulations such as CNS lesions, optogenetics and/or optical imaging technologies, and other genetic manipulation and screening tools, to probe the neurobiological and neurogenetic mechanisms that contribute to alcohol's effects, with reasonable confidence that such observations have relevance for human alcohol abuse.

By way of example, Pena-Oliver and colleagues (2016) investigated genetic associations between impulsivity and initiation of drug taking using a two-step approach (Pena-Oliver et al. 2016). First, they identified genes whose expression level in prefrontal cortex, striatum, and accumbens was associated with impulsive behaviour using the 5-CSRTT across 10 BXD recombinant inbred (BXD RI) mouse strains and their progenitor C57BL/6J and DBA2/J strains. Behavioural data were correlated with regional gene expression using GeneNetwork (www.genenetwork.org) to identify 44 genes whose probability of association with impulsivity in this task exceeded a false discovery rate of <0.05 . The authors then interrogated the IMAGEN database of 1,423 human adolescents for potential associations of SNPs in

human homologues of those genes identified in the mouse study, with brain activation during impulsive performance in the Monetary Incentive Delay task, and with novelty-seeking scores from the Temperament and Character Inventory, as well as alcohol experience. There was a significant overall association between the human homologues of impulsivity-related genes and the percentage of premature responses in the Monetary Incentive Delay task and with fMRI BOLD-response in ventral striatum (VS) during reward anticipation. Further analysis revealed that the G allele (major) of the intronic SNP rs6438839 in the KALRN gene was significantly associated with increased activation of ventral striatum. Additionally, the A-allele (minor) of KALRN intronic SNP rs463050 within the same haplotype block was associated with an increased frequency of binge drinking (Pena-Oliver et al. 2016).

These findings illustrate the utility of identifying potential candidate genes in mouse studies using well-characterized behavioural tests that can then be used to increase the power of human genetic studies of homologous behaviours which may then serve as behavioural endophenotypes for complex human disorders.

8 Withdrawal from Alcohol

So far, we have dealt with the difficulties associated with assessing behaviours in animals and humans that might allow us to proceed with confidence from animal findings to human experimentation, or to the clinic. However, when it comes to studying the effects of alcohol (or other addictive drugs) there is an equally important discussion to be had regarding treatment-related parameters and what constitutes equivalent “treatment” regimens in animal and human experiments. Such a discussion is particularly important when considering the long-term consequences of alcohol abuse.

A defining feature of AUD is the persistent, long-term consumption of large amounts of the alcohol, typically resulting tolerance developing to some of its effects; the development of dependence as revealed by withdrawal signs and symptoms on cessation of use; and the development or emergence of various toxic effects arising from chronic high-dose alcohol itself, its metabolite acetaldehyde, or secondary to alcohol-induced organ damage especially hepatic disease. Furthermore, withdrawal from alcohol is itself associated with neurobiological changes that underlie some of the symptoms of withdrawal, but that may also have an impact on long-term brain function after the withdrawal symptoms themselves subside. For instance, there has been a long-standing interest in the effects of repeated episodes of withdrawal from ethanol (detoxification) on central nervous system functioning in human and non-human animal studies (Duka and Stephens 2014). Reproducing in animal models many of these impactful clinical features of AUD remains an important but challenging task.

There are several ways that health and regulatory authorities use to define unwise or irresponsible drinking. For instance, in many countries it is illegal to drive with blood alcohol levels exceeding a certain blood concentration limit, most often 50 or

80 mg/dL. UK governmental recommendations point to consumption in excess of 4 units of alcohol per day for a man, and 3 units for a woman, as being likely to compromise health. Common definitions of binge drinking refer to blood alcohol levels of 80 mg/dL in a single sitting (Lange and Voas 2000; NIAAA 2004). Some alcoholic patients are likely to reach and maintain blood alcohol levels much in excess of these levels for protracted periods of time. A significant roadblock to research is therefore that, in the human psychopharmacology laboratory, it is most often considered unethical and unsafe to give sufficient alcohol to subjects to approach these kinds of blood alcohol levels on even a single occasion, and on multiple occasions with the aim of modelling alcohol abuse is clearly out of the question.

But even limiting ourselves to studying the effects of a single intoxication event by an acute dose of alcohol, which aspects should we be modelling? The overall amount? The maximum blood alcohol level achieved? The time to reach peak blood concentrations? The speed of offset? Equally, what aspects of drinking patterns seen in humans should the non-human animal researcher, interested in the longer-term effects of chronic alcohol intake, need to consider? First and clearly, a major issue arises from the simple fact that rodents and humans differ markedly in their ability to metabolize alcohol, so that attempts at equalizing consumption (say on a body weight basis) simply do not allow parallels in blood alcohol concentrations over a 24-h time period. And how should the animal researcher integrate features of human alcohol abuse such as drunkenness and blackouts into their models? Some of these problems are clearly insoluble at an operational level.

Several methods of administering alcohol to rodents to achieve rapid, high blood alcohol levels (say, greater than 100 mg/dL) have been developed and effectively used to induce behavioural and neurobiological consequences that appear at some level to parallel the consequences of alcohol abuse seen in human (Perez-Cervera et al. 2023). Arguably a better, or at least alternative, way of modelling alcohol abuse in animals is not to focus on the “input” side (i.e. modelling the dynamics of blood and brain alcohol levels), but rather focus on the “output” side by modelling the consequences of alcohol abuse, whether behavioural or neurobiological. A number of attempts at establishing such parallels between behavioural outcomes have been documented in the literature, particularly in the context of binge drinking.

9 Binge Drinking and Withdrawal

The term binge drinking was originally used to describe periods of excessive drinking among alcoholics, followed by periods of abstinence. But over the last 20–30 years, binge drinking has been more frequently used to describe excessive bouts of drinking of alcohol within a single short time-period, often with harmful consequences, increasingly common among adolescents and college students (Wechsler et al. 1994; Midanik et al. 1996). Interest in understanding the type of excessive binge drinking is driven by many concerns about harm, including a fear

that a binge-drinking pattern of alcohol consumption may cause brain damage in humans (and also demonstrated in non-human animals) (Hunt 1993).

As said, there have been/are several definitions of binge drinking: The National Institute on Alcohol Abuse and Alcoholism (NIAAA), for instance, defines “a ‘binge’ [as] a pattern of drinking alcohol that brings BAC to about 0.08 gram-per cent or above. For the typical adult, this pattern corresponds to consuming 5 or more (for males) or 4 or more (for females) drinks within about 2 hours” (NIAAA 2004). The reader will note that this definition ignores differences in body size, in natural tolerance, and/or developed tolerance due to past use, etc. For that reason, in our own studies of binge drinking, we have used a more behavioural approach based on the Alcohol Use Questionnaire (Mehrabian and Russell 1978), which incorporates speed of drinking, with (behavioural) measures of “numbers of times being drunk in the last six months” (with drunkenness defined as loss of coordination, nausea, and/or the inability to speak clearly, or blackout) and the percentage of times getting drunk when drinking (Townshend and Duka 2002). Although some of the differences in how we define binge drinking may give rise to some confusion both in the scientific literature and among the public, it is likely that the multiple definitions tap into closely related phenomena.

In addition, binge drinking is characterized by repeated bouts of drinking leading to high levels of alcohol in the brain, followed by periods in which brain alcohol levels return to zero. We have proposed therefore that binge drinking may lead to brain damage and cognitive dysfunctions, which may resemble the neurotoxic effects described with repeated withdrawals from alcohol in pharmacologically dependent animals and humans (Veatch and Gonzalez 1999; Crews et al. 2001; Duka et al. 2003, 2004; Stephens et al. 2005a, b; Stephens and Duka 2008).

Several rodent models of binge drinking have been developed and tested, though we note that most of these do not (look to) model the volitional aspect of human drinking. For instance, intermittent alcohol vapour administration over several days with concentrations of alcohol in blood reaching as much as 250 mg/dL leads to several features typical of alcohol dependence in humans. These include altered sleep patterns (Criado et al. 2008; Ehlers and Criado 2010) and kindling of withdrawal seizures (Becker et al. 1997a, b). Reports suggest that such treatments also lead to reduced amplitude of Event-Related Potentials (ERPs) suggesting impairments in cognitive functions (Criado and Ehlers 2010). However, the extent to which these changes in rodents map onto homologous changes in human binge drinkers has not been tested, so that, while these observations are of interest in their own right, we do not know the extent to which they provide an adequate model of the consequences of human binge drinking.

Other models use acute i.p. or oral gavage administration of ethanol to achieve high blood alcohol levels. One such model provided a 4-day ethanol “binge” of 3 g/kg administered via oral gavage every 8 h, leading to a cumulative blood alcohol levels of 250 mg/dL. Such treatments induce brain tissue shrinkage with increased lateral ventricular volumes (Zahr et al. 2009). Similar “binge” ethanol exposure in adult rats (induced by daily i.p. injections) causes necrotic neurodegeneration after as little as 2 days of exposure (Obernier et al. 2002). While binge drinking in humans

can have multiple adverse consequence, as far as we are aware, no such extreme consequences have been observed in human binge drinking; so although these reports may point to potential consequences of extreme alcohol abuse in humans, the validity of such approaches as a model of binge drinking is questionable.

Because human binge drinking is often characterized (probably incorrectly) as a mostly adolescent phenomenon, many researchers have been particularly interested in modelling the effects of alcohol as a function of developmental stages. For instance, Crews et al. (2000) found that young adolescent rats show a different pattern of brain damage after binge ethanol administration from that found in adult rats; specifically damage to the associated frontal cortical olfactory regions was seen in the adolescent, but not adult rats. Subsequent animal studies have confirmed such neurotoxic effects of excessive alcohol drinking in the adolescent brain, including in relation to changes in neurogenesis in the hippocampus (Crews et al. 2000, 2016; Ehlers et al. 2013) and functional connectivity in different areas of the cortex (Rapp et al. 2022).

In line, studies in human adolescents and university students, that examined the effects of heavy binge drinking, reported alcohol-related structural (De Bellis et al. 2000, 2005; Nagel et al. 2005; Medina et al. 2007) and functional (Hartley et al. 2004; Tapert et al. 2004; Townshend and Duka 2005) brain abnormalities. As the human prefrontal cortical lobes continue to mature into the early-mid twenties (Casey et al. 2000; Gogtay et al. 2004), there has been a widely held concern that this late developing area is especially sensitive to heavy alcohol use, also because findings from rodent studies appear to map onto or parallel human observations. However, even for effects like this there is some way to go before we can regard such observations as homologous. That is, development of the rodent brain takes place with a time course quite different from that of the human brain, so that “adolescence” in the rat may reflect quite different stages in brain development from human “adolescence”. Moreover, there are aspects and subregions of human prefrontal cortex that have no homologous structure in the rodent model (e.g. Laubach et al. 2018; Schaeffer et al. 2020). Great care must therefore be taken in mapping rodent neurobiological findings onto human binge drinking, especially in relation to effects by alcohol on the prefrontal cortex and functions dependent on its subregions.

The previous paragraphs concern themselves with the consequences of exposure methods on withdrawal from and on neurotoxic effects by alcohol. Similar models of alcohol exposure have also been used to study their impact on motivation for alcohol. For instance, rats exposed to repeated cycles of intoxication and withdrawal, using the ethanol vapour method to achieve blood level substantially greater than 200 mg/dL, increase their voluntary intake of ethanol (Rimondini et al. 2002; Sommer et al. 2008), and show greater motivation for ethanol (Schulteis et al. 1996; Meinhardt and Sommer 2015; Perez-Cervera et al. 2023).

A particularly interesting model was developed by Spanagel and Holter (1999) that allowed animals to choose among four different drinks with regard to alcohol concentrations (0%, 5%, 10%, and 20% v/v). The bottles were introduced and continuously present in the animal's cage, so became part of their everyday life (very much like alcohol for some young adults). With experience, the average ad lib

daily alcohol intake reached approximately 6.5 g/kg. Next, following different periods of voluntary alcohol drinking, the animals were deprived for 1 or more days and, following the deprivation period, alcohol would again be made available. This (alcohol deprivation effect) experience produced dramatic increases in drinking by rats, which the authors described as compulsive. Moreover, this same group showed an increased reactivity to stressful stimuli during the periods of abstinence (Sanchis-Segura and Spanagel 2006). This model studying the long-term consequences of drinking, and the mechanisms of relapse (Vengeliene et al. 2014), has considerable face validity, but, like all the other methods outlined in this section, has somewhat unclear theoretical footings; and it is difficult to know whether or to what extent potentially important neurobiological findings, such as changes in NMDA receptors associated with the alcohol deprivation effect (Vengeliene et al. 2005), are likely to reflect the human condition.

A different model that gives animals ad lib access to alcohol, but would not be described as free choice, is the model used by us (Stephens et al. 2001) in which animals are trained to consume alcohol, using free access to a 5% alcohol nutritionally complete liquid diet as their sole food source. By alternating periods of alcohol administration (8 days alcohol diet followed by 3 days non-alcohol diet) this procedure allowed us to control overall alcohol consumption and patterns of intake. Animals consumed alcohol at an equivalent dose of 15–20 g/kg/day and blood alcohol reached a level of 100 mg/dL (Ripley et al. 2003). Using this procedure, we were able to demonstrate that 24 days of alcohol interspersed with two 3-day periods of alcohol deprivation lead to dependence as measured by increased sensitivity to convulsions 7 days after the last withdrawal (Stephens et al. 2001).

One benefit of our model is that by including, in addition to a control group that does not take any alcohol, a group which is exposed to 24 days of alcohol intake but without the 3-day alcohol-free periods, it is possible to assess and isolate not just the effects of chronic, high levels of alcohol intake, but of (its interaction with) repeated withdrawal from alcohol experience. Moreover, we showed that animals with the 3 periods of withdrawal from alcohol, compared to a single withdrawal experience, showed greater sensitivity to repeated pentylenetetrazol-induced proconvulsant activity suggesting a progressive experience-dependent physical dependency effect (Ripley et al. 2002).

While our model is not “better” than other consumption models outlined here (and its “face value” is arguably worse than, e.g., the Spanagel model), we have made some effort to map the behavioural changes induced by our “binge” model onto homologous behavioural changes in binge-drinking humans and alcoholic patients. For instance, we reported that rats exposed to repeated episodes of withdrawal show impairments in aversive conditioning (Stephens et al. 2001), an effect also observed using a homologous task in young human binge drinkers (Stephens et al. 2005a, b; Stephens and Duka 2008). And we have observed other, similar parallel changes in a number of laboratory measures in which we were able to develop closely homologous behavioural tests in rats and humans (see Stephens and Duka 2008). This includes studies looking at choice under conflict in animals and humans; using a negative-patterning-type task, in which presentation of either of

2 cues signalled reward availability, but not when presented in compound, we found that AUD patients were impaired, especially when they had experienced multiple detoxifications in the past (Duka et al. 2011a, b). In parallel, when we studied performance on a similar, homologous “Incentive Conflict Task” in rodents (Borlikova et al. 2006), similar deficits were seen after repeated episodes of ethanol withdrawal. Note here that the fact that these behavioural deficits in AUD patients can be experimentally induced in laboratory rodents by alcohol exposure and withdrawal suggests that this aspect of the underlying brain pathology in AUD (which we found to involve the ventromedial prefrontal cortex and superior frontal gyrus, Duka et al. 2011a, b) is a consequence of drinking, rather than predating (and potentially causing) AUD (Stephens and Duka 2008). For additional review of parallels between animal and human findings specific to alcohol withdrawal and binge drinking, see Kouimtsidis et al. (2019).

Of course, the opportunities for establishing homologous findings in the rodent model and the human are limited and function best in carefully controlled laboratory experiments as outlined above. The problem then shifts to the relevance of behaviour from the carefully controlled human laboratory to behaviour of alcohol users and abusers in the real world. And whilst in some cases, it may be possible to make quite direct links between human laboratory studies and real-world behaviours (e.g. fear conditioning in the laboratory and aspects of normal and abnormal anxiety), in many cases, the link is much more tenuous, so that the human laboratory findings may be better viewed as analogous to the real-world situation.

Indeed, there are many situations in which it is impossible to achieve the ideal, or even a moderately useful or informative, “rodent model – human laboratory model – human clinical experience” triad, especially where it would be unethical or unfeasible to conduct the human laboratory test. For instance, we found that rats that have undergone repeated withdrawals subsequent to a conditioning experiment generalize their fear learning to cues not previously paired with the aversive stimulus (Stephens et al. 2005a, b); to carry out the analogous experiment in humans would require fear conditioning to be established prior to experience of binge drinking, followed by test. This is clearly impractical, as well as unethical, though we have found analogous inappropriate generalization in binge drinkers in an aversive conditioning paradigm (Stephens et al. 2005a, b).

9.1 Adolescent Drinking

A final word on adolescents and binge drinking. With the persistently high incidence rates in binge drinking and drunkenness with its wide, harmful consequences (including violent criminal behaviour) in particular among adolescents, research studying binge drinking in adolescent animals and humans is critical. The challenge of this approach is not only (or less) to model the binge-drinking procedure, to mimic the drinking behaviour seen in adolescents, but to choose the appropriate age in animals that reflects the developmental cerebral stage in humans.

As we and others have noted (Lees et al. 2019), adolescence is a period of rapid brain reorganization through “pruning” and myelination during which brain structure and function may be especially sensitive to alcohol effects. Indeed, teenagers with alcohol use disorders show reduced hippocampal (De Bellis et al. 2000; Nagel et al. 2005) and prefrontal cortex volume (De Bellis et al. 2005; Medina et al. 2007), whereas fMRI studies indicate altered responses to verbal (Tapert et al. 2004) or visual (Crego et al. 2010) working memory tasks as well as a verbal encoding tasks (Schweinsburg et al. 2010). It would be important then to develop homologous models on non-human animals, but to what extent is this feasible? Clearly, verbal memory lies outside the possibilities of animal studies, but inasmuch as processes that underlie verbal working memory reflect similar processes as those underlying visual working memory, then parallel tests might be developed. Equally, if it is established that a rodent model of adolescent alcohol abuse leads to similar consequences for, say, prefrontal cortex function as is seen in human adolescents, then it would make sense to use behavioural tasks requiring intact function of those areas in rodents to study consequences of ethanol abuse; especially if tasks can be developed that have close parallels in humans, and are known to be impaired in human adolescent alcohol abuse, irrespective of whether there is a close parallel between the details of alcohol treatments (amounts or timing) in rodents and humans. Again and as we argued above in relation to AUD, it seems more important to establish homology in the behavioural outputs of animal models than in achieving close similarities between human patterns of drinking and alcohol treatment in the model (i.e. on the “input” side of the model).

10 Conclusion

We argued in our original contribution to this volume, and we argue again, that a continuing weakness in much laboratory research on alcohol (or other drugs of abuse) is the uncritical attribution of “face validity” to behavioural analyses of alcohol’s effects. This weakness is not unique to research on alcohol and drug abuse and addiction, but a wider problem for much preclinical psychopharmacology research in most areas of mental health (Nestler and Hyman 2010). We argue that a more rigorous (though less ambitious) approach might be to eschew attempts at developing animal models of the general human condition, in favour of establishing limited, but closely homologous behavioural tests in non-human animals and humans that allow a better understanding of the psychological processes impacted by alcohol abuse, and governing alcohol-seeking behaviour, as well as more reliable (though limited) predictions from the animal test to the homologous human test. In parallel, it might be possible to use such limited human tests as “biomarkers” or “intermediate behavioural phenotypes” for the particular condition of interest (Duka et al. 2011a). Such tests would not try to model the entire human condition, but would be concerned at identifying fundamental aspects of the underlying behavioural (or neurobiological or physiological) pathology that give rise to, if

untreated, the wider disorder. We suggest several aspects of alcohol-related behaviour for which parallel tests might be developed (or have already been developed) for rodents and humans, though in the present article we have not extensively explored potential biomarkers (but see Duka et al. 2011a).

And whilst the reasons for the paucity of effective treatments or interventions for alcohol abuse and addiction that successfully transition from research to clinical practice are numerous and multifaceted, we believe that the focus on direct (analogous) modelling patterns of human alcohol abuse in animals is a likely contributor; making predictions for human alcohol abuse from observations of the consequences of a particular treatment regimen for a particular behaviour in animals fraught with difficulties and risky. Nevertheless, we are struck by the ability of some animal models of alcohol abuse to mimic behavioural outcomes in human alcoholic patients, or binge drinkers in behavioural tests designed to be closely homologous between the human and the rodent. Such similarities in the behavioural output of human alcohol abuse and the rodent model might indicate that some rodent models are nonetheless able to mimic some important aspects of the human abuse pattern.

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Alcohol-Induced Changes in Brain Microstructure: Uncovering Novel Pathophysiological Mechanisms of AUD Using Translational DTI in Humans and Rodents



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Abstract Alcohol use disorder (AUD) induces significant structural alterations in both gray and white matter, contributing to cognitive and functional impairments. This chapter presents a translational neuroimaging approach using

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diffusion-weighted MRI in humans and rodents to uncover novel pathophysiological mechanisms underlying AUD. Our studies demonstrate that increased mean diffusivity (MD) in gray matter reflects microglial reactivity and reduced extracellular space tortuosity, leading to enhanced volume neurotransmission. In white matter, fractional anisotropy (FA) reductions indicate progressive deterioration of key tracts, particularly the fimbria/fornix, linked to impaired cognitive flexibility. Importantly, longitudinal analyses reveal that white matter degeneration continues during early abstinence, suggesting that neuroinflammation and demyelination persist beyond alcohol cessation. Finally, we discuss how neuromodulatory interventions, such as transcranial magnetic stimulation (TMS), may promote recovery by enhancing myelin plasticity. These findings provide crucial insights into AUD's neurobiological underpinnings and highlight potential therapeutic targets for improving treatment outcomes.

Keywords Alcohol use disorder · Diffusion-weighted MRI · Dopamine · Executive function · Extracellular space · Fractional anisotropy · Mean diffusivity · Microglia · Myelin · Neuroinflammation · Rat · Tissue microstructure · Transcranial magnetic stimulation · Translation · Volume conduction

1 Introduction

About a quarter of the world's adult population consumes alcohol. The harms associated with alcohol consumption, particularly chronic use, pose a significant public health challenge and impose a substantial economic burden. Millions of individuals suffer from alcohol use disorder (AUD) or alcohol dependence, a chronic, often life-threatening condition, characterized by frequent dysfunctional drinking, poor control over the drinking behavior, and long-lasting dysphoric states, particularly when access to alcohol is limited or prevented (MacKillop et al. 2022). Despite extensive research on the pleiotropic effects of alcohol on the body and brain, and the pathogenesis of AUD, these insights have had limited impact on clinical practice. The failure to translate basic research into effective novel treatments has raised concerns about the efficacy of the current research paradigm, including the utility of experimental animal models in studying psychiatric disorders such as AUD (Heilig et al. 2019).

Research on the neurobiology of alcohol addiction faces two main challenges. First, this multifaceted and inherently human condition can only be partially modeled in animals. Second, although several seemingly analogous responses to alcohol and other drugs have been observed and operationalized, cross-species behavioral comparisons – particularly between humans and rodents – remain challenging. For a recent discussion on progress and limitations in this field, see Crombag et al. in this edition.

In this context, we aimed to develop an experimental framework for monitoring disease progression and treatment development based on objectively comparable parameters between rodents and humans, rooted in biophysical phenomena. Magnetic resonance imaging (MRI) emerged as a suitable translational tool for this purpose, enabling the acquisition of diverse tissue information through different imaging contrasts, which reflect various aspects of tissue composition.

Excessive alcohol consumption leads to structural alterations in both white and gray matter, ultimately resulting in the well-documented brain shrinkage observed in individuals with AUD. The histopathological changes underlying these alterations include disruptions in myelination and axonal integrity, as well as dendritic and synaptic modifications (Harper and Corbett 1990) and region-specific neuronal loss (Harper 1998). It is also critical to recognize that alcohol exposure affects not only neurons but also glial cells, including astrocytes, oligodendrocytes, and microglia (Miguel-Hidalgo 2018). Given these diverse cellular changes, neuroimaging techniques, particularly MRI, provide a powerful means of assessing alcohol-induced brain damage by offering detailed insights into the brain's microstructural composition.

The translational capability of MRI is a significant yet often underappreciated advantage. MRI can be applied across species, facilitating research in both human and animal models. This capability is particularly valuable for investigating the causal relationship between alcohol consumption and brain changes through controlled animal experiments, which is challenging in human studies due to confounding factors such as lifestyle, nutrition, tobacco and other substance use, comorbid conditions, and medications. A reverse translational approach, in which MRI-detected alterations in patients are replicated in animal models to explore underlying neurobiological mechanisms, has proven effective in establishing causality in AUD (De Santis et al. 2019a, b).

In this review, we describe a series of experiments conducted in humans and rodents using diffusion-weighted (dw) MRI measures to identify novel and significant pathophysiological mechanisms underlying the effects of alcohol on the brain and the development of AUD. Our approach is illustrated in Fig. 1 and main results are summarized in Table 1. This work highlights the power of translational neuroimaging in advancing our understanding of alcohol-related neurobiological processes.

2 Early Proof-of-Concept-Studies

In a study using proton magnetic resonance spectroscopy to noninvasively measure the chemical composition of brain tissue, we found similar metabolite concentrations in the brains of humans and rats (Hermann et al. 2012), providing the first direct evidence in humans for a hyperglutamatergic state during acute alcohol withdrawal. A less frequently noted finding from this experiment, but one that has been recently confirmed by meta-analyses, was the reduction in N-acetylaspartate (NAA) levels in

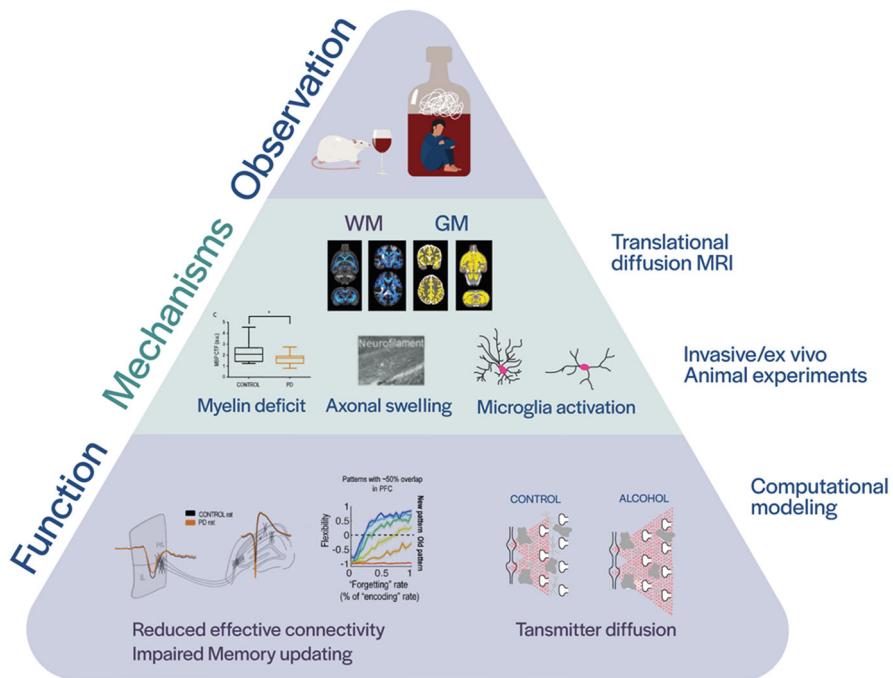


Fig. 1 Translational neuroimaging approach to uncover pathophysiological mechanisms in AUD. The top illustrates similar DTI findings in GM and WM across humans and rodent models. The middle level identifies myelin deficits, axonal swelling, and microglial process retraction as underlying mechanisms. The bottom level highlights neurophysiological and computational modeling results, revealing impaired WM communication and altered GM extracellular diffusion dynamics, specifically investigated in the fimbria/fornix and for dopamine signaling. The potential ramifications for our understanding of AUD pathology, biomarker development, and treatment strategies will be discussed

the prefrontal cortex and hippocampus following chronic alcohol use, with normalization occurring after a few weeks of abstinence (Frischknecht et al. 2017; Kirkland et al. 2022). NAA is an amino acid derivative found in high concentrations in the axons and dendrites of neurons. It is synthesized in neuronal mitochondria, exported to the cytosolic compartment, and diffuses through the extracellular fluid, where it functions as an organic osmolyte regulating cellular water distribution. NAA is rapidly taken up by oligodendrocytes, where it serves as a critical source of acetate for myelin lipid synthesis (Baslow 2003). Considering subsequent findings (De Santis et al. 2019a; Pérez-Cervera et al. 2023), this reduction in NAA levels likely reflected alterations in axonal function, myelin plasticity, and bioenergetic processes (Meyerhoff et al. 2013).

In pioneering neuroimaging research, we demonstrated that multiparametric approaches can yield valuable biomarkers for the early diagnosis of and response to treatment in AUD. In a rat model of AUD, the combination of different MRI contrasts accurately classified baseline, alcohol consumption, and abstinence states,

Table 1 Summary of key findings from our DTI studies in AUD patients and rats

Paper	DTI results	Mechanistic experiments	Computational modeling	Additional observations	Implications
Cosa et al. (2017)	Persistent WM and GM alterations in rats after 1-month alcohol drinking		Multi-modal MRI classifier distinct brain signatures of alcohol effects	MD as major contributor to the classifier	Identifies DTI as a sensitive tool for AUD effects
De Santis et al. (2019a, b)	↓ WM-FA comparable in patients and rats worsening in early abstinence		Mathematical modeling suggests demyelination and/or glial reaction	FA reduction linked to preadmission drinking patterns	Unveils an ongoing process that progresses in the absence of alcohol Highlights translational validity of rat models in AUD research
De Santis et al. (2020)	↑ GM-MD comparable in patients and rats Persisting in early abstinence	Microglial reaction linked to MD changes	MD changes due to reduced ECS tortuosity Altered ECS geometry predicts increased volume transmission		Hypothesis: ↑ diffusion of transmitters such as dopamine may enhance alcohol's addictive effects
Pérez-Cervera et al. (2023)	Differential vulnerability of WM tracts to alcohol effects Fimbria/ fornix most affected in patients and rats	↓ Myelin basic protein ↓ HC-PFC effective connectivity	Disrupted HC-PFC signaling reduces memory updating	FA reduction in Fimbria/fornix associated with cognitive flexibility in patients	Links fimbria vulnerability to AUD pathophysiology
Selim et al. (2024)	↓ WM-FA in AUD patients worsening in early abstinence	TMS to mPFC halted WM deterioration in abstinence		Reduction of craving and relapse after active dTMS altered functional connectivity in PFC	dTMS is a potential therapeutic intervention to recover WM deficits in AUD

WM white matter, GM gray matter, FA fractional anisotropy, MD mean diffusivity

as well as the effects of naltrexone treatment (Cosa et al. 2017). A similar methodology has also proven effective in patients with AUD (Ruiz-España et al. 2023). Notably, these multimodal studies identified water diffusion measures in the brain parenchyma as particularly informative for distinguishing AUD-associated states in both white and gray matter. Consistent with these findings, a machine learning study applied to a large dataset successfully predicted future binge-drinking patterns in adolescents based on structural MRI data, including diffusion tensor imaging (DTI) (Rane et al. 2022). These findings provide crucial insights into the neurobiological substrates that may predispose individuals to alcohol addiction.

3 Diffusion-Weighted Imaging: Basic Principles and Metrics

DTI is a noninvasive MRI technique that capitalizes on the diffusion of water molecules within tissue to infer microstructural properties of the brain. At its core, DTI involves the measurement of water diffusion in multiple directions, and the diffusion process is modeled mathematically as a tensor – a 3×3 matrix that encapsulates both the magnitude and orientation of diffusion. From this tensor, eigenvalues and eigenvectors are derived to calculate key metrics such as fractional anisotropy (FA) and mean diffusivity (MD). FA quantifies the degree of anisotropy, reflecting the directional preference of water diffusion. In contrast, MD provides an average measure of water diffusion across all directions, offering insights into the overall mobility of water molecules within tissue.

Given the similar cellular composition of brain parenchyma between rodents and humans, the physical properties measured by DTI are largely comparable across these species. Interestingly, FA and MD measurements reveal distinct characteristics that vary between tissue types. For example, highly organized structures that constrain water diffusion along a specific direction, such as axonal tracts in white matter, result in high FA values. For the same reason, a loss of fibers within an axonal tract leads to a reduction in FA and an increase in MD, as the loss of organized structural elements in a region of tissue facilitates the overall rate of water diffusion in all directions. Consequently, FA is commonly used to assess the integrity of white matter tracts, and its reduction – frequently accompanied by an increase in MD – is often interpreted as a biomarker of axonal damage.

However, interpreting DTI findings in biological terms is not as straightforward as the above example suggests and presents significant challenges (De Santis et al. 2019b). The measures of diffusivity reflect contributions from all water compartments, including both intracellular and extracellular spaces (De Santis et al. 2023). Additionally, DTI metrics are influenced by various microstructural factors, such as axonal density, myelination, and the complexity of fiber architecture, including the presence of crossing fibers. The interplay of these factors complicates the interpretation of FA and MD, making it difficult to attribute changes in these metrics to a

single underlying biological process. These limitations highlight the necessity of complementary imaging techniques and advanced analytical approaches to disentangle the distinct contributions of microstructural components to the observed diffusion properties.

3.1 Gray Matter Analysis with Diffusion-Weighted MRI: Alcohol Changes the Extracellular Space Geometry

While DTI has traditionally been employed to assess white matter integrity, it can also provide valuable insights into the microstructure of gray matter. Here, the preferred biomarker is MD due to the low degree of anisotropy characterizing its microstructure. Microstructural information obtained from MD has the potential to complement and, crucially, precede macroscopic measures such as regional volumes and cortical thickness. These macroscopic measures are typically used as surrogate markers of neuronal degeneration but are believed to detect changes only when they are relatively advanced (Kantarci et al. 2005).

Following a reverse translation approach, we investigated the gray matter of both AUD patients and chronically drinking rats using a two-bottle free-choice paradigm (De Santis et al. 2020). We observed a widespread increase in MD in both species. In the Marchigian alcohol-preferring rat line (Ciccocioppo et al. 2006), we demonstrated that one month of chronic alcohol consumption (4–6 g/kg/day) was sufficient to induce the same MD effect. In both humans and rats, elevated MD levels persisted into early abstinence. This finding was consistent with our previous observations in this animal model, where a support vector machine classifier effectively and accurately distinguished between naïve and alcohol-exposed subjects. However, classification performance dropped to chance level when differentiating between drinkers and abstainers (Cosa et al. 2017). This result suggested that alcohol-induced microstructural changes persist for at least the initial phase of abstinence (2–6 weeks). But what could explain the increased MD?

To elucidate this, we used an animal model and employed an invasive technique called real-time iontophoresis (Syková and Nicholson 2008) to precisely quantify diffusion in the extracellular space of the gray matter parenchyma. Our findings revealed a slight decrease in total volume fraction, accompanied by a significant reduction in extracellular space tortuosity – a geometric parameter that describes the complexity of the diffusion path through a convoluted structure (Syková and Nicholson 2008). This alcohol-induced decrease in tortuosity suggests a reduction in diffusion barriers, potentially reflecting microstructural alterations in the brain's extracellular matrix.

3.2 Increased MD Reflects Microglia Reaction in AUD

What caused the reduction in tortuosity? At this point, we conducted a thorough immunohistological investigation of the tissues with reduced tortuosity. We quantified the density and morphology of glial cells, such as astrocytes and microglia, assessed the extent of neurodegenerative processes, and examined extracellular matrix proteins such as metalloproteins. The results indicated that only one cell type could explain the change in mean water diffusivity: the microglia (De Santis et al. 2020). The fundamental change observed was the retraction of cellular processes in these cells with stellate morphology and dense ramifications, a change associated with inflammatory processes.

Inflammation has been proposed as a significant mechanism underlying alcohol-related damage (Crews et al. 2017). Immune markers in alcohol-dependent individuals correlate with lifetime alcohol consumption and the age of drinking onset, with some markers remaining elevated even during prolonged periods of abstinence (Leclercq et al. 2012; Portelli et al. 2019; Mednova et al. 2022). Persistent high levels of depression, anxiety, and craving, which are strong triggers for resuming heavy drinking after abstinence, have been linked to elevated levels of peripheral inflammation and the presence of a leaky and dysbiotic gut (Leclercq et al. 2014), reviewed in this volume (Leclercq and de Timary 2024).

Pioneering preclinical work highlighted the innate immune system, particularly the role of microglia and Toll-like receptor signaling, as potential mediators of the peripheral to central inflammatory response (Alfonso-Loeches et al. 2010; Pascual et al. 2011; Erickson et al. 2019; Patel et al. 2021; Crews et al. 2021). In a recent meta-analysis of humans, monkeys and rodents with chronic alcohol consumption/AUD, we compared expression profiles from nearly one-thousand samples of addiction-related brain regions, including more than 500 samples from the prefrontal cortex (Friske et al. 2024). This cross-species analysis revealed over-activated pathways to cause neuroinflammatory responses as well as impairment in blood-brain-barrier (BBB) integrity. However, while evidence clearly indicates an inflammatory process in AUD, it remains unclear whether and to what extent microglia contributes to the pathogenesis and progression of AUD in humans. It is also uncertain whether microglial activation is an epiphenomenon or a counteradaptation to defend or restore homeostasis (Czeh et al. 2011). Therefore, the molecular profile of the immune response needs to be clarified (Salem et al. 2024), and more robust evidence in humans is required.

An MRI biomarker of neuroinflammation, such as the increase in mean diffusivity (MD), could pave way for significant noninvasive longitudinal studies. We demonstrated that neuroinflammatory changes involving microglial reactivation leave a measurable biomarker detectable by MRI (de Santis et al. 2020). To establish a causal link between the microglial response and the increase in MD, we conducted two crucial experiments. First, we eliminated microglial cells using PLX5622, a highly selective inhibitor of a transmembrane tyrosine kinase receptor (CSFR1) that is essential for microglia proliferation and acquired MRI data before and after

treatment. The observed increase in MD, along with histological confirmation of the virtual elimination of microglia, supported our hypothesis. Second, we induced an inflammatory response in the brain by injecting lipopolysaccharide (LPS), a component of the bacterial wall, into brain tissue. This reactivated the microglial cells, causing the characteristic retraction of their cellular processes, and concurrently, MD significantly increased (de Santis et al. 2020).

Overall, our studies demonstrated the presence of a neuroinflammatory process associated with alcohol consumption and early abstinence in a rat model of AUD. This neuroinflammation produced changes in diffusivity in the extracellular space that were detectable by MRI. The same MRI changes were observed in AUD patients at the beginning of their detoxification process and during early abstinence, suggesting the presence of an inflammatory process in these patients as well.

3.3 Functional Consequences of Increased MD

Changes in diffusivity within the brain's extracellular space not only serve as a compelling biomarker of inflammation but also have significant implications for cellular, metabolic, and neurotransmission processes that rely on solute movement within this space. As a result, these alterations may have a direct impact on cognitive functioning. Indeed, a study in rats exposed to chronic intermittent ethanol vapor reported increased MD in the medial prefrontal cortex, which was associated with deficits in the retrieval and recall of fear memories (Somkuwar et al. 2021). Similarly, in alcohol-dependent patients, elevated MD levels were observed in the frontal, temporal, and parahippocampal regions, as well as in the cerebellum, compared to controls. These changes correlated with impaired verbal episodic memory performance. Notably, this association was not linked to volumetric shrinkage in these areas, suggesting that regional microstructural rather than macrostructural alterations in the brain parenchyma may partly underlie episodic memory deficits in alcohol dependence (Charnaud et al. 2009).

The observed reduction in tortuosity, which accounted for the increase in MD detected by DTI, also indicated a significant enhancement in solute diffusion through the brain's extracellular space. This finding may be critical for understanding the pharmacodynamic effects of alcohol, as its motivational and emotional impacts – which fluctuate considerably throughout the course of AUD – are mediated by neurotransmitters such as glutamate, monoamines, and peptides (Spanagel 2009; Hansson et al. 2019). These neurotransmitters partially exert their effects through extrasynaptic receptors reached via long-range diffusion across the extracellular space, forming a hormone-like signaling mechanism in the brain known as volume transmission (Fuxe and Agnati 1991). Consequently, alterations in the extracellular space are expected to influence the dynamics of these neurotransmitter systems.

To explore the functional impact of this change in alcohol-exposed subjects, we mathematically modeled how a tortuosity reduction of the magnitude observed experimentally might influence the diffusion of extrasynaptically released

neurotransmitters, such as dopamine. The model revealed a significant increase in the spatial reach of the released neurotransmitter, enhancing volume neurotransmission. This implies that the same amount of dopamine would diffuse farther and at a higher concentration within the same timeframe (De Santis et al. 2020). Meta-analyses have reported a modest increase in dopamine (and other monoamines) release in response to ethanol (Iliff et al. 2012; Hirth et al. 2016; Lundgaard et al. 2018). Given that this modest dopamine increase alone is unlikely to account for alcohol's addictive properties in certain individuals, we hypothesize that the synergistic interaction between ethanol – a weak primary reinforcer with a moderate effect on dopamine levels – and progressively enhanced volume neurotransmission due to increased extracellular diffusivity may represent a novel mechanism underlying alcohol's slow onset yet potent addictive potential. While further experimental research is necessary to validate this hypothesis, these findings already illustrate the mechanistic insights that can be derived from studying the neurobiological basis of DTI phenomena.

Investigating the impact of MD changes on other biochemical processes that heavily depend on extracellular space diffusivity could provide valuable insights. First, fluid transfer pathways involved in the clearance of waste products and metabolites through the glymphatic system may be affected (Iliff et al. 2012). Second, a subset of microglia plays a crucial role in structural plasticity, including synapse pruning and formation, which are essential for learning (Parkhurst et al. 2013). A reduction in the microglial pool and altered ramification patterns could, therefore, promote the formation of more persistent or rigid memories. These effects may interact with the increased diffusion range and enhanced volume neurotransmission reported here, potentially resulting in a distinct form of functional plasticity. For instance, prolonged elevations in neurotransmitter concentrations, such as dopamine, glutamate, or neuropeptides, combined with reduced synapse turnover, could facilitate the transformation of alcohol's relatively weak primary reinforcing effects into powerful habit-forming mechanisms, ultimately contributing to addiction in susceptible individuals (Giannone et al. 2024). Understanding these processes and identifying strategies to reverse them may aid in the development of more effective treatment interventions (Fig. 2).

4 White Matter Analysis with Diffusion-Weighted MRI: Tract-Dependent Vulnerability

White matter alterations in patients with AUD have been extensively documented (Harper and Kril 1985; Pfefferbaum et al. 2009, 2014; Alhassoon et al. 2012; Konrad et al. 2012; Monnig et al. 2015; Spindler et al. 2022; Chirokoff et al. 2024). These changes correlate with pre-detoxification drinking levels and, as we will see later, continue to progress for at least six weeks following alcohol withdrawal (De Santis et al. 2019a). While these alterations are widespread, mapping DTI parameters in

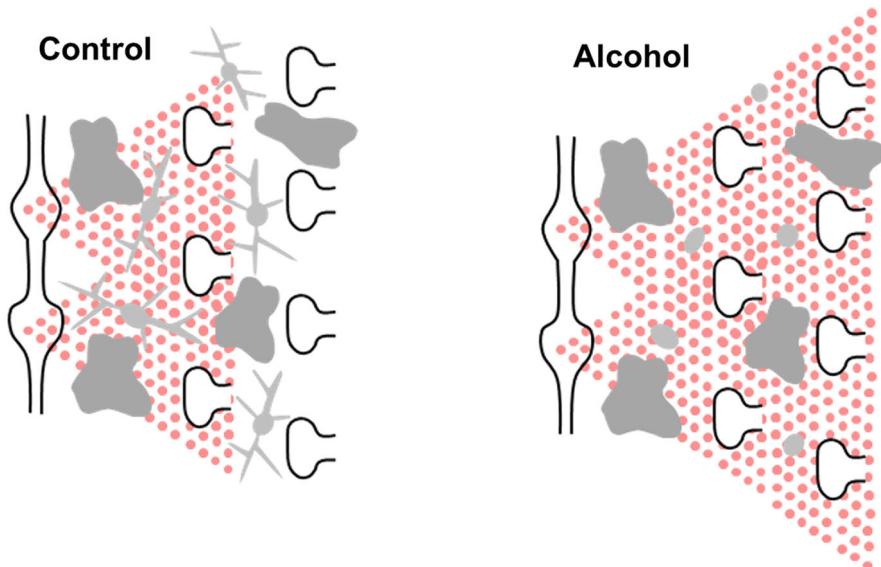


Fig. 2 Increased volume neurotransmission due to altered diffusivity in the extracellular space after chronic alcohol exposure. While synaptic neurotransmission is typically confined to the narrow synaptic cleft between the pre- and postsynaptic elements, certain neurotransmitters are released into the extracellular space, where chemical signaling occurs through diffusion (e.g., in *en passant* synapses). This process is referred to as volume neurotransmission (a). In such cases, the extracellular space, rather than the axon, serves as the primary communication channel. Consequently, changes in the diffusivity of this compartment can have a profound impact on neurotransmission. For instance, an increase in mean diffusivity due to the removal of diffusion barriers would enhance the number of postsynaptic elements activated by neurotransmitter release (b)

AUD patients compared to age- and sex-matched controls reveals a pattern of region-specific vulnerability. Frontal and superior white matter tracts consistently exhibit the most significant abnormalities in alcoholics, whereas more posterior and inferior bundles are relatively unaffected (Pfefferbaum et al. 2009).

A meta-analysis of over 900 subjects identified four significant clusters of microstructural white matter alterations in AUD patients, specifically in the genu and body of the corpus callosum, anterior and posterior cingulum, fornix, and the right posterior limb of the internal capsule (Spindler et al. 2022). In a recent study, we performed a formal analysis of effect sizes in an AUD cohort showing that the fimbria/fornix experienced the most substantial reduction in FA at two weeks of abstinence, with this reduction nearly double the average of the affected tracts (Pérez-Cervera et al. 2023). Notably, these same axonal bundles were preferentially affected in two different rat models of AUD: alcohol-preferring msP rats (De Santis et al. 2019a) and chronically intermittently exposed (post-dependent) rats (Pérez-Cervera et al. 2023). This suggests a fundamental biological principle that determines heterogeneous white matter vulnerability, generalizable across species.

Indeed, even a single episode of binge drinking appears to produce alterations in the genu and fornix (Pfefferbaum et al. 2015).

Furthermore, these patterns of region-specific white matter vulnerability are not limited to the most severe forms of AUD. Negative associations between alcohol intake and brain microstructure are evident even in individuals consuming an average of only one to two alcohol units daily, with these associations becoming stronger as alcohol intake increases. The fornix and corpus callosum were prominently affected, showing again the largest effect sizes (Daviet et al. 2022).

Other substance use also significantly affects white matter microstructure, as demonstrated by findings from diffusion-weighted imaging studies. Meta-analyses have established that stimulant and opioid use is associated with decreased FA in major white matter tracts in adult population (Beard et al. 2019; Suchting et al. 2021; Warner et al. 2024). Similarly, medium-scale studies on nicotine and cannabis users have reported comparable FA reductions (Manza et al. 2020; Huang et al. 2020); however, these findings are complex, as smaller studies have yielded variable results, and comprehensive meta-analyses have yet to be conducted. Interestingly, for certain substances, particularly nicotine, the impact on FA appears to be strongly age-dependent. In adolescent and young adult smokers, increased FA in specific tracts has occasionally been observed, possibly reflecting developmental or compensatory changes (Gogliettino et al. 2016).

Further systematic investigations, particularly through meta-analyses, are necessary to elucidate these patterns more clearly. Emerging evidence suggests that different drug classes may exhibit specific regional profiles of white matter damage. For instance, the fornix is most affected in individuals with AUD, while nicotine use is linked to pronounced alterations in the anterior limb of the internal capsule, and opioid use correlates most significantly with changes in the posterior thalamic radiation. Such region-specific white matter responses may serve as biomarkers for drug-specific tract damage, offering insights into the neurobiological underpinnings of substance use and potential avenues for targeted interventions.

4.1 The Neurobiological Substrate of White Matter Alterations

As already mentioned, conventional diffusion MRI lacks the specificity to differentiate between various tissue sub-compartments, thus hindering direct interpretations of the underlying neurobiological substrates. The reduction in FA and increase in MD in the white matter of AUD patients and rat models may indicate axonal damage, decreased myelin content, or even an inflammatory glial reaction, as shown by mathematical modeling in De Santis et al. 2019a. Therefore, we set out to investigate histologically the changes underlying DTI alterations, using the animal model. We found a decrease in the staining intensity of the myelin basic protein (MBP). MBP is essential for myelin assembly (Boggs 2006), and its loss can trigger

myelin breakdown in demyelinating diseases (Weil et al. 2016). Evidence of MBP reduction in AUD patients was found using Western blot analysis (Bhattacharya et al. 2007). However, comorbid factors such as tobacco co-abuse or liver cirrhosis can complicate the establishment of causal associations of MBP in AUD studies (Papp-Peka et al. 2017). A recent preclinical study in mice subjected to alcohol binge drinking also showed reduced MBP staining in the hippocampus and prefrontal cortex (Rice and Gu 2019). Our work extends these findings to the protracted abstinence stage in alcohol-dependent rats, highlighting the vulnerability of the fimbria/fornix and the persistence of myelin damage. Overall, animal studies demonstrate that bouts of binge drinking during adolescence (Rice and Gu 2019) and relatively short periods (four weeks) of excessive alcohol intake in adult rats (De Santis et al. 2019a) are sufficient to induce significant white matter alterations. These changes can persist into protracted abstinence, particularly in rats with a history of alcohol dependence (Somkuwar et al. 2021; Pérez-Cervera et al. 2023).

The origin of white matter damage remains unclear and requires further experimental investigation. However, a potential clue lies in the previously mentioned microglial reaction. There is a strong relationship between microglia and oligodendrocytes in myelination processes. Oligodendrocytes are particularly vulnerable to oxidative stress and prolonged exposure to proinflammatory factors secreted by microglia. Accordingly, there is documented evidence of direct toxic effects of alcohol on myelinating cells (Rice and Gu 2019). Regardless of the mechanism, our results reveal a causal relationship between chronic alcohol drinking in rats and demyelination in the fimbria/fornix (Pérez-Cervera et al. 2023).

4.2 Progression of Diffusivity Alterations During Early Abstinence

Longitudinal DTI acquisitions have been employed to assess microstructural integrity in the white matter of abstinent AUD patients from one to several years after their last drinking episode (Alhassoon et al. 2012; Pfefferbaum et al. 2014). These studies reported a recovery of DTI values toward control levels in long-term abstinent subjects, providing a microstructural basis for the observed clinical improvement. However, AUD is characterized by a chronically relapsing-remitting course that may continue over a lifetime, with most individuals treated for AUD known to relapse into hazardous alcohol consumption within six months of treatment (Wikiewitz and Marlatt 2007).

What, then, occurs in the brain's microstructure during the critical early phase of alcohol abstinence? To address this question, we acquired longitudinal DTI data in AUD patients and rat models at various intervals from 2 to 6 weeks during early abstinence (De Santis et al. 2019a). Our findings in both species indicated that the reduction in FA in white matter tracts progressed rather than recovered. Specifically, FA decreased after 3 weeks of abstinence and further diminished at 6 weeks

compared to 3 weeks. This progression of DTI alterations during early abstinence suggests the presence of an underlying process that continues to evolve soon after the cessation of alcohol consumption, challenging the conventional notion that microstructural damage begins to repair immediately after stopping alcohol intake. A latent neuroinflammatory process or even rebound inflammation triggered by alcohol withdrawal is plausible mechanism for this observation. Importantly, this finding of progressive white matter deterioration has been recently replicated in an independent cohort of AUD patients (Selim et al. 2024).

4.3 Systems Neuroscience and Cognitive Consequences

The described microstructural alterations are expected to have significant functional implications. Abnormalities in the white matter tracts connecting regions of the mesolimbic pathway, which play a crucial role in the rewarding effects of drugs, are associated with higher impulsivity and disruptions in the reward network (Wang et al. 2016). The fimbria, for instance, is the primary pathway connecting the hippocampus and the prefrontal cortex, playing a fundamental role in memory formation and extinction, executive function, and emotional processing (Ji and Maren 2007).

In the post-dependent rat model of AUD, we investigated the functional consequences of alterations in the fimbria/fornix using *in vivo* electrophysiological recordings. We measured the effective connectivity from the hippocampus to the prefrontal cortex by recording the amplitude of the evoked activity in the latter in response to neuronal firing in the former. This approach allowed us to measure input and output activities, as well as the directionality, providing a measure of how efficiently hippocampal activity influences the prefrontal cortex. It is important to distinguish this from functional connectivity measures commonly used in fMRI or EEG studies (Bullmore and Sporns 2009), where connectivity refers just to the correlation or coherence between two signals, without directionality or evidence of an interaction. We found lower effective connectivity in post-dependent animals during abstinence, suggesting a reduced capacity of the hippocampus to influence information processing in the prefrontal cortex (Pérez-Cervera et al. 2023).

The hippocampal projection to the prefrontal cortex is essential not only for memory formation but also for extinction learning, a process that suppresses maladaptive memories (Holmes et al. 2012; Barak and Goltseker 2023). Studies have demonstrated that the extinction of a fear-context association, when the stimulus is absent, relies on the hippocampal projection (Ji and Maren 2007; Garcia et al. 2008), and its deactivation inhibits this process (Garcia et al. 2008). Moreover, anticipatory neuronal firing in the prefrontal cortex in response to reward expectation is regulated by the hippocampal connection and is prevented by its inactivation (Burton et al. 2009). In rats, the acquisition of new learning rules is also linked to increased functional coupling between these two structures (Burton et al. 2009). Consistent with these findings, our utilization of a simple computational network model,

simulating hippocampal and neocortical dynamics during memory formation, revealed that impaired hippocampal-prefrontal communication leads to a decrease in extinction and an increase in the cue-reactivation of old memory at the expense of retrieving newly encoded memory associations. Consequently, the system becomes unable to update its memory base, becoming trapped in old memories and disconnecting behavioral outcomes from environmental changes.

Evidence supporting the role of hippocampal-prefrontal interactions in the post-dependent alcohol phenotype includes our observations, as well as those of others, of decreased performance in test of executive function such as attentional set-shifting, delay discounting or recall of aversive memories (Meinhardt et al. 2021; Somkuwar et al. 2021). Post-dependent rats demonstrated behavioral inflexibility, particularly under higher cognitive load. This deficit persisted for at least one month of abstinence, contributing to an increased propensity for relapse in this AUD model. In humans, the hippocampal input to the prefrontal cortex is crucial for stress regulation (Rocher et al. 2004; Vouimba and Richter-Levin 2005; Pittenger and Duman 2008), which may link microstructural alterations in the fornix to relapse proneness (Sinha 2001; Milivojevic and Sinha, *in press*). Consistent with this interpretation, we previously demonstrated that post-dependent rats exhibit hypersensitivity to stress and stress-induced alcohol consumption (Sommer et al. 2008), as well as increased responding to alcohol-predicting cues in the reinstatement paradigm (Meinhardt et al. 2013; Hirth et al. 2016).

Moreover, hippocampal dysfunction could underlie the attenuated activation of the dorsolateral prefrontal cortex in AUD patients, associated with reduced cognitive flexibility and delayed extinction of nonadaptive behaviors when reinforcement contingencies change (Li et al. 2009). This view is supported by our finding of a significant correlation between FA reduction in the fimbria/fornix and reduced cognitive flexibility in AUD patients, as ascertained, e.g., by the trail making test especially under time pressure (Pérez-Cervera et al. 2023). Additional findings (Crespi et al. 2019; Le Berre et al. 2017) suggest that a reduction in FA is linked to cognitive performance in AUD patients, particularly in executive functions such as cognitive flexibility and inhibitory control. These cognitive functions are notably impaired in AUD patients (Stephan et al. 2017) and are associated with increased craving and relapse risk in addicted individuals (Zilverstand et al. 2018).

Overall, the hippocampus may play a more significant role in the addiction cycle in AUD than commonly attributed, being central to its pathophysiology. At the initial stages of alcohol exposure, an intact fimbria/fornix supports hippocampal connections important for cue-reward associations, contributing to incentive learning and the stabilization of alcohol-related behaviors (e.g., habituation). Later, in the absence of reward, fimbria/fornix dysfunction would impair effective connectivity from the hippocampus to the prefrontal cortex, hindering the learning of new contingencies that could direct adaptive behavioral control toward resource-saving computational processes (Pérez-Cervera et al. 2023), thereby favoring less flexible or habitual responses to alcohol-related stimuli (Giannone et al. 2024).

4.4 Enhancing White Matter Microstructure Improves Functional Connectivity and Clinical Outcomes

While progressive white matter deterioration is consistently observed during the initial weeks of abstinence, evidence from longitudinal studies suggests partial recovery over longer periods, correlating with improvements in cognitive function and a reduced risk of relapse (Alhassoon et al. 2012; Pfefferbaum et al. 2014). This finding highlights the importance of extended rehabilitation beyond standard clinical detoxification protocols to mitigate the prolonged vulnerability associated with early abstinence. However, in some individuals, white matter damage may persist for extended periods. A notable study comparing relapsers and abstainers six to nine months after detoxification found that relapsers exhibited lower white matter integrity in the corpus callosum and the right stria terminalis/fornix, as indicated by DTI metrics. This difference was associated with relapse scores and persisted despite comparable lifetime and recent drinking histories. These findings suggest a direct correlation between white matter preservation and relapse risk (Zou et al. 2018), emphasizing the potential role of white matter integrity as a biomarker for sustained abstinence.

A potential avenue for accelerating white matter recovery has emerged from a secondary analysis of a trial investigating transcranial magnetic stimulation (TMS) in AUD patients (Harel et al. 2022). This double-blind, randomized, sham-controlled study targeted the medial prefrontal and anterior cingulate cortices in approximately 50 recently abstinent patients. The results demonstrated that active TMS significantly reduced post-treatment craving and heavy drinking days compared to the sham group. Importantly, further analysis (Selim et al. 2024) revealed that TMS halted the progression of FA reductions during the critical early abstinence period, thereby preserving white matter integrity. Functional connectivity analyses of the tracts where TMS preserved white matter integrity indicated functional recovery, pinpointing restored communication between cortical regions in the posterior cingulate and dorsomedial prefrontal cortices. These regions remained persistently modulated after the TMS intervention. Given that each dTMS session was preceded by craving provocation through multi-sensoric cue exposure to the patient's favored drink involved (Harel et al. 2022), we proposed that myelin plasticity – or the increase in fiber myelination in response to heightened neuronal activity – should be considered one of the therapeutic mechanisms underlying TMS. By providing mechanistic insights into the alcohol-dependent brain, these findings highlight the potential of TMS to accelerate recovery processes and inform novel therapeutic strategies for AUD.

5 Conclusions and Future Directions

Alcohol consumption significantly impacts brain microstructure, as demonstrated by translational neuroimaging studies in both humans and rodents. These studies reveal alcohol-induced alterations in both gray and white matter, contributing to cognitive and functional impairments. In white matter, FA progressively declines during early abstinence, reflecting deteriorating tract integrity. Notably, the fimbria/fornix, a critical tract for memory updating and learning, is particularly affected, likely contributing to reduced cognitive flexibility during this vulnerable period. Although the precise mechanisms underlying alcohol toxicity remain unclear, evidence suggests that demyelination and axonal swelling, likely driven by neuroinflammation and glial cell dysfunction, play a central role.

In gray matter, increased MD following periods of alcohol consumption is attributed to changes in extracellular space geometry, including reduced tortuosity due to microglial process retraction. This surface reduction amplifies the extracellular diffusion of neurotransmitters such as dopamine while simultaneously impairing synaptic plasticity. Together, these changes provide mechanistic insights into how alcohol disrupts brain communication and function.

Future research must address several critical areas. Elucidating the role of neuroinflammation in AUD pathogenesis, particularly the dynamic and heterogeneous actions of glial cells such as microglia and astrocytes, is essential. Advances in diffusion-weighted MRI techniques, including noninvasive imaging of glial cell responses, present promising opportunities for a more detailed characterization of cellular processes (Garcia-Hernandez et al. 2022). Another key avenue is the development of biomarkers for regional and tract-specific white matter damage to differentiate drug-specific effects from other potential confounding factors and to improve mechanistic understanding. This effort should be complemented by the adaptation of MRI research methods for clinical practice using standard 1.5 Tesla MRI scanners, enabling broad application and early identification of brain vulnerability in at-risk populations.

Furthermore, it is important to investigate how reduced FA in major white matter tracts manifests in everyday life (Reichert et al. 2024; Liu et al. 2025). Initial findings support the notion that compromised white matter integrity in anterior brain systems contributes to impairments in inhibitory control networks, ultimately reducing the ability to refrain from substance use (Chirokoff et al. 2024).

Finally, exploring the therapeutic potential of noninvasive neuromodulatory techniques, such as TMS or temporal interference electrical stimulation (Violante et al. 2023), holds promise for accelerating white matter recovery through mechanisms such as myelin plasticity. These integrative approaches have the potential to not only enhance our understanding of alcohol-induced brain pathology but also contribute to the development of targeted interventions and personalized treatment strategies, ultimately improving clinical outcomes for individuals with AUD.

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Part IV

Treatment Approaches to AUD

New Approaches for Alcohol Use Disorder Treatment via Memory Retrieval and Reconsolidation Manipulations



Segev Barak and Koral Goltseker

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Abstract Relapse to alcohol seeking and drinking is a major clinical challenge in alcohol use disorder and is frequently brought about by cue-induced craving, caused by exposure to cues that evoke alcohol-related memories. It has been postulated that memories become labile for manipulation shortly after their retrieval and then restabilize in a “memory reconsolidation” process. Disruption or interference with the reconsolidation of drug-associated memories has been suggested as a possible strategy to reduce or even prevent cue-induced craving and relapse. Here, we review literature demonstrating the capacity of behavioral or pharmacological manipulations to reduce relapse in animal models and humans when applied after a short retrieval of memories associated with alcohol, suggestively disrupting the reconsolidation of such memories. We suggest that while there is a clear potential of using post-retrieval manipulations to target specific relapse-evoking memories, future research should be more systematic, standardized, and translational.

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Specifically, we discuss several critical limitations and boundary conditions, which should be addressed to improve consistency and replicability in the field and lead to the development of an efficient reconsolidation-based relapse prevention therapy.

Keyword Addiction · Alcohol · Animal models · Aversion therapy · Counterconditioning · Memory reconsolidation · Memory retrieval · Relapse

1 Introduction

Alcohol use disorder (AUD) is a relapsing disorder. Even with successful pharmaceutical and/or psychological treatment, 60–70% of patients relapse within the first year of abstinence (Sinha 2011; Witteman et al. 2015). Pharmacotherapy that is available for AUD is very limited and is not effective for relapse prevention. Relapse to alcohol abuse is often triggered by craving, induced by exposure to environmental cues previously associated with the reinforcing properties of the drug (Niaura et al. 1988; Bouton 2002; Witteman et al. 2015; Venniro et al. 2016). Therefore, disruption or attenuation of the cue-alcohol associative memories is expected to reduce cue-induced craving and relapse.

It has been increasingly accepted over the past two decades that the retrieval of consolidated memories induces their temporal destabilization, which is followed by their restabilization in a process termed “reconsolidation” (Nader and Hardt 2009; Lee et al. 2017). Certain pharmacological manipulations applied following memory reactivation via retrieval of that memory can attenuate the subsequent behavioral expression of the target memory. This was taken as evidence of the disruption of the ongoing reconsolidation process (Przybylski et al. 1999; Nader et al. 2000; Barak and Goltseker 2021). Thus, the term “reconsolidation window” was proposed, implying that interference with memory reconsolidation during this 5–6 h window of opportunity can attenuate the retrieved memory (Nader and Hardt 2009; Lee et al. 2017).

Research on such memory flexibility has been applied in the drug addiction field (both preclinically and clinically). Accordingly, it has been shown that interference with the reconsolidation process could attenuate and even prevent relapse to drug seeking and consumption (Valjent et al. 2006; Barak et al. 2013; Dunbar and Taylor 2017; Exton-McGuinness and Milton 2018; Goltseker et al. 2019; Taujanskaite et al. 2020; Barak and Goltseker 2021). Drug seeking or intake has also been attenuated by applying competing novel learning shortly following memory retrieval, suggested to reflect the incorporation of new information into the retrieved memory trace (Gordon 1977; Monfils et al. 2009; Schiller et al. 2010; Auber et al. 2013; Olshavsky et al. 2013; Goltseker et al. 2017, 2021; Lee et al. 2017; Paulus et al. 2019; Barak and Goltseker 2021).

This review surveys preclinical and clinical studies addressing manipulations applied in conjunction with retrieval of alcohol-associated memories, together

aimed at reducing relapse-related behaviors. Most of these studies, conducted in animal models and in human subjects, were considered within the theoretical framework of “memory reconsolidation.” This review indicates that alcohol-associated memories can potentially be disrupted by post-retrieval manipulation, possibly due to interference with the reconsolidation process, leading to reduced relapse. However, given the theoretical debates, replicability issues, and inconsistency that currently characterize the field (Barak and Goltseker 2021), this review also discusses several points that should be considered for future studies on reconsolidation-related topics in general, and those related to alcohol and drugs of abuse in particular.

2 Pharmacological Interference with Alcohol Memory Reconsolidation

Memory reconsolidation has been shown to depend on de novo protein synthesis, as protein synthesis inhibitors have been repeatedly shown to disrupt the behavioral expression of a memory (typically, responses to a cue) (Nader et al. 2000; Lee et al. 2017). Other pharmacological interventions were also shown to disrupt memory reconsolidation, in particular, NMDA and β -adrenergic receptor blockade (Lee et al. 2017).

The same pharmacological targets have also been investigated as potential targets for disrupting alcohol memory reconsolidation (Barak and Goltseker 2021). Thus, pharmacological studies on alcohol-associated memory reconsolidation have focused on protein synthesis inhibition (von der Goltz et al. 2009; Barak et al. 2013; Lin et al. 2014), β -adrenergic receptor (Wouda et al. 2010; Font and Cunningham 2012; Milton et al. 2012; Lonergan et al. 2016; Schramm et al. 2016; Chesworth and Corbit 2018), and NMDA receptor blockade (von der Goltz et al. 2009; Wouda et al. 2010; Milton et al. 2012; Vengeliene et al. 2015; Puaud et al. 2018; Das et al. 2019).

2.1 Protein Synthesis Inhibition

The most consistent and well-established finding in memory reconsolidation studies is that the protein synthesis inhibitors administered after memory reactivation disrupt the behavioral expression of a memory, pointing to a role for protein synthesis in the reconsolidation process (Nader and Hardt 2009; Lee et al. 2017; Taujanskaite et al. 2020). However, only a few studies have tested the role of protein synthesis in the reconsolidation of alcohol-related memories. For instance, intracerebroventricular administration of the protein synthesis inhibitor anisomycin after memory retrieval (a 5-min extinction session) disrupted alcohol seeking in an operant self-

administration paradigm for at least a week (von der Goltz et al. 2009). Similarly, injection of anisomycin into the central amygdala (CeA) following memory retrieval reduced alcohol seeking and self-administration (Barak et al. 2013).

The crucial involvement of protein synthesis in the reconsolidation of alcohol-associated memories came with the demonstration of the role of the mammalian (mechanistic) target of rapamycin complex 1 (mTORC1) pathway in memory retrieval and reconsolidation (Barak et al. 2013). mTORC1 is a kinase that plays a role in the translation of a subset of proteins, including synaptic proteins, and has been implicated in synaptic plasticity and in learning and memory (Hoeffner and Klann 2010; Neasta et al. 2014). The retrieval of alcohol-associated memories induced activation of the mTORC1 pathway in the CeA, and in the orbitofrontal and prelimbic cortices, which led to increased levels of several synaptic proteins for which expression is regulated by mTORC1 (Barak et al. 2013). Systemic or intra-CeA administration of the mTORC1 inhibitor rapamycin (20 mg/kg) following alcohol memory retrieval disrupted the reconsolidation of alcohol-related memories, leading to long-lasting (14 days) suppression of relapse to alcohol consumption. Critically, when rapamycin was injected 5 h after memory retrieval, it had no effect on subsequent relapse, indicating that mTORC1 inhibition should be conducted shortly after memory retrieval, i.e., within the “reconsolidation window.”

Interestingly, alcohol memories were retrieved not only by the stimuli of the operant setting associated with alcohol, but also by the intrinsic sensory properties of alcohol per se (i.e., odor-taste cues) given in the home cage. Barak et al. (2013) suggested that the latter retrieval method may evoke alcohol memories in a more general manner, as odor and taste are common characteristics of many experiences with alcohol and are generalizable beyond specific contexts and cues.

Rapamycin was also shown to disrupt the reconsolidation of alcohol memories formed in a place-conditioning paradigm (Lin et al. 2014). Specifically, the post-retrieval systemic administration of rapamycin (10 mg/kg) decreased the expression of alcohol-conditioned place preference (CPP). This effect was shown to last 14 days and was not reversed by a priming injection of alcohol (Lin et al. 2014).

2.2 *β-Adrenergic Receptor Blockade*

Early pharmacological interventions with memory reconsolidation involved the inhibition of β-adrenergic receptors (Roulet and Sara 1998; Przybylski et al. 1999; Milton et al. 2008). However, the effects of such treatment on alcohol memory reconsolidation remain somewhat inconclusive. In a mouse CPP paradigm, the β-adrenergic receptor blocker propranolol (10 or 30 mg/kg) did not affect the reconsolidation of alcohol-related memories when given after such memory retrieval (Font and Cunningham, 2012), despite being effective for other drugs of abuse (e.g., Fricks-Gleason and Marshall 2008; Robinson et al. 2011; Xue et al. 2017).

In a rat operant self-administration study, propranolol (2 µg per hemisphere) or vehicle was injected into the basolateral amygdala (BLA) following a training

session aimed at retrieving alcohol-related memories. When tested a day later, propranolol-treated rats showed reduced responses for alcohol in the first six trials. However, no difference between groups was found in the subsequent 12 trials, probably due to extinction in the control vehicle-treated group (Chesworth and Corbit 2018), thus limiting the conclusions of this study. In another operant self-administration study in rats, administration of propranolol (10 mg/kg) 30 min prior to the retrieval of alcohol-related memories had no effect on alcohol-seeking behavior (Milton et al. 2012). In a subsequent study, however, systemic β -adrenergic receptor blockade was shown to impair reconsolidation of certain aspects of alcohol-associated memories, namely, those involving second-order conditioning. In contrast, the adrenergic prodrug dipivefrin (10 μ g/kg) enhanced such reconsolidation, suggesting that the reconsolidation of specific aspects of alcohol memories can be bidirectionally modulated by reducing or enhancing central adrenergic signaling (Schramm et al. 2016). In another study, a single post-retrieval injection of propranolol (10 mg/kg) following a memory-retrieval session did not affect the reconsolidation of alcohol memories. Moreover, repeated post-retrieval injections of propranolol had no effect on extinction (Williams and Harding 2014). It is also of note that alcohol-seeking behavior was reduced only when propranolol was given following memory retrieval in 2–3 sessions (Wouda et al. 2010), raising the possibility that the reconsolidation of alcohol memories can be impaired only by repeated administration of β -adrenergic blockers.

Unlike most protein synthesis inhibitors, which cannot be used on human subjects, propranolol is an FDA-approved drug for various clinical indications and can, therefore, potentially be used with human AUD patients. In a double-blind, small sample size study of hazardous drinkers, treatment-seeking adults diagnosed with substance dependence received double-blind propranolol or placebo in six bi-weekly sessions (over 3 weeks) prior to memory retrieval via exposure to drug-related visual cues and self-reported craving measurement (Lonergan et al. 2016). Propranolol given prior to alcohol memory retrieval was found to reduce self-reported craving intensity only by the sixth session (Lonergan et al. 2016).

Taken together, these mixed findings suggest that the efficacy of β -adrenergic receptor blockade for disrupting reactivated memories might depend on methodological parameters, such as the number of repeated retrieval-propranolol cycles. Moreover, since the adrenergic system plays a well-documented role in arousal and attention (Aston-Jones et al. 1999; Robbins 2000; De Martino et al. 2008; Thiele and Bellgrove 2018), it is possible that β -adrenergic receptor blockers alter the arousal associated with alcohol cues, thereby affecting the intensity of memory destabilization and reconsolidation.

2.3 NMDA Receptor Blockade

Another pharmacological manipulation widely used for disrupting memory reconsolidation is the blockade of NMDA receptors. Indeed, such manipulation

was shown to at least partly interfere with the reconsolidation of alcohol-associated memories in several studies. In an operant self-administration study, rats were trained to press a lever in response to olfactory and auditory cues paired to alcohol delivery. Following a period of abstinence, alcohol memories were activated via a short (5 min) re-exposure to the alcohol-associated cues and non-reinforced lever pressing. The NMDA receptor antagonist MK-801 (0.1 mg/kg), injected immediately following memory retrieval, reduced cue-induced increase in alcohol seeking, as compared to vehicle-treated controls. However, 7 days later, MK-801-treated rats only showed a non-significant trend toward reduced alcohol seeking (von der Goltz et al. 2009). This finding may indicate that the effects of NDMA receptor blockade might be temporary and decay with time, suggesting that cue-drug memory was not permanently affected, as expected from disruption of reconsolidation mechanisms. Moreover, in the same study, the FDA-approved drug acamprosate, a combined GABA receptor agonist/NMDA receptor antagonist used for alcohol use disorder treatment, failed to affect alcohol seeking when injected after alcohol memory retrieval (von der Goltz et al. 2009).

When given repeatedly after several sessions of memory retrieval, the effects of MK-801 on alcohol memory reconsolidation and seeking behavior were less conclusive. In one study, rats were first trained to nose poke for alcohol rewards in response to cues signaling alcohol availability and delivery. After an abstinence period of 3 weeks, memories were retrieved upon presentation of the alcohol-associated cues in a 20-min session, followed by MK-801 or saline injection. Alcohol seeking was tested 24 h later. The cycle of retrieval, MK-801 treatment and testing were repeated three times. Only in a trend toward reduction in alcohol seeking upon such treatment was observed (Wouda et al. 2010).

In a well-controlled study, injection of MK-801 30 min before (rather than after) alcohol memory retrieval was shown to disrupt the reconsolidation of alcohol memories and reduce alcohol seeking (Milton et al. 2012). In this study, the test was performed by comparing lever pressing in the presence of the alcohol-predicting versus non-predicting cues. Rats treated with MK-801 before memory retrieval showed similar degrees of lever pressing for both types of cues, whereas saline-treated controls increased lever pressing upon presentation of the alcohol-paired cues (Milton et al. 2012). However, when retrieving memory with a short non-reinforced lever-responding session rather than alcohol cues, alcohol seeking was found to be unaffected. The authors interpreted these findings as suggesting that operant memories are more resistant to NMDA receptor blockade following retrieval, as compared with Pavlovian cue-alcohol memories (Puaud et al. 2018). This suggestion is consistent with previous reports showing that targeting memories underlying operant behavior via reconsolidation mechanisms has been particularly challenging (Exton-McGuinness et al. 2019, 2014), although other manipulations were shown to be more effective in operant settings (Xue et al. 2012; Exton-McGuinness et al. 2014; Exton-McGuinness and Lee 2015; Luo et al. 2015; Goltseker et al. 2021).

Memantine, another NMDA receptor antagonist, was also shown to disrupt alcohol seeking in a rat operant self-administration procedure, but surprisingly reduced seeking behavior, regardless of memory retrieval (Vengeliene et al. 2015).

Rats receiving two memantine injections (20 mg/kg) or vehicle, given both shortly and 4 h following a memory retrieval (5 min training session), showed reductions in a cue-induced alcohol-seeking test conducted 24 h later, compared with vehicle-treated controls. However, rats that received memantine with no prior memory retrieval also showed reduced alcohol seeking. This finding suggests that memantine suppressed alcohol seeking 24 h after its administration, regardless of memory retrieval (Vengeliene et al. 2015), and emphasizes the importance of crucial control conditions in alcohol memory reconsolidation studies, namely, no treatment and no-retrieval controls.

NDMA receptor blockade was also considered in human hazardous drinkers, where the administration of ketamine following the retrieval of the alcohol-associated memories reduced the reinforcing effects of alcohol and long-term (up to 9 months) drinking levels, compared with ketamine given without retrieval or with retrieval with no ketamine administration (Das et al. 2019). Thus, targeting the NMDA receptor may have clinical benefits in reducing alcohol relapse, presumably by affecting reconsolidation mechanisms.

In summary, blocking NMDA receptors appears to be a promising strategy for disrupting alcohol memory reconsolidation, with current results seemingly more consistent than those from studies targeting the adrenergic system. Still, temporal and procedural parameters should be carefully chosen in future efforts to ensure successful and long-lasting effect. Moreover, a close examination of the available data reveals that manipulations in which NMDA receptors were blocked had more pronounced effects on newer rather than on older memories (Barak and Goltseker 2021).

3 Behavioral Interference with Alcohol Memory Reconsolidation

Pharmacological treatments given during memory reconsolidation may have side effects and may even be toxic (Tronson and Taylor 2013; Lee et al. 2017; Barak and Goltseker 2021). It has been shown in fear memory and drug memory studies that behavioral interventions given following memory retrieval (presumably during the reconsolidation window) can have stronger and longer effects of suppressed behavioral responses, as compared with behavioral interventions given without prior memory retrieval (Monfils et al. 2009; Ma et al. 2012; Xue et al. 2012; Hutton-Bedbrook and McNally 2013; Sartor and Aston-Jones 2014).

The most-studied behavioral intervention applied following retrieval is extinction training. While extinction inhibits the conditioned response, it does not prevent the return of the response that may occur due to the passage of time (spontaneous recovery) or upon re-exposure to the reinforcer (reinstatement) or to the learning context (renewal) (Barak and Ben Hamida 2012). However, it has been suggested that when extinction training is applied following memory retrieval, such training

prevents the return of the conditioned response, i.e., the previous memory is disrupted (Monfils et al. 2009; Xue et al. 2012; Hutton-Bedbrook and McNally 2013; Kuijer et al. 2020). Using this approach, Cofresi et al. (2017) showed that memory retrieval prior to extinction training reduced alcohol-seeking behavior, as compared with extinction with no memory retrieval. In this study, alcohol was paired with a visual cue. Over the following 14 sessions of extinction training in which the cue was presented without alcohol, the retrieval group received an hour-long time out in the home cage between the first two extinction trials, so as to retrieve alcohol memories and initiate their reconsolidation. In a test session, rats that underwent extinction training during memory reconsolidation then showed reduced spontaneous recovery and reinstatement of the conditioned response to alcohol-associated cues, suggesting that the retrieval-extinction procedure reduced relapse to alcohol seeking (Cofresi et al. 2017).

Using an elegant experimental design, it was demonstrated that extinction suppresses alcohol-seeking behavior both not only when given after memory retrieval, but also when given before a memory-retrieval session (Millan et al. 2013). In this study, rats self-administered decarbonated beer in one context (context A), whereas extinction training was conducted in a distinct context (B). Rats then received a 50-min extinction session, with an additional 10-min retrieval session given either 70 min before extinction (the retrieval-extinction group) or after extinction (the extinction-retrieval group). In a test conducted in the alcohol-associated context A, animals that underwent extinction before or after memory retrieval showed a reduced renewal effect (context-induced reinstatement) of alcohol-seeking behavior, compared with no-retrieval controls (Millan et al. 2013). Although the capacity of retrieval-extinction to reduce alcohol seeking can be interpreted as extinction occurring during the reconsolidation window, in turn leading to memory updating, the similar outcome of extinction-retrieval training cannot be interpreted in terms of reconsolidation. An alternative explanation is that retrieval + extinction sessions (regardless of their order) are more effective in reducing responding for alcohol, compared with a single extinction training (no-retrieval controls), despite the total extinction time being equal (60 min). Moreover, retrieval-extinction facilitated the reacquisition of alcohol self-administration, stressing the limitation of this procedure in reducing alcohol seeking. Together, these findings suggest that the retrieval-extinction approach has limited effectiveness in disrupting the memory and seeking response (also see Luyten and Beckers 2017).

Another behavioral approach aimed at reducing alcohol and drug seeking via post-retrieval, reconsolidation mechanisms uses reassociation of the alcohol/drug-associated cues with an aversive outcome, i.e., application of aversive counterconditioning or punishment training following memory retrieval. In this approach, a cue or action that was previously paired with the reinforcing effects of alcohol is re-associated with aversive consequences (Cannon et al. 1981). Cue-aversion therapy, based on counterconditioning, showed stronger effects than extinction in reducing relapse in animal models and human studies (Van Gucht et al. 2010; Tunstall et al. 2012) and helped alcohol drinkers remain abstinent for longer periods (Elkins et al. 2017). These effects are, however, typically transient (Bouton and Peck

1992; Brooks et al. 1995; van Dis et al. 2019), and relapse can occur (Bouton and Peck 1992; Brooks et al. 1995).

Using a place-conditioning paradigm, Goltseker et al. (2017) showed that the application of aversive counterconditioning shortly after the retrieval of a context-cocaine memory prevented the expression of cocaine CPP in a prime-induced reinstatement test, considered to model the relapse to cocaine seeking (Goltseker et al. 2017). This effect was long-lasting (at least 35 days) and was seen only when counterconditioning followed memory retrieval. No effect was observed when the gap between retrieval and counterconditioning was 5 h. Moreover, counterconditioning prevented reinstatement of drug seeking only when applied after, but not before, memory retrieval (Goltseker et al. 2017). This is in contrast to the previous observation of the equivalent effects of retrieval-extinction and extinction-retrieval procedures on alcohol seeking (Millan et al. 2013), suggesting that the disruption of drug seeking is indeed mediated by memory reconsolidation mechanisms.

Using a similar approach, the same group demonstrated that a relapse to alcohol seeking could be prevented by aversive counterconditioning conducted during alcohol memory reconsolidation in both classical and operant learning paradigms (Goltseker et al. 2021). In this alcohol-CPP study, following establishment of CPP, the alcohol-associated context was counterconditioned with an aversive experience, specifically, a “flood” of cold water (Goltseker and Barak 2018), preceded by memory retrieval. Similar to the cocaine study described above, aversive counterconditioning conducted shortly following alcohol memory retrieval prevented the reinstatement of alcohol CPP, suggesting that aversive training had disrupted the retrieved alcohol memory (Goltseker et al. 2021). In fact, mice that underwent retrieval-counterconditioning manipulation avoided the alcohol-associated context during testing (Goltseker et al. 2021), suggesting that aversive information presented following memory retrieval can be incorporated into the originally-retrieved memory, thereby updating the information and perhaps even replacing the previous association (Das et al. 2015a; Goltseker et al. 2017; Lee et al. 2017; Gisquet-Verrier and Riccio 2018; Barak and Goltseker 2021; Goltseker et al. 2021). An interesting finding of the study was that retrieval followed by aversive counterconditioning was characterized by the upregulation of brain-derived neurotrophic factor (*Bdnf*) mRNA expression in the medial prefrontal cortex, suggesting that BDNF plays a role in the memory updating process (Goltseker et al. 2021).

The retrieval-counterconditioning paradigm was also adjusted to an operant self-administration procedure that models relapse-like alcohol-related behaviors (Burattini et al. 2006; Goltseker et al. 2019). Here, in an operant alcohol self-administration procedure, rats were trained to lever press for alcohol in context A for 2 months. Then, the alcohol memory was retrieved by exposing the rats to the odor-taste alcohol cue for 10 min in the home cages, whereas control rats received the same punishment training with no prior memory retrieval (Goltseker et al. 2021). As expected, the control (no-retrieval) group showed renewal of alcohol seeking (i.e., non-reinforced lever pressing) when returned to the alcohol-associated context A, modeling context-induced relapse to alcohol seeking (Goltseker et al. 2021). However, when alcohol memory retrieval was applied prior to the

punishment, the renewal of alcohol seeking was suppressed. In addition, when memory retrieval was given long before the punishment, the rats showed reinstatement, demonstrating the punishment to be effective in preventing relapse only when given during the reconsolidation window. Interestingly, this renewal effect, or context-induced reinstatement of seeking behavior, can model the high rates of relapse which are commonly observed in AUD patients, who even after successful treatment in the clinics experience strong cravings and relapse upon re-exposure to the environment in which they once consumed alcohol (Witteman et al. 2015).

In a laboratory-controlled experiment, the post-retrieval counterconditioning procedure was also shown to successfully update an appetitive memory with aversive information in humans (Gera et al. 2019). Moreover, this approach was also shown to be beneficial in modulating craving and drinking patterns in hazardous alcohol drinkers (Das et al. 2015a, 2018; Gale et al. 2020). In these studies, abstinent hazardous alcohol drinkers received alcohol memory retrieval by being presenting with a glass of beer and then taking it away unexpectedly before the first sip (Das et al. 2015a, 2018, 2019; Hon et al. 2016). Alcohol cues were then re-associated with gustatory and visual disgust (eight pairings for each modality) (Das et al. 2015a). The results showed subsequent reductions in alcohol cue valuation and alcohol craving (Das et al. 2015a). Furthermore, this procedure was reported to suppress drinking in a long-lasting manner (i.e., for 9 months) (Gale et al. 2020). Taken together, these findings suggest that similar to what has been reported in animal models, counterconditioning applied following alcohol memory retrieval in humans can lead to integration of the new information into the memory, by “rewriting” the valence of alcohol cues.

An additional strategy for targeting alcohol memory reconsolidation in hazardous drinkers in a non-pharmacological manner is reappraisal of maladaptive alcohol memories, which utilizes a cognitive psychotherapy given within the memory reconsolidation window (Hon et al. 2016). Another form of interference yielded unexpected results, whereby high working memory load reduced alcohol craving in heavy drinkers when given before memory retrieval, with no such effects being seen when given after retrieval (Kaag et al. 2018). Together, the few attempts to reduce alcohol craving and relapse by post-retrieval behavioral and/or cognitive manipulation point to therapeutic potential, however, further exploration and thorough characterization of this direction of therapy are still needed.

4 Summary and Conclusions

In this review, we surveyed studies that utilized two primary mechanisms shown to disrupt performance via interference with the memory reconsolidation process: a) disruption of alcohol memory reconsolidation via pharmacological manipulations that are thought to prevent the restabilization of the memories and b) updating, replacing, or incorporating new (typically conflicting) information into the original cue-alcohol memory, via behavioral and/or cognitive training conducted following

memory retrieval, i.e., during the “reconsolidation window,” when memory is considered to be flexible (Fig. 1).

We have recently raised several critical remarks regarding the standardization of research and the replicability of results in the reconsolidation field in general, and specifically, in drug and alcohol memory reconsolidation studies (Barak and Goltseker 2021). Furthermore, we also raised concerns regarding the translational limitations of reconsolidation-based treatment strategies (Barak and Goltseker 2021). Below is a summary of the points most relevant for studies on alcohol memory reconsolidation.

4.1 Methodological Standardization and Inconsistent Findings

Most studies on memory reconsolidation in animal models have relied on classical fear conditioning memories (Nader and Hardt 2009; Lee et al. 2017). Even in this relatively standard and simple classical conditioning paradigm, inconsistent findings in fear-memory reconsolidation have been reported, presumably due to methodological variability (Barak and Ben Hamida 2012; Luyten et al. 2021; Schroyens et al. 2021). Studies on reconsolidation of drug- and alcohol-associated memories typically include even greater methodological variability, due to the diverse nature of these studies. Thus, addiction-like behaviors are modeled both in classical and operant learning paradigms, as detailed above, with various very different protocols that may reflect different aspects of addiction being used. Therefore, inconsistency in

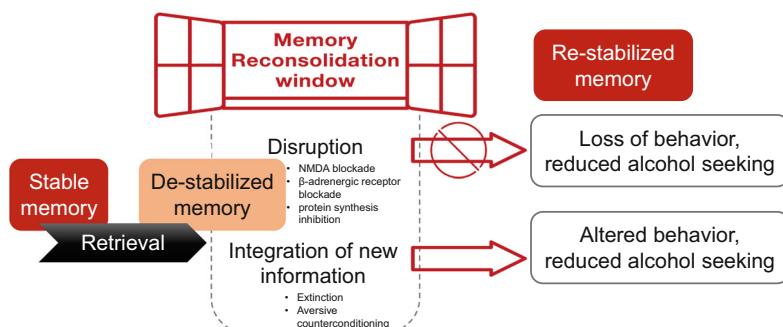


Fig. 1 Reducing alcohol seeking by post-retrieval manipulation – schematic illustration. According to the reconsolidation hypothesis, stable memories de-stabilize upon retrieval and undergo a time-dependent process of restabilization. Amnestic pharmacological treatment delivered shortly after memory retrieval (i.e., during the “reconsolidation window”) can disrupt the restabilization process and prevent cue-induced craving and alcohol seeking (amnestic pharmacological agents). Alternatively, new information introduced following retrieval via behavioral manipulation (e.g., extinction or aversive counterconditioning) can be incorporated into the original memory, thereby preventing alcohol seeking, and even leading to avoidance of alcohol-related cues

findings with a given amnestic drug or behavioral intervention could be attributed not only to the limited efficacy of the treatment in disrupting the reconsolidation process, but also to the absence of standardized protocols with optimal experimental parameters.

Manipulations of alcohol and drug-associated memory reconsolidation were shown to be more effective in classical conditioning paradigms (e.g., CPP), as compared with drug-memories formed in operant paradigms (Barak and Goltseker 2021). For example, in an alcohol study that tested a similar post-retrieval treatment both in CPP and operant alcohol self-administration procedures, manipulation led to a complete abolition of drug seeking in CPP, but only to a partial decrease in seeking of the operant response (Goltseker et al. 2021). A similar pattern was observed with other drugs of abuse (e.g., Xue et al. 2012). Indeed, memories formed in operant procedures are thought to be less sensitive to memory reconsolidation manipulations, and it seems that effects are demonstrated only within a limited window of procedural parameters (Hernandez and Kelley 2004; Brown et al. 2008; Mierzejewski et al. 2009; Xue et al. 2012; Exton-McGuinness et al. 2014; Piva et al. 2020). It is important to bear in mind that while place-conditioning procedures may provide convenient models of alcohol/drug reward and seeking, they are not considered as models of addiction (Goltseker et al. 2019; Barak and Goltseker 2021). Rather, operant self-administration procedures model various aspects of addiction phenotypes with considerably higher validity. Thus, the limited and inconsistent findings of reconsolidation experiments conducted in operant settings are a critical limitation of this approach as a translational research field (see below).

Importantly, even when using the same conditioning paradigm (e.g., operant alcohol self-administration), the specific training protocols used by different research laboratories vary considerably. In particular, there are differences in the duration of training prior to manipulation, in the reinforcement schedules used for training and testing, in the doses of drugs administered, in withdrawal periods prior to memory retrieval (if any), in the memory-retrieval methodology itself, in the timing of manipulation (i.e., before/after memory retrieval), and in post-manipulation testing (under extinction conditions or not, number of tests sessions and more). Therefore, the absence of standardization in experimental design and procedure may largely account for the inconsistency in the findings in the field of alcohol and drug memory reconsolidation (Barak and Goltseker 2021). Relatedly, a publication bias, whereby negative results are not published, was suggested as affecting reconsolidation studies in other types of memories (Schroyens et al. 2021) and may also occur in the case of alcohol memory reconsolidation.

It is also important to bear in mind that negative results following post-retrieval manipulations can reflect the low effectiveness of the manipulation in disrupting memory reconsolidation, but can also reflect non-successful reactivation of the memories via retrieval. To ensure that the retrieval procedures are validated in the experimental protocol, it would be beneficial to use treatments previously shown to potently disrupt memory reconsolidation in various experimental procedures (e.g., using protein synthesis inhibitors (Nader et al. 2000; Lee et al. 2017; Exton-McGuinness and Milton 2018; Taujanskaite et al. 2020; Barak and Goltseker 2021)).

A related methodological concern that can affect theoretical interpretation of the data comes from the fact that retrieval procedures are typically based on a short non-reinforced presentation of the cue in an extinction-like session. Disruption of memory reconsolidation and extinction training may yield similar effects, i.e., reduced performance in a retention test (Barak and Ben Hamida 2012; Barak and Goltseker 2021). However, following extinction, the conditioned response may return, presumably reflecting the ability of the previous memory trace to control behavior. Thus, testing the return of the extinguished behavior via spontaneous recovery, renewal and reinstatement tests can potentially distinguish between the effects of extinction and reconsolidation disruption, as the conditioned response is expected to return only in the former (Duvarci and Nader 2004; Barak and Ben Hamida 2012; Barak and Goltseker 2021).

Finally, manipulations that target the reconsolidation process should be applied shortly after memory retrieval (i.e., within the memory reconsolidation window), and not before memory retrieval, as the memory retrieval is thought to initiate the reconsolidation process. Nevertheless, in the case of pharmacological manipulation, pharmacokinetic and pharmacodynamic considerations might justify earlier administration of amnestic drugs. However, applying manipulations before memory retrieval can potentially affect memory retrieval itself, and not only the memory reconsolidation process, limiting the theoretical interpretation of the results.

4.2 *Applicative and Clinical Limitations*

Disruption of drug- and alcohol-associated memory reconsolidation has been proposed as a strategy to prevent cue-induced craving and relapse in substance use disorders (Milton 2013; Exton-McGuinness and Milton 2018; Monfils and Holmes 2018; Goltseker et al. 2019; Barak and Goltseker 2021). However, several limitations or “boundary conditions” on memory reconsolidation have been discussed in the literature (e.g., Dunbar and Taylor 2017; Treanor et al. 2017; Exton-McGuinness and Milton 2018; Monfils and Holmes 2018), which may substantially limit the translation of memory reconsolidation approaches into clinical applications.

Alcohol induces not only rewarding, but also aversive effects (Cappell et al. 1973), with extensive training being required to achieve high and stable levels of self-administration. For example, operant alcohol self-administration usually requires an initiation phase, in which rodents are exposed to alcohol in the home cage in 2-bottle choice procedures for several weeks before starting operant training that continues for several additional weeks. Therefore, rodents are typically trained to drink alcohol for 1.5–3 months prior to testing (Carnicella et al. 2014). Such extensive training, which is parallel to the extensive exposure to alcohol seen in human AUD patients, affects two of the boundary conditions suggested to blunt the susceptibility of memory reconsolidation for disruptive manipulations, namely, the age of the cue-alcohol memory and its strength. Importantly, AUD patients always have a long and intensive history of alcohol consumption. Hence, their alcohol-

associated memories are old and strong, making this methodological necessity a translational advantage. However, as suggested in the literature (Dunbar and Taylor 2017; Treanor et al. 2017; Exton-McGuinness and Milton 2018; Monfils and Holmes 2018), self-administration memories in animal models, as the strong and intensive memories in AUD patients, become less susceptible to changes and to reconsolidation manipulation. Nevertheless, when effects on alcohol memory reconsolidation are demonstrated despite the extensive training obstacle, the effects likely have greater translational validity.

In addition, in experiments conducted in the laboratory, the retrieval of a specific cue-alcohol memory via a short presentation of the cue allows targeting of specific memories in a relatively precise manner. In contrast, clinical situations are obviously not as “sterile.” Patients treated in the clinic already have well-consolidated and intensive alcohol-associated memories in which the reinforcing effects of alcohol are associated with multiple contexts and stimuli, leading to heavily habitual and even compulsive responses. Therefore, in the clinical setting, memories comprise complex networks of multiple stimuli and responses and reinforcements that are all interconnected (Barak and Goltseker 2021). Thus, targeting an isolated “cue-alcohol” memory trace is likely to yield very limited clinical outcomes. Indeed, translation of laboratory findings of reconsolidation studies to clinical settings has encountered difficulties (Das et al. 2015b; Jobes et al. 2015; Treanor et al. 2017). A potential solution for this challenge would be to retrieve the memory using odor-taste cues (Barak et al. 2013; Goltseker et al. 2021). Since the odor and taste of alcohol are an intrinsic characteristic of any experience with this substance, they are expected to prompt reactivation of multiple memories associated with the alcohol, allowing their simultaneous targeting.

Finally, the drug-taking context typically differs greatly from the context of clinical treatment. This gap may cause renewal of the conditioned response, leading to “context-induced relapse” whereby patients return of their natural environment upon completion of clinical therapy. This clinical issue can be modeled in the laboratory by renewal experiments in which the acquisition of alcohol self-administration is conducted in one context (context A) and the treatment (e.g., extinction, counterconditioning, punishment) is given in another context (context B). To demonstrate renewal and relapse-like behavior, the animals are subsequently tested in the alcohol-associated context A again, leading to the return of the previous behavior acquired in context A (ABA renewal design) (Bouton 2002; Marchant and Kaganovsky 2015; Marchant et al. 2018, 2019; Goltseker et al. 2021). Recently, we reported that application of a punishment following alcohol memory retrieval in an ABA-experimental design attenuated the context-induced relapse-like effect in operant self-administration model in rats, suggesting that using memory retrieval and reconsolidation mechanisms might allow for overcoming the context-dependency issue (Goltseker et al. 2021).

The concept of memory reconsolidation and the theoretical interpretation of results in this framework have been controversial, and alternative theoretical interpretation has been suggested (e.g., Gisquet-Verrier and Riccio 2018; Kiley and Parks 2021). Thus, as amnestic pharmacological treatments modify the internal state of the

subject, it has been suggested that new information can be associated or encoded with the post-retrieval active memory and become a part of it, thus causing state-dependency (Gisquet-Verrier and Riccio 2018). According to this hypothesis, the internal state induced by treatments such as propranolol, MK-801, or rapamycin is integrated into the contextual cue-alcohol memory, which could be retrieved after such integration only in this specific internal state. This hypothesis, therefore, provides a testable prediction, namely, that the conditioned response (alcohol seeking) will be restored following infusion of these “amnestic” drugs (Gisquet-Verrier and Riccio 2018; Kiley and Parks 2021). Nevertheless, the finding that alcohol seeking can be disrupted by post-retrieval manipulation is still valid in both interpretations.

In summary, in this review we surveyed evidence for the potential of reconsolidation disruption and aversive counterconditioning manipulation in attenuating alcohol relapse. However, the inconsistency of findings in the field, along with the methodological and conceptual weaknesses discussed above, may limit the replicability and potential translational value of these findings. Therefore, there is a clear need for more systematic, well-controlled, and standardized research that will address these critical issues in future.

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Approach-Bias Retraining and Other Training Interventions as Add-On in the Treatment of AUD Patients



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Abstract In the past two decades, a variety of cognitive training interventions have been developed to help people overcome their addictive behaviors. Conceptually, it is important to distinguish between programs in which reactions to addiction-relevant cues are trained (varieties of cognitive bias modification, CBM) and programs in which general abilities are trained such as working memory or mindfulness. CBM was first developed to study the hypothesized causal role in mental disorders: by directly manipulating the bias, it was investigated to what extent this influenced disorder-relevant behavior. In these proof-of-principle studies, the bias was temporarily modified in volunteers, either temporarily increased or decreased, with corresponding effects on behavior (e.g., beer consumption), in case the bias was successfully manipulated. In subsequent clinical randomized controlled trials (RCTs), training (away from the substance vs. sham training) was added to clinical treatment. These studies have demonstrated that CBM, as added to treatment, reduces relapse with a small effect of about 10% (similar effect size as for medication, with the strongest evidence for approach-bias modification). This has not been found for general ability training (e.g., working memory training), although effects on other psychological functions have been found (e.g., impulsivity). Mindfulness

also has been found to help people overcome addictions, and different from CBM, also as stand-alone intervention. Research on (neuro-)cognitive mechanisms underlying approach-bias modification has pointed to a new perspective in which automatic inferences rather than associations are influenced by training, which has led to the development of a new variety of training: ABC training.

Keywords Addiction · Alcohol use disorder · Approach bias · Approach bias retraining · Cognitive-bias modification · Cognitive training · Mindfulness · Treatment · Working memory training

Abbreviations

AAT	Approach-avoidance task
ABC	New variety of cognitive-bias modification, with personalized antecedents, behavioral alternatives, and consequences
ApB	Approach bias
ApBM	Approach bias modification
AtB	Attentional bias
AtBM	Attentional bias modification
AUD	Alcohol use disorder
CBM	Cognitive-bias modification (family of interventions, aimed at directly targeting different cognitive biases, including AtB, ApB, and memory biases)
CBT	Cognitive behavior therapy
EC	Evaluative conditioning
IAT	Implicit association test
mPFC	Medial prefrontal cortex
RCT	Randomized controlled trial
RT	Reaction time
SUD	Substance use disorder
tDCS	Transcranial direct current stimulation (form of neuromodulation)
TMS	Transcranial magnetic stimulation (form of neuromodulation)
WM	Working memory

1 Introduction

This chapter focuses on (neuro)cognitive training as a therapeutic add-on in the treatment of alcohol use disorders (AUDs). After a series of successful randomized controlled trials (RCTs), one specific type of training, approach-bias retraining (Eberl et al. 2013; Manning et al. 2021; Rinck et al. 2018; Salemink et al. 2021; Wiers et al. 2011), has been added as suggested additions to the treatment of AUD in

the clinical guidelines in the countries where the supportive large RCTs took place (Haber 2021; Kiefer et al. 2021 Australia and Germany, respectively). However, approach-bias re-training is only one instance of a larger family of training interventions, called cognitive-bias modification (CBM) interventions. These interventions target the re-training of relatively automatic or impulsive reactions to addiction-related stimuli referred to as “cognitive biases.” Other types of training interventions do not use substance-related cues and target more general functions, such as working memory training and mindfulness training (see Fig. 1); these will be briefly discussed in Sect. 5.

The first section discusses the background of different types of CBM; the second reviews the current state of the evidence for the effectiveness of CBM as an add-on to the treatment of AUD, with a brief note on the current (absence of) evidence as stand-alone intervention. The third section reviews other forms of targeted training as an add-on to the treatment of AUD, forms that do not fall under the umbrella of CBM. The fourth section reviews recent work on underlying (neuro-)cognitive mechanisms in CBM, with an emphasis on approach-bias retraining. In the fifth section, we briefly review two instances of the other type of more general cognitive training that has been used in (alcohol) addiction: working memory training and mindfulness meditation. In the sixth section, we sketch out new avenues to improve targeted training as an add-on to the treatment of AUD and other addictions.

2 Cognitive Bias Modification, Background and Taxonomy

In CBM, different types of cognitive biases have been targeted. Most studies target one of three cognitive biases, namely biases in attention (attentional bias modification, or AtBM), biases in action tendencies (in addiction, typically a tendency to approach addiction cues, hence approach bias modification, or ApBM),¹ or biases in (evaluative) memory (see for an early review: Wiers et al. 2013b). Note that in the broad field of internalizing disorders (varieties of anxiety and mood disorders), another type of cognitive bias has often been successfully targeted using CBM: interpretation bias (Hallion and Ruscio 2011; Krebs et al. 2018). This has not been done as an add-on to treatment in addiction, although there is preliminary work that interpretation biases can also be found in AUD patients, but were difficult to modify in social drinkers (Woud et al. 2014, 2015). In healthy subjects with high scores on social anxiety and drinking, there is initial evidence of comorbidity-specific interpretation biases (Chow et al. 2018). In some sense, the recently developed novel ABC training (Wiers et al. 2020), discussed in Sect. 6 below, bears some resemblance to interpretation bias retraining, and could also be used to address biases of

¹Note that both attentional bias modification and approach bias modification have sometimes been abbreviated to ABM, which is unhandy for obvious reasons; therefore, we have argued to consistently use AtBM and ApBM (Rinck et al. 2018).

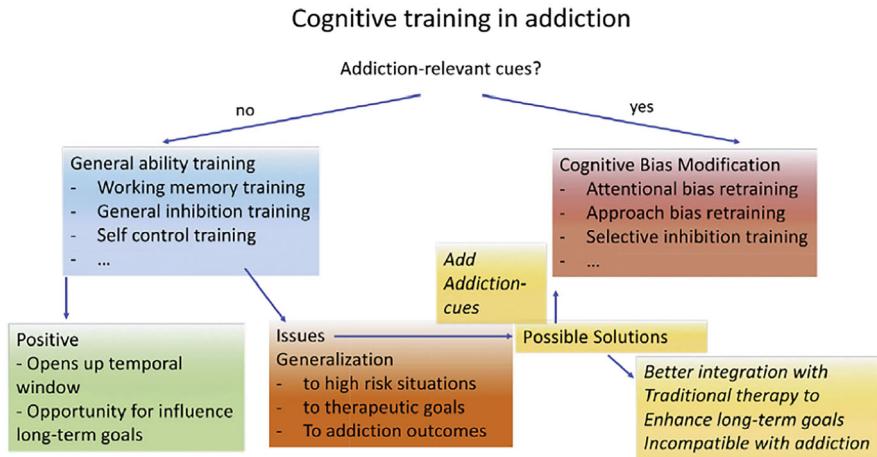


Fig. 1 A classification scheme concerning different types of training used in addiction. The major division is between training varieties that use addiction-related stimuli, in order to change stimulus-related reactions (i.e., aspects of cue reactivity) and varieties of training that do not use addiction-related stimuli, which aim to change general processes, such as working memory, self-control, or inhibition. Reproduced with permission from Wiers (2018)

specific comorbidity subgroups. In the following, we will introduce the three main types of CBM used in (alcohol) addiction: AtBM, ApBM, and varieties of CBM targeting (evaluative) memories.

2.1 Attentional Bias (AtB)

Biases in attention may play an important role in many mental disorders, including anxieties (Bar-Haim et al. 2007), mood disorders (Peckham et al. 2010), and addictions (Field and Cox 2008, but see Field et al. 2016 for a more critical appraisal). The most commonly used tasks to assess attentional biases in addiction have been the addiction-Stroop task (Cox et al. 2006), and the visual or dot-probe task (Field and Cox 2008). The addiction-Stroop assesses whether participants are relatively slow in color-naming words that relate to an addictive behavior. In the dot-probe task, participants see two stimuli presented simultaneously on the screen (in addiction, typically two pictures), after which one of the two is replaced with a probe to which a participant has to react (e.g., a small arrow pointing up or down, which has to be indicated by the participant). When the participant is quicker and more accurate to react to probes replacing one category of pictures (e.g., alcohol), than the contrast category (e.g., non-alcoholic drinks), this is taken as an indication of an attentional bias for alcohol (see Fig. 2 for an example). Although the dot-probe task is intuitive and easy to use, the reliability is poor (e.g., Ataya et al. 2012). More reliable (but less frequently used) are eye-movement measures (Field et al. 2009),

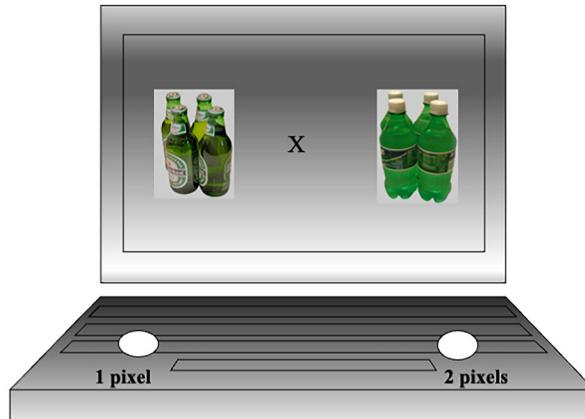


Fig. 2 In the dot-probe assessment task, two stimuli are shown simultaneously (here one picture of drinks with alcohol and one of drinks without alcohol), followed by the probe (one or two pixels) which replaces one of the two pictures, to which the participant responds (e.g., left if the probe is a single pixel and right if it concerns two pixels). The AtB is derived from the difference in RT between responses where the probe replaces alcohol vs. non-alcoholic drinks. In an assessment task, probes replace alcoholic and non-alcoholic drinks equally often. In a training, this is changed; probes occur either more frequently after alcohol (in proof-of-principle studies) to test if this increases the desire to drink or more frequently behind non-alcoholic drinks (also used in clinical context)

which can demonstrate a stimulus category participants preferentially divert attention to or dwell upon. Recently, a new behavioral measure has been developed that indirectly assesses attentional capture (without assessment of eye movements): the dual-probe task. In this task, participants see two video-streams, one disorder-relevant and one irrelevant (e.g., ads for alcohol vs. non-alcoholic drinks), upon which occasionally unique probes are projected that participants have to identify, revealing which stream they were looking at (Cahill et al. 2021; Grafton et al. 2021; MacLeod et al. 2019; Wiechert et al. 2021). A recent study (Wiechert et al. 2021), assessing attentional capture by ads for alcoholic vs. non-alcohol drinks in undergraduate volunteers, predicted habitual drinking, subsequent drinking in a taste test and increased craving in this situation, and importantly, demonstrated excellent reliability (0.90), which starkly contrasts with the poor-to-modest reliabilities of the dot probe (typically around 0.30).

An attentional bias for substance-related cues has been demonstrated across many studies (review: Field and Cox 2008), although there have also been inconsistencies (Field et al. 2016). This is not unique for addiction; an attentional bias (AtB) for disorder-related stimuli has been reported in many forms of psychopathology. Importantly, more fine-grained analyses have revealed differences in the time course of AtB, with most evidence supporting the perspective that in anxiety disorders, threat stimuli grab attention (short time course, attentional engagement). In the dot-probe task, this is assessed with a brief stimulus duration, for example of 150 ms for the pairs of stimuli, followed by the probe. In anxiety, the quick

attentional deployment is typically followed by avoidance, the so-called vigilance-avoidance pattern (Mogg et al. 1995). In contrast, in depression and related disorders, relevant negative stimuli tend to capture attention, which implies issues with disengagement (longer time course). In the dot-probe task, this is measured with longer presentation times of the stimuli, where an AtB is interpreted as an attentional disengagement problem (Koster et al. 2005; Oehlberg et al. 2012). It is as-yet unclear whether AtB in addiction resembles more the engagement AtB typically found in anxieties, or the difficulties with disengagement AtB typically found in mood disorders. There is some evidence in support of only relatively late processes (and hence disengagement problems), both in heavy drinkers (Field et al. 2004) and in heroin-addicted patients (Franken et al. 2000). Yet, other studies found evidence for early engagement in AUD (Ingjaldsson et al. 2003; Noël et al. 2006) and opioid dependence (Frankland et al. 2016). An EEG study (with good time resolution) detected an early component (N1) in attentional responses to alcohol cues in AUD patients (Dickter et al. 2014). Hence, the nature of AtB in addiction could differ per stage of addiction (e.g., disengagement problems in early stages of addiction and engagement in severe addiction) and per addictive behavior. Although this topic is relatively understudied, it is an important line of research as it could inform effective ways to modify AtB. Notably, new measures are currently under development to assess AtB in a more reliable way (Gladwin et al. 2020; Wiechert et al. 2021). This is important because current measures are not reliable enough to assess AtB at an individual level (the level where clinical decisions are made), and the low reliability also makes it difficult to assess whether procedures aimed at modifying AtB (varieties of AtBM) succeed in changing the bias.

Finally, there is recent work relating substance AtB in (alcohol) addiction to a general AtB for reward cues, or more precisely the extent to which participants are distracted by general reward cues, based on sign-tracking in animal paradigms (Albertella et al. 2021, 2019a, b; Anderson 2016; Le Pelley et al. 2015; Watson et al. 2019). It is an interesting question to what extent an attentional bias for reward may precede addiction problems (e.g., van Hemel-Ruiter et al. 2015), with addiction stimuli becoming instantiations of a general tendency to attend to cues of potential reward.

2.2 *Attentional Bias Modification (AtBM)*

In the last two decades of the twentieth century, hundreds of studies had demonstrated that AtBs were correlated with several mental disorders, mostly in anxiety, both in cross-sectional studies and in longitudinal studies. However, this observation does not prove a causal role of AtB in the etiology or maintenance of the disorder. For this reason, experimental manipulations were developed to (temporarily) change the bias of interest (here AtB), and studies set out to test the effects of these changes on relevant symptoms. Following a first experimental study in which an interpretation bias was experimentally manipulated (Mathews and Mackintosh 2000), Colin

MacLeod, who had decades earlier developed one of the most frequently used assessment tasks for AtB, the dot-probe task (MacLeod et al. 1986), and colleagues published the first study of AtBM (MacLeod et al. 2002). It is important to note that the goal of this study was to *test the hypothesized causal role of AtB* in anxiety-related symptoms, and not to examine treatment effects. To that end, they invited university students with medium anxiety levels, who were randomized to training to attend toward threat stimuli or to training to attend away from threat. In multiple studies, the authors found that the latter group got less stressed by a subsequent stressful task (solving anagrams), with some evidence indicating that these changes were correlated: those participants who developed the most pronounced attentional avoidance of negative information were the same individuals for whom the AtBM procedure most attenuated the negative emotional impact of the subsequent stress procedure.

Following these early experimental or “proof-of-principle” studies (aimed at establishing causality of the bias in healthy volunteers, Wiers et al. 2018), clinical randomized controlled trials (RCTs) followed. In these, AtBM was used to prevent anxiety when given prior to a major life change that causes stress (See et al. 2009), or as a tool in the treatment of anxiety (Amir et al. 2009; Price et al. 2016). There is, however, still unclarity regarding the efficacy of CBM in this domain (Cristea et al. 2015; Fodor et al. 2020; MacLeod and Grafton 2016), with some arguments for low or no effectiveness also coming back in discussions about the efficacy of CBM in addiction (next section).

In the domain of addiction, first proof-of-principle studies were also conducted with undergraduate student volunteers (Field et al. 2007; Field and Eastwood 2005; Schoenmakers et al. 2007; Wiers et al. 2006). For example, following the “split design” used by MacLeod et al. (2002), see Wiers et al. (2006 for a Figure), Field and Eastwood randomized students to a condition in which they received training to attend to pictures representing alcohol or to a condition where they received training to attend to pictures of non-alcoholic drinks. As in the original study, the manipulation was simple: most or all probes replaced one of the two categories (alcohol in the “attend-alcohol” condition, and non-alcoholic drinks in the “attend non-alcohol” condition). They observed that the attend-alcohol group increased AtB for alcohol, whereas the attend non-alcohol group decreased AtB for alcohol. These effects generalized to other behavior, with an increase for the attend-alcohol group in urge to drink and actual drinking in a taste test. Generalization to untrained pictures was not examined in this study (no untrained pictures were included in the assessment), but was tested in subsequent studies (Field et al. 2007; Schoenmakers et al. 2007). These provided evidence for the conclusion that attentional bias can be successfully manipulated in healthy volunteers, but that the evidence for generalized effects was meager at best (a conclusion that held in later reviews, Wiers et al. 2018).

Given the at least somewhat promising findings of malleability of AtB in hazardous drinkers, a first clinical RCT was performed, in which AUD patients received five sessions of AtBM in addition to their regular (cognitive behavior therapy, CBT) treatment. The AtBM included novel pictures in each training session, to foster generalization (Schoenmakers et al. 2010). Although the study sample was small

($N = 43$), significant effects were found on alcohol AtB, including effects on untrained pictures (reduction in the experimental condition, and an *increase* in a control condition in which patients received irrelevant training using the same stimuli). Note that this *increase in alcohol AtB* was also found in another study in the absence of training (Cox et al. 2002), and in the control condition of the largest clinical RCT so far, including both AtBM and ApBM (Rinck et al. 2018). Hence, this increase in alcohol AtB appears to be the default development of AtB after detoxification. Another interesting finding, also regarding the still largely open questions about the nature of substance AtB in addiction, was that AtB was successfully changed for the medium-long presentation time (500 ms, large effect size), but no effects were found for early engagement (brief presentation time, 200 ms, Schoenmakers et al. 2010). Finally, promising clinical effects were found; patients in the experimental group had a shorter treatment duration (standard CBT-based therapy; the therapists who judged successful treatment termination were blind to experimental condition), as well as later relapse, compared with patients in the control condition (Schoenmakers et al. 2010). These promising findings are qualified by the small sample size. However, in the largest clinical RCT so far ($N = 1,405$, Rinck et al. 2018), the AtBM condition also exhibited reduced relapse at 1 year follow-up compared with control conditions (11% less relapse compared with the combined control conditions). While these results in clinical RCTs are promising, one caveat is that dot-probe-based training is often conceived as boring and irrelevant by participants (Beard et al. 2012). As an illustration, in the clinical RCT by Schoenmakers et al. (2010), patients were asked after the training to guess whether they received active or sham training, and almost all patients answered sham training. While this is an encouraging finding from an experimentalist perspective (it is less likely that the effects are based on a placebo effect), it is less desirable from a clinical perspective, and could even lead to an anti-placebo effect (reducing the effectiveness, because of the idea of doing something irrelevant). One could argue that, for clinical applications, one should use placebo effects and avoid anti-placebo effects (Larsen et al. 2021).

In addition to work using a training variety of the dot-probe task, other researchers used a Stroop-based training paradigm as developed by Fadardi and Cox (the alcohol attentional control training program; AACTP, Fadardi and Cox 2009). In this training, participants receive training to systematically avoid (personally relevant) alcohol stimuli, using a series of progressively more difficult tests. Specifically, participants are instructed to respond with a color name, first of the background color of a picture, then of a thin colored line surrounding a bottle, and in the third series the bottles are presented in pairs and the participant is to name the color of the line surrounding the non-alcohol containing bottle. The program also contains psychoeducation about the role of AtB, and the training includes feature-relevant task instructions (e.g., to color-name the line surrounding the non-alcohol containing bottle). This contrasts with dot-probe-based AtBM, where no rationale or feature-relevant instructions are given (participants keep on reacting to the probes following the pairs of stimuli and are not informed that they are systematically trained away from alcohol—although they are likely to notice this at some point).

This difference is important for two reasons. On the one hand, it makes the training more engaging and relevant for participants than dot-probe-based AtBM. On the other hand, the same characteristic also makes it more difficult to create an active control condition and to assess effects of the intervention independent of possible placebo effects.

The first study tested AACTP in hazardous and harmful drinkers (Fadardi and Cox 2009) and found a reduction in drinking and an increase in motivation to change drinking, both in hazardous and harmful drinkers (who reduced their weekly alcohol consumption by some 15% from baseline to follow-up). However, it should be noted that no control condition was included. In a subsequent study, the AACTP was combined with a motivational intervention in a 2×2 factorial design in hazardous drinkers (Cox et al. 2015). Compared with the no interventions control group, AACTP led to reduced drinking in the short term, while the motivational intervention led to reductions in the longer term (6 months follow-up), and perhaps surprisingly, the combined intervention did not increase effects. To the best of our knowledge, AACTP has not been tested as an add-on to treatment for AUD. However, it has been tested as an add-on in the treatment of heroin-dependent patients undergoing methadone maintenance therapy ($N = 48$; Ziaeef et al. 2016). The experimental group showed a greater reduction in drug AtB, and in physiological cue reactivity, assessed with blood volume pulse, to indicate changes in sympathetic arousal and in temptation to use in response to drug cues. Effects on relapse were modest (effect on 3 months but not on 6 months follow-up), but low statistical power may have played a role.

In sum, although not many studies tested AtBM as an add-on to clinical treatment of AUD, the two available (dot-probe training) studies found promising effects (Rinck et al. 2018; Schoenmakers et al. 2010) as did an (AACTP) study in opioid-dependent patients (Ziaeef et al. 2016). However, a recent study testing add-on effects of gamified AtBM to the treatment of alcohol and cannabis use disorders found no effects (Heitmann et al. 2021). The current state of the evidence is further discussed in Sect. 3.

2.3 Approach Bias

In emotion research, a distinction is made between appraisals, which concern a rough first evaluation of a stimulus, and action tendencies, which represent the immediate action readiness component in emotions (Frijda 1986; Frijda et al. 1989, 2014). Motivationally salient stimuli typically elicit an action tendency to either approach or avoid the stimulus. Specifically, approach action tendencies are usually observed for attractive stimuli, and avoidance tendencies for aversive stimuli, with anger being the major exception (negative evaluation combined with approach tendencies, Carver and Harmon-Jones 2009). Given the importance of action tendencies in emotional responses (in addition to appraisals) and the emphasis on attentional bias in the addiction literature, researchers started to assess action

tendencies in relation to addictive behaviors in the first decade of the century. A *manikin* task was developed in which participants move a matchstick figure toward or away from a focal category (e.g., alcohol, Field et al. 2008; e.g., cigarettes, Mogg et al. 2003), with the typical finding that (heavy) substance users are faster to make the manikin approach than to avoid this category, as compared to a control category. Note that this is a so-called relevant feature task with explicit instructions about the relevant feature that participants need to respond to: In one block, they are instructed to approach alcohol (and avoid non-alcohol containing drinks), and in another block reversed contingencies are instructed (avoid alcohol, approach non-alcohol). An approach bias (stronger tendency to approach alcohol) is estimated based on the difference in average RTs in the two blocks.

Another task developed to assess action tendencies is the AAT (approach-avoidance task), going back to the seminal work of Solarz (1960), who first demonstrated that participants are faster to react to positive words with an approach reaction and to negative words with an avoid reaction. Chen and Bargh (1999) developed an approach-avoidance task using a lever, and Rinck and Becker (2007) optimized this in a joystick task. This task includes a zoom feature, so that the size of the stimulus changes upon a response: it increases upon a pull movement (yielding a sensation of approach) and decreases upon a push movement (avoidance). This version was subsequently adapted to an irrelevant-feature task (see Fig. 3) to assess an approach bias for alcohol (Wiers et al. 2009), and other substances (cannabis: Cousijn 2011; cigarettes: Wiers et al. 2013a, b, c), as well as gambling-related stimuli (Boffo et al. 2018). In this irrelevant-feature AAT, participants react with a joystick to a characteristic of the stimulus unrelated to the content, such as format



Fig. 3 The approach avoidance task (AAT). In the irrelevant-feature version, participants react to the format of the picture (e.g., pull portrait, push landscape pictures). Upon pulling, the picture zooms in, creating a sense of approach; upon pushing, the picture zooms out (shrinks), creating a sense of avoidance. An alcohol-approach bias is assessed when participants are faster to pull than to push alcohol pictures, in comparison with the same difference for a contrast category (e.g., non-alcoholic drinks). In the training versions, alcohol pictures come predominantly in the format that is pulled (approach-alcohol training, only relevant in proof-of-principle studies) or in the format that is pushed (avoid-alcohol training, also clinically relevant)

(e.g., pull pictures in landscape format, push pictures in portrait format, Wiers et al. 2009) or tilt (e.g., pull pictures with a slight left tilt and push pictures with a slight right tilt, Cousijn et al. 2011). Note that it is merely historical coincidence that the manikin task has been primarily used in a relevant feature version, while the AAT task has been primarily used in an irrelevant version, both tasks can be designed either as relevant or irrelevant-feature task (see Field et al. 2011 for a direct comparison).

Notably, cues of addictive behaviors seem to give rise to an automatically activated action tendency in this task (in the sense that participants are faster to approach the addiction-related stimuli than to avoid them, even though they are instructed to react to a feature that is unrelated to the contents of the picture, Boffo et al. 2018; Cousijn et al. 2011; Wiers et al. 2009). This contrasts with general emotion research in which the compatibility effect was found for general positive and negative stimuli with relevant feature or explicit instructions, but not when irrelevant-feature instructions were used (Rotteveel and Phaf 2004). This suggests that the automatic activation of action tendencies may be stronger than for general emotionally relevant stimuli in addictive behaviors or for appetitive stimuli, as an approach bias was also found in G-allele carriers of the OPRM1 gene, but not for general positive and negative stimuli (Wiers et al. 2009). This allelic variation has also been associated with cue-induced craving (e.g., Van Den Wildenberg et al. 2007) and with increased neural cue reactivity to substance cues (Bach et al. 2015; Filbey et al. 2008; Korucuoglu et al. 2017).

An advantage of the irrelevant-feature instructions in this assessment task (the irrelevant-feature AAT) is that it can be easily changed to a bias modification instrument without changing the instructions, similar to dot-probe-based AtBM (Wiers et al. 2010). However, this comes with a cost, as the reliability (internal consistency) of irrelevant-feature tasks is lower than that of relevant feature tasks (Field et al. 2011). With both types of tasks, heavy substance users (and gamblers) have been found to have an approach bias, which is typically not found in non-users or light users (review: Kakuschke et al. 2019). It should be noted that these findings indicate group differences, but that there is a substantial minority of AUD patients who do not demonstrate an approach bias for alcohol, but rather an avoidance bias (e.g., Piercy et al. 2021).

Although in the original AAT, a joystick was used, AATs with response keys have also been used, which might take away part of the embodied nature of the response, but still yielded effects in some studies (e.g., Peeters et al. 2012). A recent study in the domain of problematic porn use directly compared assessment with a joystick and a keyboard. It found better results for the joystick (Kahveci et al. 2020), which is therefore still recommended (but may become harder to obtain over time). For this reason, researchers are testing mobile versions, which include arm movements using a phone or tablet (Boendermaker et al. 2015a; Zech et al. 2020) and a VR version where the (avatar) body moves toward the stimulus (Rougier et al. 2018). Note that also an approach-avoid version of the implicit association task (IAT) has been developed, in which four categories of words (two pairs: approach or avoid and alcohol or non-alcohol) are sorted using two response keys (Ostafin and

Palfai 2006). In one sorting condition, participants use the same response key for alcohol words and approach words (and the other key for non-alcohol words and avoid words). In the other sorting condition, alcohol words require the same response as avoid words (and non-alcohol words as approach words). The IAT effect concerns the difference in RTs (and errors) between these two sorting conditions (Greenwald et al. 2003, 2021). When participants are faster to sort alcohol with approach words, this is interpreted as a relatively stronger memory association between alcohol and approach tendencies, compared with alcohol and avoid tendencies (assuming that the effect is more driven by alcoholic than non-alcoholic drinks). Note that there is some controversy concerning the exact interpretation (construct validity) of IAT scores (De Houwer et al. 2005, 2020; Greenwald et al. 2009; Rothermund and Wentura 2004), but it is clear that the IAT is a reliable measure, much more reliable than irrelevant-feature measures (De Houwer and De Bruycker 2007; Greenwald et al. 2021; Roefs et al. 2011).

2.4 Approach Bias Modification (*ApBM*)

Following the same logic of AtBM, the assessment alcohol AAT (Wiers et al. 2009), was transformed into a task aimed at modifying the approach bias, in a first proof-of-principle study in hazardously drinking students (Wiers et al. 2010). Specifically, students were randomly assigned to an approach-alcohol condition or an avoid-alcohol condition (split design as in MacLeod et al. 2002; Field and Eastwood 2005). In both conditions, the AAT started with the usual irrelevant-feature assessment task. Participants were instructed to respond with a pull movement to one type of pictures (e.g., landscape) and with a push movement to the other type of pictures (e.g., portrait). These responses were first practiced using gray rectangles, followed by pictures of alcohol and non-alcohol drinks, of which half were pulled and half pushed of both types. Then, without notification or change in instruction, the task transformed into a training task, where alcohol pictures were consistently pulled, and non-alcohol pictures pushed (approach-alcohol condition) or alcohol pictures were consistently pushed and non-alcoholic drinks pulled (avoid-alcohol condition). This manipulation resulted in a generalized change in approach bias on the AAT both for trained and for untrained pictures, so that participants in the approach-alcohol condition became faster in pulling alcohol (and pushing non-alcoholic drinks) and participants in the avoid-alcohol condition became faster in pushing alcohol (and pulling non-alcoholic drinks). Interestingly, an effect was also found on the approach-avoid IAT using words (which is a strong generalization, as participants were trained with a training version of the joystick AAT using pictures). Moreover, in participants who were successfully trained, an effect was found in a subsequent taste test, where heavy drinkers who had been successfully trained to avoid alcohol drank less beer than heavy drinkers who had been successfully trained to approach alcohol (no difference was found in light drinkers). Note that these generalized

effects were unexpected, as they had not been found after a single session of AtBM in healthy volunteers (Field et al. 2007; Schoenmakers et al. 2007).

Given these promising findings in a first proof-of-principle study, ApBM was tested as an add-on to regular treatment in a first large clinical RCT ($N = 214$, Wiers et al. 2011). Two experimental conditions were included, both consisting of four sessions of ApBM in which participants were consistently trained (four sessions including 200 trials each) to respond with a push response to alcohol pictures and with a pull response to non-alcohol pictures. The one difference between the two experimental conditions was that one used an irrelevant-feature version (as in the proof-of-principle study described above: instructions remained the same, but now alcohol was consistently pushed away), while patients in the other condition were explicitly instructed to push away alcohol pictures and to pull non-alcohol pictures. Given that the crucial procedural details (contingencies) did not differ between these groups, nor did they differ in any of the outcome measures, they were combined into one active ApBM group, as were the two control conditions which included either only a continued assessment task (equally often pushing and pulling both alcohol and non-alcohol pictures) or no training at all. As in the proof-of-principle study, generalized effects were found on untrained pictures in the AAT assessment task and on the verbal IAT (strong generalization). While patients were faster (on average) to sort alcohol with approach words before training (alcohol-approach association dominated), this changed to faster sorting of alcohol with avoid words in the active ApBM group, while no change was observed in the control group. The most striking result came at the one-year follow-up, where it was found that patients in the experimental conditions had a 13% lower chance of relapse 1 year after treatment discharge (46% vs. 59%). Of note, the reduced relapse rate was not mediated by the change in alcohol-approach tendencies, as assessed either with the AAT or with the IAT. However, a subsequent more fine-grained analysis into components of the IAT suggested that an increased avoidance bias for alcohol stimuli partly mediated the improved clinical outcomes (Gladwin et al. 2015). This pattern is congruent with the rationale of ApBM, but is at odds with another study which reported that a stronger AAT tendency to avoid alcohol during treatment was predictive of relapse (Spruyt et al. 2013; see Wiers et al. 2013c; De Houwer et al. 2020, for possible explanations). In short, this relates to an alternative interpretation of automatic processes in addiction, discussed later in ABC training, focusing on automatic inferences. From this interpretation, some people may interpret the task as what they desire (to not be attracted by alcohol anymore), while others react on what the substance invokes in them (a desire to approach). This could be related to the distinction between first- and second-order desires (desires what you desire, here, not to desire alcohol anymore) in philosophy (Frankfurt 1971).

In a series of subsequent studies, the results of reduced relapse rates caused by ApBM were replicated. First, in a replication study including 509 patients (Eberl et al. 2013), participants were either trained to avoid alcohol during 12 sessions, or they received no training (as the first study found no difference between an active and this passive control condition) as an add-on to their (CBT-based) inpatient treatment. Patients in the active training condition were found to have 9% less

chance to have relapsed 1 year later compared to the (passive) control condition. In this study, both mediation and moderation were observed, with the change in alcohol-approach tendency (assessed with the AAT) mediating the clinical outcome, and the strength of the alcohol-approach bias at pretest predicting stronger change in bias.

In subsequent analyses, the optimal number of sessions was investigated, including predictors of the number of sessions needed (defined as the point where the learning curve became flat, Eberl et al. 2014). The mean number of sessions was six, but there was large variability, with some patients needing only two sessions and others still improving in the 12th session (note that learning can take even longer in AUD patients with Korsakow syndrome, Loijen et al. 2018). Disappointingly, none of the baseline variables predicted individual differences in the learning rate.

Second, the largest CBM RCT so far combined ApBM and AtBM (Rinck et al. 2018) as an add-on to the treatment of AUD. Specifically, 1,405 AUD patients were randomized over 7 conditions: 3 active CBM conditions, which consisted of 6 sessions of ApBM, 6 sessions of AtBM, or 3 of each; compared to 3 matched control conditions (same setup without a training contingency, hence prolonged assessment); and a no training control condition. Participants in all three CBM conditions exhibited less relapse compared with the control conditions (8.4% on average). Mediation and moderation effects were not replicated, but it should be noted that many data were missing for the bias measures, as the study took place during regular treatment.

Third, the most recent of this series of studies in the same clinic (Salemink et al. 2021) assessed effects of ApBM in 729 AUD patients, of whom 20% also had an internalizing disorder (anxiety or depression). Patients received either 12 sessions of ApBM or no training as an add-on to treatment (as in Eberl et al. 2013, note that these are unique patients, not overlapping with those of the Eberl et al. 2013, analyses). In this study, adding ApBM to treatment led to 10% less relapse a year after treatment discharge. Interestingly, results were better for patients who had a comorbid internalizing disorder, compared with the AUD-only patients.

All of these studies took place in the same clinic, with the same core team of researchers. Therefore, an important question is whether the results would replicate in a different setting. In another series of studies, Manning and colleagues tested effects of ApBM in Australia, where the setting was different; it was used as an add-on during detoxification. In a first study, 83 participants were randomized to ApBM or sham training during the detox period (Manning et al. 2016). Primary outcome variable was continuous abstinence during the 2 weeks after detox. Abstinence was higher in the ApBM condition: at statistical trend level in the intention-to-treat analysis, and significantly in the per-protocol analysis (including only patients who performed all four sessions of training). In a recent larger replication multicenter RCT (Manning et al. 2021), 300 patients were randomized to receive either ApBM or sham training. Patients receiving ApBM were 12% less likely to have relapsed during the 2 weeks follow-up. In the per-protocol analysis, this was 17%. In a follow-up study of the same sample with outcomes after 3, 6, 9, and 12 months, the difference was still significant after 3 months but not anymore after, although the

absolute difference was still 7% less relapse after 12 months in people who had received the training (Manning et al. 2022).

In summary, in two series of RCTs across different settings, ApBM has been found to consistently improve treatment outcomes, with 7 to 17% reductions in relapse 1 year after treatment discharge, which has led to the inclusion of this type of CBM as an advised add-on to the clinical treatment of AUD in the countries where these trials took place (Germany and Australia; see introduction). However, it should be mentioned that there is one (as-yet unpublished) recent RCT we are aware of, which did not find an add-on effect of CBM in the treatment of AUD (in Belgium, Spruyt et al. unpublished data); see Table 1. Note that the latter study may have been underpowered for replicating the small effects that were found earlier, especially when evaluating a binary outcome (relapse or not). Note further that there are other studies on effects of CBM in AUD patients, but these were not primarily powered for clinical outcomes (but for example for neural effects of training: Wiers et al. 2015a, discussed in the next section), and studies that explored the combined effects of CBM with neurostimulation (den Uyl et al. 2017, 2018; Dubuson et al. 2021, discussed in Sect. 5).

Further, although effects of ApBM as add-on to the treatment of AUD have been almost exclusively positive, it does not imply that ApBM is a magic bullet against all alcohol problems. For instance, it was not found to be effective as stand-alone intervention for problem drinkers administered over the web (Van Deursen 2019; Wiers et al. 2015a, b, c). In both studies, problem drinkers successfully decreased drinking, both in the CBM conditions and in the placebo-control conditions (non-specific time effect), which is the general conclusion concerning the effectiveness of CBM in heavy or problem drinkers over the web (Jones et al. 2018; Van Deursen 2019; Wiers et al. 2015a, b, c). In addition, in a study with hazardously drinking students not motivated to change, ApBM did not yield effects (Lindgren et al. 2015). In sum, it seems that in studies where ApBM was added to abstinence-oriented treatment for patients motivated to change their drinking behavior, ApBM has almost consistently shown to have beneficial effects. However, when participants only want to reduce their drinking or are not motivated to change their drinking, no differential effects are found in comparison with an active control condition (in volunteers who want to reduce drinking, reduced drinking is found across conditions, and in volunteers who participate for other reasons, typically only short-lived effects are found in case the bias is successfully changed, or no effects on drinking behavior are found; see Wiers et al. 2018 for a review).

ApBM has also been tested for other addictive behaviors, mostly for cigarette smoking (Kong et al. 2015; Machulska et al. 2016; Wen et al. 2020; Wittekind et al. 2019b). As in the alcohol studies, some studies were web-based only, and these did not find (differential) effects (Wen et al. 2020; Wittekind et al. 2019a). Yet, most similar to the conditions where an almost consistent effect has been found as an add-on to the abstinence-oriented treatment of AUD is a study where ApBM was also added to a well-established smoking cessation program (Wittekind et al. 2019b), and this study also found no effects. Before we conclude that ApBM does not work for smoking, it may be good to point to two preclinical studies that modified the

Table 1 CBM as add-on to the clinical treatment of AUD

Study	Sample (n)	Experimental group/training (n)	Control group/training (n)	Sessions/time	Follow-up	Outcomes		Remarks
						Abstinence/drinking	Task (s)	
Schoenmakers et al. (2010)	AUD (43)	AtBM + TAU (21)	IAT-based sham (22)	5 sessions/3 weeks	RR: ×	VPT EG; AtB↓ CG: ×	EG: relapse 1 month later and treatment discharge 1 month earlier	
Wiers et al. (2011)	AUD (214)	ApBM + TAU (108)	Sham or no training + TAU (106)	4 sessions/1-year	RR: EG 46% < CG 59%	AAT: ΔApB; EG > CG IAT; ΔApB; EG > CG	Effects generalized to untrained stimuli (AAT) and verbal IAT	
Eberl et al. (2013)	AUD (475)	ApBM + TAU (248)	No training + TAU (227)	12 sessions/6 weeks	1-year	RR: EG 48.8% < CG 57.3%	AAT: EG: ApB→AvB CG: ×	Change in AAT partially mediated training effect on relapse rate
Clerkin et al. (2016)	SA and AUD (86)	Alc AtBM + SA control (20) Alc AtBM + SA AtBM (22)	Alc control + SA ABM (24) Alc control + SA control (20)	8 sessions/4 weeks	1-month	FU: ×	VPT: ×	Significant or trending decreased in all attention trial-level bias score parameters (but not traditional attention bias scores)
Manning et al. (2016)	AUD (83)	AAT + detoxification (41)	Sham + detoxification (42)	4 sessions/4 days	2-week	RR: EG 31.4% < CG 52.8%	✓	At the 2-week follow-up, participants reported a higher rate of abstinence in the CBM group relative to controls
Rinck et al. (2018)	AUD (1,405)	ApBM + TAU (238) AtBM + TAU (230)	Sham + TAU (316) No training + TAU (366)	6 sessions	1-year	RR: ABM 44.8% < ApBM 47.9% <	VPT: ΔAB: EG < CG AAT:	Merged control groups (sham training and no training) for analyses

		(ABBM +ApBM)/2 +TAU (255)			combine 48.6% < CG 55.6%	Δ ApB; EG > CG
Heitmann et al. (2021)	AUD or cannabis (169)	AtBBM + TAU (92)	Sham + TAU (77)	7 weeks	1-year	RR: × AC: ×
Manning et al. (2021)	AUD (300)	ApBM + TAU (147)	Sham + TAU (153)	4 sessions/ 4 days	2 weeks	RR: EG < CG by 11.9%
Salemink et al. (2021)	AUD (729)	ApBM + TAU (304)	No-training + TAU (425)	12 sessions/4 weeks	1-year	TS (EG > CG): RR: EG < CG by 10%
Schenkel et al. (2023)	AUD (434)	ApBM + SI + TAU (214)	ApBM + sham SI+ TAU (220)	6 sessions/ 2 weeks	1-year	RR: ×
Spruyt et al. (unpublished data)	AUD (155 at 1st follow-up)	AAT + VPT (49) AAT + sham VPT (43)	Sham AAT + VPT (29) sham AAT + sham VPT (34)	8 sessions	3 fol-low-ups	RR (AUDIT): × AAT: × VPT: ×
Stein et al. (2022)	AUD (242)	Standard Alc-IT + TAU (84) Improved Alc-IT + TAU (79)	Sham + TAU (79)	6 sessions/ 2 weeks	3-month	AD (↑ by 9%) HD (↓ by 7.5%)
						GNG (Alc-IT alcohol related error rate ↓)
						Standard Alc-IT (Go/NoGo = 50/50) Improved Alc-IT (Go/NoGo = 75/25) Alc-IT might be a promising add-on

n number of subjects, *EG* experimental group, *CG* control group, *TAU* treatment as usual, *ApBM* approach bias modification, *AtBBM* attentional bias modification, *ApB* approach bias, *AvB* avoidance bias, *tDCS* transcranial direct current stimulation, *SA* social anxiety, *Alc-IT* alcohol-specific inhibition training, *RR* relapse rate; × = intervention showed no effect on outcome; ↑ = increase; ↓ = decrease; AC alcohol consumption, AD abstinent days, *HD* heavy drinking days, *SI* selective inhibition training, *VPT* Visual Probe Task, *TS* treatment success, *OOT* Odd-One-Out assessment task, *FU* follow-up

procedure and found more positive effects through personalization of alternatives (Kopetz et al. 2017; Wen et al. 2021), which may be helpful because unlike ApBM in alcohol, where the alternative category is meaningful (non-alcohol containing drinks), this is not the case in standard ApBM for cigarette smoking, where visually matched alternatives are typically used such as someone holding a pen rather than a cigarette. These alternatives and the related new ABC training are discussed in Sect. 6.

Finally, while AtBM was developed in the context of anxiety disorders (MacLeod et al. 2002) and later “translated” to the field of addictions (Field et al. 2007; Schoenmakers et al. 2007, 2010), ApBM was developed in the field of addiction² (Wiers et al. 2010, 2011), and later also applied to anxiety (Amir et al. 2013) and depression, by Becker and colleagues (2019) and Vrijens et al. (2018), with promising findings. Note that in these instances, it is primarily an approach (rather than an avoidance) reaction that is trained, toward a feared object (anxiety) or toward positive stimuli (depression).

2.5 (*Evaluative*) Memory Bias

The third cognitive bias often reported in addictions concerns a memory bias. Different types of measures have been used, open-ended measures, where participants write down (or say) the first association that comes to mind (Stacy et al. 1994, 2006; Stacy 1997), where different stimuli are used, such as ambiguous words (e.g., first association to “draft”), or first behavior that comes to mind to a situation (e.g., Friday night, feeling good). Note that even earlier, a measure including multiple associations to a stimulus was developed (Szalay et al. 1992). These measures are good predictors of (prospective) addictive behaviors (reviews: Stacy et al. 2006; Stacy and Wiers 2010), and are also reliable (Shono et al. 2016). The second class of measures is reaction time-based. Most researchers use varieties of the IAT, which can be flexibly used to assess relative ease of sorting alcohol (as compared with non-alcoholic drinks) together with valence (Houben and Wiers 2008; often referred to as “implicit attitudes,” e.g., Wiers et al. 2002), or with different attributes, like arousal (Houben and Wiers 2006; Wiers et al. 2002). The aforementioned approach-avoid dimension (Ostafin and Palfai 2006), and more recently, drinking-identity associations have been studied intensively (e.g., Lindgren et al. 2012, 2016). Other measures have also been used, especially to assess implicit attitudes, including the Extrinsic Affective Simon Task (e.g., de Jong et al. 2007), and the Affect Misattribution Procedure (Payne et al. 2005, 2016). The dominant interpretation of these findings is that the more readily participants can associate a positive attribute

²Note that there is an earlier study on ApBM in the field of social cognition (Kawakami et al. 2007), but we developed the training independently; based on AtBM, the first data were collected in 2005, but publication took a while (as is often the case with new interventions).

with alcohol (or other substances), the more they drink. These attributes can be expected outcomes (e.g., combinations of positive and arousing expectancies, like fun), but also general positive or negative stimuli can be used (see Houben et al. 2010b for a direct comparison). Finally, it should be reiterated that there is discussion regarding the exact interpretation of the reaction time (RT) measures, especially regarding the IAT (De Houwer et al. 2005, 2020; Rothermund and Wentura 2004).

2.6 Evaluative Memory Bias Modification

In AtBM and ApBM, modification is typically performed with a training variant of a measurement instrument (e.g., dot-probe, alcohol-Stroop, or AAT), where a contingency is built into the task to change the bias (e.g., avoid alcohol). This is not the case in attempts to change biases in evaluative memory, where different procedures have been used, notably evaluative conditioning (EC) and selective inhibition.

In EC, a stimulus is consistently paired with a category of valenced stimuli (e.g., always when there is an alcohol picture, there is also a negative picture, e.g., Houben et al. 2010c). To the best of our knowledge, EC has not been used as an add-on in the treatment of AUD³; for that reason we only describe this method briefly here. Several proof-of-principle studies in heavy drinking volunteers have shown promising effects (Houben et al. 2010a, c; Noel et al. 2019; Tello et al. 2018; Zerhouni et al. 2019), which could stimulate researchers to test the procedure in AUD patients. Regarding the moderators of EC effects, there is growing evidence that conscious awareness of the evaluative stimuli is needed for EC effects to occur (Corneille and Stahl 2018; De Houwer et al. 2020; Hofmann et al. 2010; Sweldens et al. 2014); see also Sect. 4 below.

A second method used to change alcohol evaluations is selective inhibition. In this procedure, a specific category of stimuli is systematically followed by an inhibitory response (Chen et al. 2016; Veling et al. 2008, 2017). Typically, a Go/NoGo task is used, where, in the active condition, the focal category (e.g., alcohol) is always paired with a NoGo signal (Houben et al. 2010a, 2012). In both studies, healthy volunteers (hazardously drinking students) in the active condition showed reduced alcohol consumption in the short term (one-week follow-up). Both studies also showed effects on the evaluation of alcohol (which became more negative in the active condition), and in the second study, no effect was found on a general inhibition task (Stop task), in line with the idea that the effect of selective inhibition is achieved through stimulus devaluation and not through a general effect on inhibition (see also Fig. 1).

Selective inhibition has been successfully used across several health domains as a preventive intervention, as a first meta-analysis showed (Allom et al. 2015), but there

³One could argue that ApBM is a form of EC, as in ApBM negative *responses* are consistently paired to addiction-relevant cues.

are no published studies yet testing selective inhibition as an add-on to the treatment of AUD (one feasibility study with self-identified people with AUD online, Strickland et al. 2019). However, there are two recent studies, in which selective inhibition has been added to the treatment of AUD (one just accepted and one still under review). The first took place in the Salus Clinic Lindow, where ApBM has become part of regular treatment after consistent positive add-on effects after four large RCTs (Eberl et al. 2013; Rinck et al. 2018; Salemink et al. 2021; Wiers et al. 2011). Against this background, selective inhibition was added as extra add-on, first in the standard version as used in preclinical studies (Houben et al. 2011a, 2012), in which in the active training condition, based on the Go/NoGo task, participants always react with a NoGo response to alcohol-related stimuli. In the control condition, there is no contingency (a Go or NoGo response is paired equally often with alcohol as with non-alcohol). No extra add-on effect was found in this context, which could mean either that it does not add to ApBM which was already part of the treatment or that this specific training has no add-on effect. Regarding the specific inhibition training, it should be noted that in the most frequently used training variety of the Go/NoGo task, the inhibited category (e.g., alcohol) appears in half of the trials, while basic research has shown that the inhibition effect is optimal when the inhibited category is more rare (typically 25% is used), and there are indications that this may also yield the largest effect on evaluation (Chen et al. 2016).

In the second RCT in which selective inhibition was added to the treatment of AUD (Stein et al. 2022), both the “standard” selective inhibition condition (with 50% alcohol pictures, always triggering a NoGo reaction) and a version in which alcohol stimuli were rare (25% of the trials) and were always combined with an inhibitory response, along with a control condition (as in standard selective inhibition studies, 50% alcohol stimuli, half of the time requiring an inhibitory response, protocol: Tschuemperlin et al. 2019). While standard selective inhibition training yielded no effect, improved inhibition training with relatively rare alcohol stimuli did improve outcomes at 3 months follow-up (Stein et al. 2022). These findings indicate that optimized selective inhibition training could also be a valuable add-on training in the treatment of AUD. As such, promising findings have been found for use as add-on training in the treatment of AUD for all three frequently used forms of CBM: AtBM, ApBM, and selective inhibition.

3 Cognitive Bias Modification as Add-On in the Treatment of AUD: Update of the Evidence

Thus far, there have been two meta-analyses regarding effects of CBM in addiction. The first combined proof-of-principle (PoP) studies in healthy volunteers with clinical RCTs in AUD patients (Cristea et al. 2016). It concluded that CBM was effective in changing the targeted cognitive bias, but did not have a significant effect on clinical outcomes, and that therefore the clinical utility of CBM for addiction was

“seriously doubted.” However, this meta-analysis was criticized for combining these two types of studies (Wiers et al. 2018; see also the commentaries following the original publication in PlosOne), although they represent different stages of the experimental medicine approach to intervention development (Sheeran et al. 2017): While PoP studies are aimed at testing the causal status of a construct (e.g., cognitive bias) in relation to the problem behavior (e.g., excessive drinking), clinical RCTs are aimed at testing efficacy of the intervention in patients, and both study types should therefore not be combined into a single analysis. In PoP studies, healthy volunteers are recruited and often randomized to a condition in which the bias is temporarily *increased*, in order to study whether this leads to a temporary increase in the problem behavior (e.g., Field and Eastwood 2005; MacLeod et al. 2002; Wiers et al. 2010). Obviously, this is not done in clinical RCTs with patients (for detailed discussions regarding the different phases of the experimental medicine approach to intervention development, see Sheeran et al. 2017; Wiers et al. 2018). Importantly, participants in the large majority of included studies were healthy volunteers in PoP studies, who took part in the included studies for extrinsic motivators such as course credit or money and not because of a motivation to change their drinking (Wiers et al. 2018). Hence, the conclusion that the clinical effects of CBM were seriously doubted was based on an analysis that included primarily PoP studies in healthy volunteers, while the included clinical RCTs all found clinically relevant effects (later relapse or reduced relapse rates at one-year follow-up).

Subsequently, a first meta-analysis was done including clinical RCTs only, where an inclusion criterion was that participants were motivated to change their addictive behavior and were told that the goal of the intervention was to help them reduce their substance use (Boffo et al. 2019). In this Bayesian meta-analysis of individual participant data, 14 studies were included (all on AUD or smoking, as in Cristea et al. 2016). Small but significant effects were found on cognitive bias and, on relapse rates, no effect on substance use. The latter appears to primarily resonate the findings of Internet trials, in which participants choose their own goal, and most choose to reduce use, which they successfully do, whether they are in the active CBM condition or in an active control (sham training) condition (e.g., Wiers et al. 2015a, b, c). This meta-analysis included four studies in which a variety of CBM was added to the treatment of AUD, which have been summarized in the previous section, one assessing add-on effects of AtBM (Schoenmakers et al. 2010), and three assessing add-on effects of ApBM (Eberl et al. 2013; Wiers et al. 2011, 2015b). In addition, it included several studies in which community samples of heavy or problem drinkers received training, as a stand-alone intervention (Clerkin et al. 2016; Cox et al. 2015; Wiers et al. 2015a, b, c). While the studies of the first type found positive clinical outcomes (later or reduced relapse, only not significant in the small study focusing on neurocognitive outcomes, which will be discussed in the next paragraph, Wiers et al. 2015a, b, c), studies of the second type generally found no differential effects on alcohol use compared with the (active) control condition. There are two likely explanations for this difference, either CBM works only as add-on to clinical treatment, or only when participants have an abstinence goal, or both. This cannot be determined now, as these variables are highly correlated:

abstinence was the treatment goal in almost all clinical studies where CBM was added to treatment as usual, and was hardly ever the goal in the studies in which problem drinking volunteers participated.

Table 1 summarizes the clinical RCTs where CBM was added to clinical treatment of AUD, Table 2 summarizes other RCTs in which CBM was used to reduce problem drinking in non-clinical settings, and studies in AUD patients which had a different purpose than clinical effects (e.g., study neural effects of CBM in a small sample). We repeated the search as described in Boffo et al. (2019), and for this chapter included all studies on CBM effects in relation to alcohol use disorders.

Regarding the studies that primarily tested clinical outcomes of adding a variety of CBM to treatment of AUD, the large majority found positive effects, but these effects are rather small (around 10% less relapse at one-year follow-up, which would yield a number needed to treat (NNT) of 10, which is similar to the small effect sizes of medication for AUD (Jonas et al. 2014). There are also some negative findings (no add-on effect), which could be related to the type of CBM used (e.g., gamified rather than standard CBM, Heitmann et al. 2021), and/or treatment goal (positive findings have primarily been found in inpatient settings with an abstinence goal (Eberl et al. 2013; Manning et al. 2016, 2021; Rinck et al. 2018; Salemink et al. 2021; Schoenmakers et al. 2010; Stein et al. 2022; Wiers et al. 2011), with some exceptions (Clerkin et al. 2016, an underpowered study, $N = 86$ with four conditions; and the as-yet unpublished study by Spruyt et al. unpublished data; note that in Heitmann et al. some patients had an abstinence goal and others not, and both AUD and CUD were treated).

The studies in Table 2 can be grouped into two categories. The first concerns web-based studies where varieties of CBM have been tested as stand-alone interventions for self-identified problem drinkers, who choose their own treatment goal (almost always reduced drinking). In these studies, generally a main effect of time is found, with reduced drinking in all categories. The second category of studies focused on neural mechanisms underlying CBM in AUD patients or on combined effects of CBM and neurostimulation, discussed in the next section.

4 Cognitive Bias Modification: Underlying (Neuro)Cognitive Mechanisms

The evidence presented above indicates that CBM can produce relevant change in AUD behavior. Given the historical background of CBM, as an experimental tool to directly manipulate a cognitive bias, in order to test its hypothetical effect on (symptoms of) psychopathological problems, it is a logical next step to test not only clinical outcomes but also underlying (neuro)cognitive mechanisms. While clinical outcomes of CBM as addition to AUD have been mostly positive (see Table 1), effects on cognitive biases have not consistently been observed. Especially mediation of the clinical outcome by the change in the cognitive process has only

Table 2 CBM with primary aims other than clinical outcome

Study	Sample	Experimental group/ training (n)	Control group/ training (n)	Sessions/ time	Follow- up	Outcomes		Remarks
						Drinking	Task (s)	
<i>Aimed at reducing drinking</i>								
Wiers et al. (2015a, b, c)	Problem drinkers (136)	Web-based AAT (17) ATT100 Explicit (27) ATT100 Implicit (35) ATT90 Implicit	AAT50 sham (24)	4 sessions 2-month	PU: ×	✓	Participants in all conditions (including participants in the control-training condition) reduced their drinking	
Cox et al. (2015)	Harmful drinkers (148)	EG1: ABM & LEAP (42) EG2: LEAP (42) EG3: ABM (35)	Sham (29)	4 sessions/ 4 weeks	6-month	AC (post- test): × PU (3 months): EG1: AC↓ PU (6 months): EG1: mean AC: ×, typical AC↓	✓	AtBM significantly reduced mean weekly drinking, but only at the 3-month follow-up
Jones et al. (2018)	Heavy drinkers (246)	Alc GNG (57) Alc Stop Signal (60) General Inhibition (75)	Sham (54)	14 ses- sions/ 4 weeks	After training	AC↓ (all groups)	GNG: ×	No differences between groups
Strickland et al. (2019)	AUD recruited online (444)	cued GNG-ICT (145) WMT (150)	Arithmetic problems (149)	14 ses- sions/2 weeks	2-week	AC↓ DD↓ (ICT > WMT > CG)	GNG: ×	Modest reductions in alcohol consumption, primarily in the ICT group
Van Deursen (2019)	Problem drinkers (427)	GNG + AAT + VPT (49) GNG + AAT + sham VPT (58)	GNG + sham AAT + sham VPT (51)	12 ses- sions/6 weeks	6- month	AC↓ (all groups)	✓	Web-based GNG-EMB, AAT-ApBM, VPT-ABM, added on a brief motivational

(continued)

Table 2 (continued)

Study	Sample	Experimental group/ training (n)	Control group/ training (n)	Sessions/ time	Follow- up	Outcomes		Remarks
						Drinking	Task(s)	
Wiers et al. (2015a)	AUD inpatients (32)	AAT-ApBM (15)	CG sham (17)	6 sessions/ 3 weeks	After training	\	AAT: ×	fMRI EG: amygdala↓, nucleus accumbens: ×
<i>Investigate neural effects</i>								
Wiers et al. (2015b)	AUD inpatients (26)	AAT-ApBM (13)	CG sham (13)	6 sessions/ 3 weeks	After training	\	AAT: ×	fMRI EG: medial prefrontal cortex↓, nucleus accumbens: ×
Martínez- Maldonado et al. (2020)	AUD (33)	A-CBM-ApBM (10) N-CBM-ApBM (12)	No training (11)	8 sessions/ 3 weeks	After training	\	AAT A-CBM: ApB↓ N-CBM: ×	Resting-state EEG A-CBM: alpha synchronization↑

den Uyl et al. (2017)	AUD inpatients (91)	ApBM + tDCS (30)	Sham tDCS + ApBM (30) tDCS only (31)	4 sessions/ 1 week	1-year	RR: EG < CG	AAT: All groups ApB↓	tDCS combined with CBM showed a promising trend on treatment outcome in post-hoc analysis
den Uyl et al. (2018)	AUD patients (83)	ApBM + sham tDCS (20) ApBM + active tDCS (21)	Control ApBM + sham tDCS (22) Control ApBM + active tDCS (20)	4 sessions/ 1 week	1-year	FU: ×	VPT: × IAT: ×	
Dubuson et al. (2021)	AUD patients (125)	ICT (GNG) + tDCS (36)	neutral ICT + tDCS (28) neutral ICT + sham tDCS (34) ICT + sham tDCS (27)	5 sessions/ 5 days	1-year	RR (2 weeks): EG 13.9% < CG 36% RR (1 year): ×	✓	Short-lived effects: tDCS applied to DLPFC significantly increased abstinence rate, when combined with alcohol specific ICT, clinical outcomes might be better

n number of subjects, *EG* experimental group, *CG* control group, *Alc* alcohol, *ATT* Action Tendency Training, *LEAP* Life Enhancement and Advancement Programme, *ICT* inhibitory control training, *GNG* GoNogo, *WMT* working memory training, *A-CBM* alcohol-related memory activation + CBM, *N-CBM* neutral memory activation + CBM, *DD* drinking days, *RR* relapse rate; × = intervention showed no effect on outcome; ↑ = increase; ↓ = decrease; AC alcohol consumption, *FU* follow-up, *EMB* evaluative memory bias

seldomly been confirmed (Eberl et al. 2013), and was not supported in most published studies (Manning et al. 2021; Rinck et al. 2018; Salemink et al. 2021; Wiers et al. 2011, but see Gladwin et al. 2015). These largely negative findings could be due to the relatively poor reliability of bias assessment instruments, as discussed earlier. However, they could also indicate that we do not yet fully understand the mechanisms underlying CBM.

During the past decade, important basic research into cognitive mechanisms underlying CBM has been conducted. A specific bias in behavior (e.g., a relatively strong automatically activated tendency to approach-alcohol stimuli) can be assumed to reflect a mental-level bias (e.g., a stronger association between mental representations of alcohol and of approach actions). To the extent that CBM produces changes in this behavior, it can then be defined as a procedure that modifies this cognitive bias. Yet, it is important to understand that directly mapping (changes in) behavior onto (changes in) mental processes is problematic because it conflates the explanandum (i.e., the behavior that needs to be explained) with the explanans (i.e., the mental process with which one explains), as outlined in the functional-cognitive framework for psychological research (Hughes et al. 2016). Mental processes cannot be observed and thus can only be postulated to underlie behavior. As a result, scores on cognitive bias measurement tasks may well be explained in reference to mental processes other than originally considered. Similarly, changes in performance on these tasks (and related mediation of changes in clinical outcomes) on the basis of CBM may bear little relation to the targeted mental processes. To improve CBM (research), it is therefore important to strictly separate observable procedures and behavior (e.g., the observable bias in behavior) from explanation at the mental process level.

When CBM is defined at the procedural level (e.g., as a task that involves repeated avoidance of alcohol stimuli), theories about the mental mechanisms underlying its effects on behavior can be assessed objectively. CBM procedures typically involve conditioning (e.g., the repeated pairing of stimuli and responses) as inspired by the idea that these procedures directly change mental associations assumed to underlie addictive behavior (Phills et al. 2011; Smith and DeCoster 2000; Stacy and Wiers 2010). Yet, this associative explanation should not be taken for granted as conditioning effects do not require an associative explanation (De Houwer et al. 2020; Mitchell et al. 2009). In fact, one could argue that the bulk of scientific evidence may better fit alternative explanations (Corneille and Stahl 2018; De Houwer et al. 2020).

Accordingly, recent basic ApBM research (in healthy volunteers) suggests that its effects do not fit well with associative explanations (see Van Dessel et al. 2019 for an overview). For instance, associative theories of ApBM effects typically assume that ApBM contingencies produce automatic changes in mental associations that transfer into behavior. Yet, extensive ApBM training in healthy volunteers sometimes produces no behavior change (D. Becker et al. 2015; Cristea et al. 2016; Vandenberg and de Houwer 2011), or even reversed effects (Mertens et al. 2018). In addition, effects may depend on unexpected boundary conditions such as the belief that ApBM helps to achieve desired outcomes (Van Dessel et al. 2019). Moreover,

change in behavior can be observed on the basis of mere instructions only (Van Dessel et al. 2015). Note that while these studies were experimental studies in human volunteers with artificial stimuli, instruction-based avoidance training has also been demonstrated in problem drinkers (Moritz et al. 2019) and in smokers, where imaginal training was related to reduced craving for cigarettes a year later (Gehlenborg et al. 2021), which emphasizes the real-world relevance of these insights into possible underlying mechanisms. There is also recent research demonstrating that mere observation of stimulus-action contingencies can have effects on approach-avoidance tendencies (Van Dessel et al. 2020), although these procedures do not involve the (repeated) experience of the contingencies that is thought to be required for association formation.

These basic findings into mechanisms underlying ApBM are more readily accommodated by recent theories that explain effects on the basis of inferential processes. From this perspective, ApBM can induce changes in the automatic inferences that underlie (pathological) behavior (Van Dessel et al. 2019). For instance, during alcohol-avoidance training, patients may learn to (automatically) infer that they are willing and able to avoid alcohol. This may facilitate the implementation of similar (avoidance) actions when confronted with similar contextual cues (i.e., alcoholic drinks) in the future. This perspective fits well with the core assumption of cognitive behavior therapy (CBT), the first-choice clinical treatment of AUD in Europe, that beliefs are central in psychological suffering, and it can be used to give directions for improvements of CBM. For instance, including goal-relevant consequences of approach-avoidance actions in a CBM procedure where participants are free to choose to approach or avoid addictive stimuli produces stronger CBM effects (Van Dessel et al. 2018). This will be elaborated below (ABC training). The inferential theory of ApBM effects has shown initial heuristic, predictive, and influence value, but more research is needed to examine its value in studies with clinical groups and with other types of CBM.

CBM effects can also be explained in reference to processes at the neural level. In one study, Corinde E. Wiers et al. (2015b) investigated effects of ApBM vs. sham training on neural cue reactivity. Patients in the active training condition showed greater reductions in alcohol cue reactivity in the amygdala bilaterally, and their decreases in the right amygdala activity correlated with decreases in craving; both effects were not observed for patients in the sham-training group. These results suggest that effects on neural cue reactivity are related to the clinical effects. However, it should be noted that in the small sample recruited for fMRI research ($N = 32$), there is minimal power to find a small clinical effect, which was indeed not found, and therefore the mediation hypothesis could not be tested.

The same research team also studied the neural correlates of the change in alcohol-approach bias after ApBM (C. E. Wiers et al. 2015a), by assessing the alcohol-approach bias in the scanner (with a special joystick device without metal, $N = 26$). First, perhaps remarkably, an alcohol-approach bias was indeed found at the behavioral level. This is not self-evident for two reasons; first, as outlined above, not all alcohol-dependent patients show an approach bias (e.g., Piercy et al. 2021), and second, lying down can attenuate a neural approach reaction (Harmon-Jones and

Peterson 2009). Notably, the bias changed after ApBM at statistical trend level but not after sham training, similar to the findings of the large RCTs. The approach bias, and more specifically the alcohol pull vs. soft drink pull contrast, was related to mPFC activation. Moreover, this neural correlate of the alcohol-approach bias was more strongly reduced after ApBM training than after sham training. This reduction correlated with the behavioral change in alcohol-approach bias but not with craving. The mPFC has been related to the mental process of encoding motivational value (Hare et al. 2009, 2011), which could indicate that training helps to reduce the motivational value of alcohol, in addition to cue reactivity, which might also help to yield the add-on effects to treatment. For a review on neural correlates of CBM in general, see Wiers and Wiers (2017).

Relatedly, one area of recent research has been to add neurostimulation to CBM for AUD. It should be noted that neurostimulation has been investigated as a tool in addiction treatment by itself, with some promising recent findings (Harel et al. 2022; Zangen et al. 2021; reviews: Jansen et al. 2013; Luigjes et al. 2019). Different types of non-invasive neurostimulation have been developed, including TMS (transcranial magnetic stimulation) and tDCS (transcranial direct current stimulation). The latter type of neurostimulation has been combined with varieties of CBM in AUD. It has the advantage that the equipment is not expensive and that an active control condition can be used, which starts with a brief stimulation (less than a minute), which people often subjectively feel as an itch, similar to active stimulation (which typically lasts 15–20 min). Different brain areas can be stimulated; here typically frontal areas are stimulated (see for details the reviews and specific papers). After a proof-of-principle study in hazardous drinkers (den Uyl et al. 2016), den Uyl and colleagues (2017) combined tDCS and ApBM in AUD patients. All patients (91 in the analytical sample) received ApBM; patients in one condition received active tDCS at the same time, which was compared with a condition in which patients received sham tDCS at the same time, and a condition in which patients received active tDCS and ApBM at different times, with the goal to investigate whether learning effects in CBM could be enhanced by active neurostimulation at the same time. There was some evidence for a faster decrease of the alcohol-approach bias in the combined tDCS and ApBM condition, but this only lasted the first sessions, and overall, the approach bias changed in all patients (who all received active ApBM). There was an indication of better clinical outcomes after a year in the combined group (at statistical trend level).

In a follow-up study (den Uyl et al. 2018), a full factorial design was used, combining active vs. sham tDCS with active vs. sham AtBM ($N = 98$). The combined active training group showed a stronger negative attentional bias for alcohol (hence a stronger bias for non-alcoholic drinks) during the training sessions. No significant effects were found regarding craving (typically very low in inpatients), nor on relapse at 1-year follow-up. Finally, a recent study tested the combination of tDCS and selective inhibition (Dubuson et al. 2021), in a 2×2 factorial design ($N = 125$). A main effect of tDCS was found on short-term relapse (2 weeks), with an indication that the combination with selective inhibition leads to the best outcomes. However, these effects did not persist longer. Altogether, these results

show promise for the combination of neurostimulation and CBM, but RCTs powered for the longer-term clinical outcomes are needed.

5 Other Types of Training in AUD Treatment: Working Memory, Mindfulness

The emphasis in this chapter has been on the current status of varieties of CBM, cognitive training employing disorder-related stimuli (here alcohol cues), as an add-on in the treatment of AUD. However, it should be noted that there are also more general types of training that have been employed in the context of AUD (see also Fig. 1). First, general (neuro-) cognitive functions have been trained, like working memory (WM), and some promising results have been obtained for this type of training, in self-identified problem drinkers (Houben et al. 2011b), in AUD patients (Snider et al. 2018), and in stimulant addiction (Bickel et al. 2011). However, contrary to the findings regarding CBM, there are no studies that reported significant improvements in clinical outcomes for WM training as add-on to treatment, and the largest RCT found no effects (Wanmaker et al. 2018). This is not to say that WM training is useless in the treatment of AUD; a moderated effect was found in self-identified problem drinkers (it reduced drinking in those who were relatively fast to associate positive things with alcohol, Houben et al. 2011b), reduced impulsivity was found after WM training in people with stimulant addiction (specifically, in delay discounting, Bickel et al. 2011), and an increase in future episodic thinking was found after WM training in AUD patients (Snider et al. 2018), which can be useful in the therapeutic process, as it can be helpful in planning life after treatment. Moreover, WM training can be useful because it can increase self-efficacy in patients: actively doing something to regain their (neuro-)cognitive potential can be therapeutically meaningful (Bates et al. 2013). However, the main problem with WM training in general (most research has been done in the context of ADHD) is the often-reported lack of generalization to real-life situations (Khemiri et al. 2019; Sonuga-Barke et al. 2013). This could be remediated by matching the therapeutic intervention to the increased abilities (e.g., once episodic memory has been increased, see for further comments, Wiers 2018).

An advantage of CBM in comparison with WM training (and other forms of general function training) is that addiction-related cues are already involved in the training, which may promote the generalization to real-life situations (e.g., change the initial reaction in a risk situation, as several patients reported after returning to everyday life following treatment including ApBM, such as not going to the beer section in the supermarket or immediately closing a fridge at a party when the fridge contains beer only). Another logical next step in this line of research would be to combine WM training with CBM, and at least one study of this kind is underway (Manning et al. 2019). A different way to train executive functions, more directly related to the therapy goals, is goal-management training, which has been combined

with mindfulness meditation exercise in two small studies in polysubstance users, with promising results (Alfonso et al. 2011; Valls-Serrano et al. 2016).

Mindfulness meditation can also be regarded as a form of (non-computerized) cognitive training. It can either be incorporated into existing programs (e.g., the “urge-surfing” exercise to resist craving can be easily incorporated into CBT for AUD, Ostafin and Marlatt 2008), which is similar to how CBM is used in AUD treatment (as an add-on to regular CBT-oriented therapy). However, mindfulness-based therapy can also be a stand-alone therapy for SUDs. A recent systematic review concluded that mindfulness-based relapse prevention (MBRP) is as effective as existing evidence-based treatments for SUDs (Korecki et al. 2020). It should be noted, however, that there are several different mindfulness-based protocols for different SUDs in different stages (from indicated prevention to treatment, Korecki et al. 2020). There is ample evidence for effects on comorbid anxiety and depression symptoms (meta-analysis: Cavicchioli et al. 2018), and there are indications that the effects are partially mediated by reductions in stress and impulsivity (Korecki et al. 2020). Interesting from the perspective of this study is the finding that MBRP can lead to reduced attentional bias for substance cues (Garland et al. 2017; Spears et al. 2017, in chronic pain patients with opioid use problems and smoking cessation, respectively). A recent study found that effects of mindfulness *increased* after treatment in opioid-dependent pain patients (Garland et al. 2022), which contrasts with the typical effects of treatment (Cutler and Fishbain 2005), and CBM (Manning et al. 2022), which typically wear off. This could be related to the fact that patients can incorporate mindfulness exercises into their daily routines, also after treatment, which is not the case with the other interventions. Finally, regarding possible mechanisms in the context of this chapter, Ostafin and colleagues (2012) found that mindfulness training in heavy drinkers decoupled the predictive power of alcohol-approach associations (as assessed with an IAT) from the heavy drinking behavior: Before mindfulness training, the IAT score was predictive; after training this was no longer the case. This suggests a different mechanism than ApBM, where it has been found that the training changes the IAT scores from predominantly alcohol approach to alcohol avoid, both in heavy drinkers (Wiers et al. 2010) and in AUD patients (Wiers et al. 2011). We know of no studies combining MBRP and CBM, but this could also be an interesting avenue for further research (cf., Larsen et al. 2021).

6 Cognitive Training in (Alcohol) Addiction: New Avenues for Improvement

In addition to the avenues sketched above (combinations with general training or mindfulness and neurostimulation), there are two avenues for further research that we briefly discuss: gamification, and a new variety of training, based on emerging insights into underlying cognitive mechanisms: ABC training.

First, varieties of gamification and VR have been introduced to make CBM more attractive (or less boring) to users. This has been used primarily to make training more attractive to young substance users, in a series of studies by Boendermaker and colleagues (2015a, 2017, 2018). Results were modest, which may have been related to the target of gamification: to increase motivation to perform the training, but this in itself does not change the motivation to change the addictive behavior (e.g., binge drinking) in real life (Boendermaker et al. 2015b). In an as-yet unpublished study in AUD patients, gamified training did not outperform results of standard training; in fact, there were indications of reduced efficacy (Boffo et al. in preparation). Further, a recent RCT in patients with AUD or CUD used a gamified AtBM paradigm and found no differences with sham training (Heitmann et al. 2021), while effects have been found in AUD patients with regular ("boring") AtBM (Rinck et al. 2018; Schoenmakers et al. 2010). In conclusion, while gamification of CBM seems like a logical next step, results so far have not been very supportive, and we should not assume that it works better than traditional CBM, just because it looks more attractive. In addition to gamification (or as a gamification element), one could also bring in social elements, such as quitting together and supporting each other, not only an important element in the AA approach, but also an element in successful smoking cessation programs, when combined with contingency management (Van Den Brand et al. 2018). Contingency management (in essence using operant conditioning techniques: rewarding desired behavior such as producing drug-free urine) has been shown to be effective in different addictions, but the effects mostly disappear after discontinuing the rewards (meta-analysis: Benishek et al. 2014). For this reason, it is interesting to combine it with other elements, such as social reinforcement (Van Den Brand et al. 2018), and it could also be tried in combination with other interventions such as motivational interviewing and CBM in groups for which change is difficult to obtain, such as smoking adolescents (Kong et al. 2015). Some other studies have pioneered virtual reality (VR) versions of CBM, with first proof-of-principle studies in anxiety (Otkhmezuri et al. 2019), smoking (de Bruijn et al. 2021), and AUD (Eiler et al. 2020), which could also be used in more gamified varieties of CBM or in the conceptually new ABC training, described next.

Based on new insights into the cognitive mechanisms underlying ApBM, described above, a new variety of CBM has been proposed: ABC training (Wiers et al. 2020). CBM (including ApBM) was originally based on dual process models, either general models referring to cognitive processes in decision making and health behaviors (e.g., Hofmann et al. 2009; Strack and Deutsch 2004) or more specific models of addiction (e.g., Bechara 2005; Wiers et al. 2007). The general idea was that CBM could change relatively automatic or impulsive processes, which would provide an important addition to influencing the more reflective processes targeted in therapy (e.g., Friese et al. 2011). However, dual process models have been criticized on theoretical grounds; for example, the impulsive and reflective system cannot readily be dissociated and specific processes typically demonstrate a mixture of impulsive and reflective processes (Gladwin et al. 2011; Hommel and Wiers 2017; Keren and Schul 2009; Kruglanski and Gigerenzer 2011; Melnikoff and Bargh 2018). In addition, basic research on cognitive mechanisms underlying ApBM has

demonstrated that conscious awareness is necessary, that effects can be obtained by instruction only, and that the effects depend on important moderators such as beliefs about the implications of the learned relation, like the belief that avoiding alcohol helps to refrain from drinking (see Sect. 4, and for a review: Van Dessel et al. 2019). These results are more in line with an alternative framework: that of inferential (predictive) processing, delineated in well-supported state-of-the-art theories in cognitive neuro(science) such as predictive processing theories (Clark 2013; e.g., Friston 2010; see for an application to addiction, Wiers and Verschure 2021). From this perspective, ApBM does not produce changes in mental associations, but impacts propositional processes. Specifically, the contingencies between a stimulus, a response, and an outcome can evoke inferences (e.g., repeated avoidance of alcohol that leads to positive consequences → ‘I want to avoid alcohol’) that influence (addictive) behavior. It is assumed that all behavior is the result of the context-dependent activation of goals and inferences to achieve these goals. Note that, from this perspective, addictive behavior is goal-directed (see also Moors et al. 2017); however, the context may sometimes activate goals that lead to inferences that evoke pathological behavior and contrast with other, typically more long-term goals (e.g., health, relationships). In ABC training, these inferences are targeted more directly.

The ABC training procedure involves personally relevant antecedents (A), behaviors (B), and consequences (C). Contextual cues are important in addiction, and ABC training therefore aims to promote that relevant cues come to trigger not the addictive behavior but a personally relevant alternative behavior (B). This pattern is repeatedly practiced on the basis of consequences (Cs) that are relevant for the participant (or patient) such that the participants may learn to (automatically) infer that they will perform alternative behavior in risk situations, given the relevant positive consequences. This approach closely aligns with CBT for addiction, but adds a personalized training, in which participants repeatedly emit personally relevant alternative behaviors in risk situations, in relation to the consequences.

More specifically, in ABC training, participants are first helped to identify (1) personally relevant antecedents (e.g., coming home stressed) of the SUD, (2) alternative behaviors (Bs) that could be performed in that situation (e.g., go out for a walk, drink tea), and (3) relevant consequences of both behaviors (e.g., changes in health, money). For a given A, participants then perform training in three stages. In the first practice stage, participants react to a feature of the stimulus unrelated to the contents, and approach either the SUD-relevant stimulus or the alternative stimulus, similar to the first phase in CBM. However, the goal here is to make the personally relevant consequences of the different choices salient; for example, when the substance is approached, bars that indicate achievement of health or money goals go down, and when the alternative is performed (e.g., go for a walk), they go up. In the second slow free choice phase, participants choose themselves what they want to do in a limited set of contexts (As), and the consequences of their choices are always shown. In the third phase, participants do the same exercise under time pressure (personalized time window).

While there are no finished trials of ABC training yet, there are positive indications of potential effectiveness. First, two studies using personalized alternative behaviors in smokers found promising results (Kopetz et al. 2017; Wen et al. 2021). Second, a series of studies of ApBM including consequences in healthy students in the domain of healthy eating found better results than for regular ApBM without consequences (Van Dessel et al. 2018). Third, an as-yet unpublished first set of studies testing ABC training in healthy volunteers found promising effects (increased automatically activated negative expectancies after training compared with control training), as did a first study in volunteers of an abstinence challenge (increased rate of abstinence during the challenge compared to both traditional CBM and sham CBM). Clearly, next steps include optimizing the new intervention and testing it in AUD patients, in comparison with “traditional” ApBM.

ABC-training interventions fit well with current practice in CBT where patients learn to build new patterns of thinking (Beck and Dozois 2011). It provides patients with a context in which they can gradually gather evidence to learn these patterns and automatize their application, building on the state of the art in (cognitive) science. While this approach seems promising, ABC-training interventions still require extensive testing in studies to determine their optimal format (e.g., training in personally relevant 3D, VR, or real-life environments) and in well-designed randomized clinical trials to assess their clinical effectiveness.

7 Conclusion

Approach bias modification (ApBM) is the form of cognitive bias modification (CBM) for which most evidence has been obtained that it can be of value as an add-on in the treatment of AUD. Across multiple large RCTs, it has been found that long-term abstinence is reduced by approximately 10% when ApBM is added to treatment. It should be noted that there are also promising findings regarding other forms of CBM, such as attentional bias modification (AtBM) and selective inhibition (in the variety where rare alcohol stimuli are always inhibited), and to some extent for other forms of cognitive training such as working memory training (although not regarding the primary outcome change in addictive behaviors), as well as for non-computerized mental training in the form of mindfulness meditation.

Regarding cognitive mechanisms underlying effects of ApBM, recent research has found evidence in favor of inferential processing, rather than the associative mechanisms proposed in dual process models (e.g., effects depend on conscious awareness and expectancies, and can be achieved to some extent through instructions only). These emerging insights have led to a new variety of CBM: ABC training, which is currently tested regarding efficacy.

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New Approaches to Addiction Treatment Based on Learning and Memory



Patrick Bach and Falk Kiefer

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Abstract Preclinical studies suggest that physiological learning processes are similar to changes observed in addiction at the molecular, neuronal and structural levels. Based on the importance of classical and instrumental conditioning in the development and maintenance of addictive disorders, many have suggested cue-exposure-based extinction training of conditioned, drug-related responses as a potential treatment of addiction. Recently, the development of virtual reality-assisted cue-exposure treatment has put forward new approaches to extinction training. Recent data indicated that it may also be possible to facilitate this extinction training through pharmacological interventions that strengthen memory consolidation during cue exposure. Another potential therapeutic intervention is based on the so-called reconsolidation theory. According to this hypothesis, already-consolidated memories return to a labile state when reactivated, allowing them to undergo another phase of consolidation – reconsolidation – which can be interfered with by

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pharmacological and behavioural interventions. These approaches suggest that the extinction of drug-related memories may represent a viable treatment strategy in the future treatment of addiction.

Keywords Addiction · Cue exposure · Dependence · Extinction · LTP · Reconsolidation · Reward · Virtual reality

Abbreviations

BLA	Basolateral amygdala
CeA	Central nucleus of the amygdala
CET	Cue exposure treatment
DCS	D-cycloserine
LTD	Long-time depression
LTP	Long-term potentiation
NAc	Nucleus accumbens
NMDA	N-methyl-D-aspartate
PFC	Prefrontal cortex
VR-CET	Virtual reality-cue exposure treatment
VTA	Ventral tegmental area

1 Learning and Memory in Addiction

Substance use disorders (SUDs), including alcohol use disorder (AUD), are characterized by cravings, difficulties in controlling intake, development of tolerance and withdrawal symptoms, as well as a dramatic decline in social functioning. SUDs are chronic-relapsing diseases: even after long periods of abstinence, the risk of relapse – often precipitated by drug-associated cues – remains high (Mann et al. 2005). Several studies have suggested that three major forms of learning processes contribute to the development and maintenance of drug use: pavlovian conditioning, instrumental goal-directed learning and stimulus-response habit formation (Boening 2001; Everitt et al. 2001; Heinz et al. 2020; Hyman 2005; von der Goltz and Kiefer 2009).

Preclinical studies suggest that physiological learning processes are similar to the changes observed in addicts at the molecular, neuronal and structural levels. The brain is not a static organ, but is restructured by *neuroplastic* processes which are shaped by both stimulation and experience (Cooke and Bliss 2006; Bliss and Lomo 1973). Learning includes not only the initial perception, processing and storage of information but also the subsequent ability to orient future behaviour with regard to new information (Kandel et al. 2000). *Positive reinforcement* and *instrumental learning* play a particularly crucial role in the development of addiction. In positive

reinforced instrumental learning, consequences of hedonic behaviours initiate learning processes, in particular those that positively value the cues associated with rewards (Hyman et al. 2006). Considering the persistence of addictive disorders, it is reasonable to assume a specific and time-stable memory system. The so-called long-term memory can be broadly divided into the consciously accessible, declarative memory (or explicit memory) and the unconscious, non-declarative or *implicit memory*. Since both habit learning and simple conditioning forms are assigned to the implicit memory (as well as to the procedural memory), addiction memory is made up mainly of non-declarative contents. It has been suggested that the neuronal plasticity induced by chronic substance misuse leads to the formation of an implicit memory. Humans and animals rapidly *learn cues and contexts* that help them predict the availability of addictive drugs. Once learned, these cues and contexts initiate drug seeking, craving and relapse both in animal models and in clinical studies in humans. These observations have led to the hypothesis that addiction represents the pathological usurpation of neural processes that normally serve reward-related learning (Wise 1987). A substantial body of research suggests that several types of such neuroadaptation occur, including synapse-specific adaptations of the type thought to underlie specific, long-term associative memory (Hyman et al. 2006).

Addictive behaviour is learned predominantly via phylogenetically old brain systems involving the *mesolimbic reward system*. In this context, it has been proposed that specific learning processes and memory formation could be encoded in small groups of sparsely distributed neurons, so-called *neuronal ensembles* (Hebb 2005). An early study could already provide evidence for an ensemble-based coding in the *nucleus accumbens* (NAc), a brain region known to play a critical role in reward-based learning (Carelli et al. 1993). Following studies could show that only a minority of neurons in the NAc are active during drug seeking (Carelli and Wightman 2004), and separate populations are active in response to drug and natural rewards (Carelli et al. 2000). A recent preclinical study showed that the majority of cells in the NAc core, which were active when animals sought for cocaine, remained inactive during extinction or when mice remained in the home cage (Bobadilla et al. 2020). Using a dual cocaine and sucrose self-administration protocol, authors also found a prominent distinction between the cells constituting the cocaine – compared to the sucrose-seeking ensemble. This suggests that drugs like cocaine recruit an ensemble of NAc neurons largely distinct from neurons recruited into an ensemble coding for sucrose seeking. While the NAc can be understood as the central hub of the mesolimbic reward system, its activation and plasticity are shaped by afferent and efferent input from a large range of cortical and subcortical brain areas. Projections from the *ventral tegmental area* (VTA) of the midbrain reach into the ventral striatum, and from this relay station signals are passed on into the *prefrontal cortex* (PFC). Additionally, there are various reciprocal projections between the VTA and the hippocampus – a crucial brain area for explicit learning and memory – which links motivational and reinforcing signals together in the encoding of new cues (Lisman and Grace 2005). The core and shell areas of the *Nucleus Accumbens* (NAc) (the main part of the ventral striatum) are distinguished from each other both anatomically and functionally. While the shell region of the NAc processes the

influence of primary (unconditioned) reinforcers, the core area reacts to classically conditioned cues (Ito et al. 2004). Transient dopamine increases within the VTA-NAc circuit were implicated in mediating positive reinforced learning (Lüscher et al. 2020). In contrast, the medial habenula was implicated in withdrawal-induced dysphoria and negative reinforcement. It inhibits VTA dopamine release via its projections to the lateral habenula, which project to GABA neurons in the tail of the VTA that inhibit VTA dopamine neurons (Mechling et al. 2016). Other regions, which were implicated in negative reinforcement are the basolateral amygdala (BLA), the paraventricular thalamus (Beyeler 2016) and the amygdala (Grimm et al. 2001). The BLA also mediates the formation of associations between motivational and emotionally relevant events, and helps mediate behavioural responses to previously conditioned cues (Everitt and Robbins 2005). Furthermore, the ventral pallidum, which receives direct and indirect input from D1 and D2 medium spiny neuron populations of the NAc, has been implicated as an important hub for the integration of positive and negative reinforcement (Wulff et al. 2019). The change from reward-dependent learning to habitual and compulsive drug-seeking and drug use were associated with neural plasticity within the striato-cortical circuits. Specifically, drug-associated plasticity in the VTA had been reported, which in turn drives potentiation of excitatory afferents in the NAc and subsequently in dorsal-lateral corticostriatal areas, including the DS (Mameli et al. 2009). The shift from VS to DS engagement was associated with a shift from reward-driven to compulsive drug use (Robinson et al. 2013). For example, cocaine administration leads to long-term increases in tonic DA firing by potentiating the GABAergic input of D1 receptor medium spiny neurons on midbrain GABAergic neurons (Bocklisch et al. 2013). In addition, plasticity in striato-cortical projections was implicated in the development of habitual and compulsive drug use. Specifically, neurons from the medial PFC that project to the NAc are activated by aversive stimuli. These neurons mediate control of reward-seeking behaviour in the face of imminent punishment (Kim et al. 2017). Imaging studies have shown the prefrontal cortex to be central to attention, decision-making and executive functions in the pathogenesis of addictive behaviour (Goldstein and Volkow 2002; Kalivas and Volkow 2005). The mPFC-NAc connection however seems to get weakened in addiction through plasticity progressive potentiation of excitatory afferents in dorsal-lateral corticostriatal areas and engagement of the orbitofrontal cortex (*OFC*) (Volkow et al. 2005). A preclinical study could show that activity-dependent ablation of a neuronal ensemble in the infralimbic but not the prelimbic subregion of the PFC induced excessive alcohol seeking in rats (Pfarr et al. 2015). Results indicated a specificity of this neuronal ensemble for cue-induced drug seeking responses, as stress-induced reinstatement of drug-seeking was not affected by the ablation. A further study by the same group in Wistar rats found that cue-induced seeking of either alcohol or saccharin-activated ensembles of similar size and organization in the infralimbic cortex with largely overlapping neuronal populations (Pfarr et al. 2018). The data that functional output depends on specific neuronal ensembles within a given brain region rather than on the global activity of that region are compatible with the idea that cue memories might be represented in local

neuronal networks or neuronal ensembles. Studies investigating neuronal ensembles recruited at different stages of addiction revealed a sparse but broad distribution of activated cells across brain regions (see (Salery et al. 2021) for review). This suggests that learning of specific contexts at specific times can be encoded in distinct but interconnected neuronal ensembles. A recent study found that cells expressing immediate early genes, which were activated by cocaine administration, can form spatially defined clusters whose size is correlated with their level of activation (Gonzales et al. 2020). Further studies could show that the induction of an immediate early gene program in cocaine-activated cells provides an experience-specific transcriptional signature that is sufficient to recapitulate drug responses (Savell et al. 2020). In addition, the observed coexistence of neuronal ensembles that encode distinct experiences suggests complex patterns of intermingled ensembles and subtle mechanisms of cellular allocation to an ensemble, which highlights the importance of coupling permanent tagging of activated cells with wide-range tracing to achieve an extensive characterization of broadly distributed engrams (see Salery et al. (2021) and Körber and Sommer (2022) for review). In addition, it has been proposed that prolonged exposure to alcohol leads to neuroadaptations within the mPFC resulting in altered glutamatergic and BDNF-mediated signalling, as well as calcium homeostasis (Heilig et al. 2017). Recent evidence also indicates that prolonged alcohol exposure results in a DNA hypermethylation of the mPFC genome, which was linked to an altered activity of epigenetic enzymes that modify histone function (Heilig et al. 2017). These alcohol-induced modulations are thought to cause functional impairments that interfere with mechanisms of top-down control of motivational and emotional processes.

A recent neuroimaging study showed a blunted mPFC and VS response in individuals with stronger alcohol withdrawal symptoms and a higher DS response in these individuals, compared to patients with lower withdrawal intensity (Sinha et al. 2022). Interestingly, prazosin administration reversed this mPFC-striatal dysfunction, which in turn predicted fewer drinking days. This suggests that pharmaceutical interventions targeting the mPFC-striatal circuits might provide effective treatment approaches.

In contrast to the mPFC, the OFC was associated with increased craving and “overevaluation” of addictive stimuli (Koob and Volkow 2016). Neurons from the OFC project mainly to the DS and artificial potentiation of OFC-DS synapses induces compulsive behaviour in previously non-compulsive mice, supporting the role of the OFC in compulsive drug-seeking (Pascoli et al. 2018).

2 Dopamine and Glutamate: Key Molecules

Dopamine plays a central role in reward-related learning (Wise 2004). Directly or indirectly, all addictive drugs (including alcohol) increase levels of synaptic dopamine within the nucleus accumbens (Di Chiara and Imperato 1988). In a series of experiments, Schultz et al. (1997) investigated the circumstances under which

midbrain dopamine neurons fire in the context of reward. They found phasic bursts of dopamine transmission to be related to a reward-predicting, conditioned stimulus (i.e. a light or a tone), and not to the reward itself. The firing rate of dopamine neurons pauses following unreinforced exposure to stimuli that were previously associated with a following reward. They hypothesized that these phasic bursts and breaks together encode a prediction-error signal, and that they represent the neuronal basis for conditioning and extinction of drug–cue associations. In their “**Incentive Sensitization Theory of Addiction**” Robinson and Berridge (1993, 1998, 2000, 2001) make the assumption that the neuroadaptations that follow from repeated drug consumption render mesolimbic circuits hypersensitive to drugs and drug-associated stimuli. They therefore hypothesize that drug-associated stimuli both capture one’s attention and are motivationally salient (“incentive salience”). They emphasize that the sensitization of reward pathways does not only relate to the emotional evaluation of the drug (liking), but more importantly relates to the incentive salience of drug-related cues (wanting). The important point that Robinson and Berridge emphasize is that a history of drug learning may lead to implicit drug memories that are not accessible to conscious remembering, and that drug-related cues may therefore trigger automatic, drug-related responses the person is not necessarily aware of (see also McCusker 2001).

The similarities between “normal” learning and addiction begin with the fact that all addictive substances share the ability to increase dopamine concentrations in the NAc via projections from the VTA (Di Chiara and Imperato 1988). Computer models of reward-associated learning have been used to extend results from preclinical studies on the role of dopamine, in order to better represent the neuronal basis for the conditioning of drug–cue associations (Montague et al. 2004). These computer models are based on the hypothesis that individuals tend to direct their behaviour to increase the likelihood of obtaining future rewards. The reward system encodes its prediction of reward either as “better than expected,” with a phasic increase (positive prediction error), or “worse than expected,” with a phasic decrease (negative prediction error) of dopaminergic transmission (Schultz et al. 1997). Initially, drug-induced increases in mesolimbic dopaminergic transmission generate the signal “better than expected”, independently of the subjective hedonic effect of the substance. In contrast to natural rewards, drugs induce lasting mesolimbic dopamine surges, which have been proposed to drive “overevaluation” of drug-associated cues and to promote drug seeking at the expense of other competing behaviours. Different drug classes increase the dopamine level in the NAc, particularly by promoting dopamine release from neurons that project from the VTA (Scofield et al. 2016). These dopamine surges are thought to be an important neurobiological correlate of initial reinforcement of drug use. It was proposed that the dopamine signals promote plasticity in corticostriatal circuits, which underly positive and negative reinforcement (Pascoli et al. 2014; Scofield et al. 2016; Valjent et al. 2004). The plastic changes which are initiated in the VTA-NAc circuit may propagate to dorsal striatal (DS) and corticostriatal circuits, thereby modifying the engagement of different behavioural control circuits. Specifically, the strength of the projections from the prefrontal cortex (PFC) and orbitofrontal cortex (OFC) to the DS is thought to

underly control of goal-directed drug-taking behaviour (Lüscher et al. 2020). Protracted substance use results in a disinhibition of DA neurons on the VTA and also the Substantia nigra pars compacta (SNs), which facilitates the recruitment of the DS and is modulated by afferent inputs from the central nucleus of the amygdala (CeA). This progressive engagement of the DS is thought to underly the maintenance of drug use. Prolonged drug use can result in compulsive drug taking, which can be understood as behaviour, which persists despite negative consequences. Two alternative models were proposed as theoretical framework for explaining compulsive drug use. The “loss-of-function” model states that a loss of “top-down” control from the PFC towards the striatum is underlying compulsive drug use. This model is supported by human (Ersche et al. 2013) and animal data (Schoenbaum and Shaham 2008) showing impairments in grey matter and with matter volume and integrity in dependent individuals. Although the specific cellular correlates have not been identified yet, widespread impairments in the frontal brain structure render executive control deficits very likely, such as loss of frontal control over drug-seeking and drug-taking as a consequence of inferior frontal cortex dysfunction (Lüscher et al. 2020). A “gain of function” model has been debated for explaining compulsive drug use in the early phases of an addiction. This model suggests a “gain of function” in the OFC-DS connectivity as the basis for an overvaluation of the reinforcing value of drugs. This model is supported by animal data, which showed that OFC-DS synapses were potentiated in mice that showed compulsive drug seeking despite punishment compared to animals that did not show compulsive behaviours (Pascoli et al. 2015). The two models are not mutually exclusive, but it is most likely that the “gain-of-function” model best describes compulsive drug taking in the earlier stages of an addiction while the “loss-of-function” model better describes the situation in prolonged dependence, during which profound deficits in cognitive and executive functioning are observed (Bechara et al. 2001; Rogers et al. 1999).

Although it remains controversial whether it is the dopaminergic transmission itself that initiates learning processes, or whether these processes are caused indirectly with the help of other neuronal systems, we do know that dopamine promotes memory consolidation, and that a blockage of dopaminergic transmission has the opposite effect (Dalley et al. 2005; Lisman and Grace 2005). Changes in dopaminergic neurotransmission have not only been observed during development and maintenance of addiction, but also during withdrawal. Combined preclinical and postmortem studies have indicated a dynamic shift of dopaminergic neurotransmission during early abstinence (3 weeks) in which a strong downregulation of D1-receptors and dopamine transporters (DAT) was found during early abstinence, while D2-like receptor binding was unaffected. After 3 weeks of abstinence, data showed elevated extracellular DA levels, lack of synaptic response to D1 stimulation, and augmented motor activity, indicative of a hyperdopaminergic state (Hirth et al. 2016). A recent review of preclinical and clinical data corroborated these findings, indicating a changing dopaminergic signalling over time, thus suggesting a highly dynamic regulation of the reward system during abstinence (Hansson et al. 2019).

Glutamate neurotransmission is altered by drug actions within the central nervous system either directly via actions on N-methyl-D-aspartic acid (NMDA)-receptors, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and metabotropic glutamate receptors (mGluR) of different subtypes (D'Souza 2015). Whereas the dopamine system mediates cue-induced “wanting,” the glutamatergic system seems to be involved in learning processes that mediate sensitization. A growing body of evidence suggests that the beginning of sensitization after exposure to an addictive drug is dependent on glutamatergic transmission mediating NMDA-receptor-dependent LTP at excitatory synapses in the mesolimbic dopamine system (for a review, see (Scofield et al. 2016)). Such NMDA-receptor-dependent and LTP-mediated synaptic plasticity is known to be one of the basic mechanisms of learning and memory consolidation. Glutamatergic signals in the NAc and cortical regions are tightly interlinked with dopaminergic activity in these areas and drug-induced dopamine releases in the NAc can modulate excitatory glutamatergic transmission. For example, cocaine induces increases in synaptic dopamine levels, which in turn activates presynaptic and postsynaptic D1 dopamine receptors, which increases glutamatergic neurotransmission (Pierce et al. 1996b). For alcohol, in vivo microdialysis studies reported alcohol-induced increases of glutamate levels (Moghaddam and Bolinao 1994), possibly due to inhibition of GABA interneurons that in turn inhibit presynaptic glutamate terminals and via activation of D1 receptors (Deng et al. 2009). In addition, alcohol and drugs seem to progressively facilitate presynaptic and postsynaptic glutamate transmission, which was reported for the amygdala (Zhu et al. 2007). Drug-induced alterations in glutamatergic neurotransmission play a role in learning, such as instrumental learning and pavlovian conditioning. Specifically, changes in glutamatergic neurotransmission in the NAc were implicated in response-reinforcement learning during the acquisition of food-reinforced responding (Kelley et al. 1997). Contrary, the injection of an NMDA receptor antagonist (AP-5) into the NAc impaired the acquisition of food-reinforced responses. Furthermore, co-administration of low doses of a D1 receptor antagonist (SCH23390) together with AP-5 potentiated the impairment in the acquisition of instrumental learning, which was observed for the single drugs. This suggests that a glutamate–dopamine interaction might be a key mechanism in the acquisition of positive-reinforced instrumental learning (Smith-Roe and Kelley 2000). In addition, repeated cocaine or amphetamine administration enhances the responsiveness to glutamatergic transmission within mesolimbic dopamine neurons (White et al. 1995; Zhang et al. 1997) and alters the expression of glutamate receptor subunits, in particular, in the mesolimbic system (Ghasemzadeh et al. 1999), as well as increasing the responsivity of the mesolimbic glutamatergic system (Pierce et al. 1996a). Furthermore, cocaine administration can produce NMDA receptor-dependent long-term potentiation at excitatory synapses on dopaminergic cells in the VTA (Ungless et al. 2001) and also a long-term depression at excitatory synapses between afferents from the PFC and NAc dopamine neurons that lasts for at least 2 weeks (Thomas et al. 2001). These findings also align with the supposed transient role of the VTA in the initiation of sensitization, while the NAc is supposed to take

over a more important role for maintained sensitization (van Huijstee and Mansvelder 2015).

Disruptions in glutamate homeostasis following drug use were reported for different glutamate receptor types (e.g. NMDA, AMPA receptors and mGluR) and also for different subtypes of glutamate transporters (e.g. GLT-1 and EAATs) (Spencer and Kalivas 2017). Recent studies implicated the role of mGluR2 receptors in the control over drug-seeking. mGluR2 deficits were found after chronic alcohol exposure in the infralimbic cortex of rats. In addition, the escalation of ethanol seeking in these rats was abolished by restoring mGluR2 expression in the infralimbic cortex via viral-mediated gene transfer (Meinhardt et al. 2013). In contrast, a neuron-specific prefrontal mGluR2 knockdown created a phenotype of excessive alcohol seeking, further supporting the role of frontal mGluR2 receptors in escalating drug seeking (Meinhardt et al. 2021). Further studies have shown that amphetamine administration reduces glutamate transporter (EEAT) function in midbrain dopamine neurons, resulting in potentiated glutamatergic transmission (Underhill et al. 2014; Wan et al. 2017). Acute administration of cocaine similarly induces long-term potentiation in VTA dopamine cells, which is hypothesized to contribute to the transition to compulsive drug use (Lüscher et al. 2020).

3 The Role of LTP and Neural Plasticity in Addiction

The persistence of addictive behaviour, in particular the long-lasting risk of relapse, presumably depends on the time-stability of implicit drug-associated memories. The question of how memories persist is therefore highly relevant to understanding how addictive disorders are maintained. As with the case of physiological long-term memory (Kandel et al. 2000), we can assume that there are processes on the synaptic level involved. The physical reorganization of synapses and networks can also be assumed to play a role (Chklovskii et al. 2004). In 1973, Bliss and Lomo found repetitive stimulation of afferent fibres to result in reinforced and long-lasting synaptic transmissions (Bliss and Lomo 1973). The authors called this phenomenon “**long-term potentiation**” (LTP), and the reverse process “long-time depression” (LTD). Metabotropic Glutamate receptors and NMDA receptors play a critical role in the induction of LTP. Both LTP and LTD are well-established physiological models that are capable of explaining the associative modulation of synaptic connections and experience-dependent plasticity within the brain (Malenka 2003; Lüscher and Huber 2010).

Numerous studies have shown an induction of LTP by dopaminergic transmission at the cellular level (Jay 2003). Furthermore, a growing body of evidence suggests that the initiation of sensitization, after exposure to an addictive drug, depends on the glutamatergic transmission that mediates NMDA-receptor-dependent LTP, which takes place at excitatory synapses in the mesolimbic dopamine system (Kauer 2004). Behavioural sensitization, indicated by increased locomotor reaction after repeated drug application, is an important animal model that is useful

for studying drug-induced neuronal adaptations (Kauer 2004). An early study already demonstrated that cocaine-induced behavioural sensitization can be blocked by NMDA-receptor antagonists (Karler et al. 1989). This finding formed the basis for the hypothesis that addictive drugs initiate plastic changes to dopaminergic synapses in the VTA via LTP (Ungless et al. 2001) and that these plastic changes may underlie the persistence of drug-seeking behaviour (Engblom et al. 2008). Several drugs have been demonstrated to cause LTP in the VTA (Saal et al. 2003). Pharmacological blockades of NMDA receptors in the VTA have been shown to decrease both conditioned place preference induced by cocaine administration as well as behavioural sensitization (Harris and Aston-Jones 2003). Following studies have demonstrated that addictive drugs induce potentiation of excitatory dopaminergic synapses in the VTA and also in other brain areas involved in addictive disorders, such as the NAc and the PFC (Hyman et al. 2006; Kauer 2004; Kauer and Malenka 2007; Mameli et al. 2009).

Recent preclinical data showed that dopamine acutely modulates excitatory transmission via effects on NMDA and AMPA receptors and, importantly, induces lasting alterations of afferent transmission onto dopamine D1 medium spiny neurons (D1R-MSNs) in the NAc, which in turn promote excitatory glutamatergic neurotransmission via increasing the numbers of postsynaptic AMPA receptors (Pascoli et al. 2014; Valjent et al. 2004). The coincidence of heightened D1R-MSNs activation and glutamatergic neurotransmission promotes LTP and potentiation of excitatory cortical and hippocampal afferents and thus altering circuit function (van Zessen et al. 2021). In contrast, the dopamine D2 receptor (D2R) MSN population in the NAc that prevent the induction of LTP are silenced by cocaine administration, suggesting a dichotomy between D1R-MSNs and D2R-MSNs in the NAc. This recent data highlights the intricate interaction between dopaminergic and glutamatergic neurotransmission on LTP in mediating learning processes in addiction.

4 Treatment Approaches: Cue-Exposure Therapy

Because of the importance of both classical and instrumental conditioning in the development and maintenance of addictive disorders, many have advocated for *cue-exposure-based extinction training* (CET) of conditioned drug-related responses as a potentially effective treatment for addiction (e.g. Drummond et al. 1990; Loeber and Mann 2006) (Fig. 1). We still know very little about the neurobiological effects of such psychotherapeutic interventions, but this proposed treatment can be compared to existing extinction therapies currently used to treat several other psychiatric disorders. Still, a randomized controlled study by our own workgroup provided the first evidence that CET (i.e. nine CET sessions over 3 weeks vs. treatment as usual) can reduce alcohol cue-induced brain activation in the anterior cingulate gyrus and the insula, as well as limbic and frontal regions (Vollstadt-Klein et al. 2011). CET exposes drug addicts to conditioned drug stimuli as a means of reducing drug

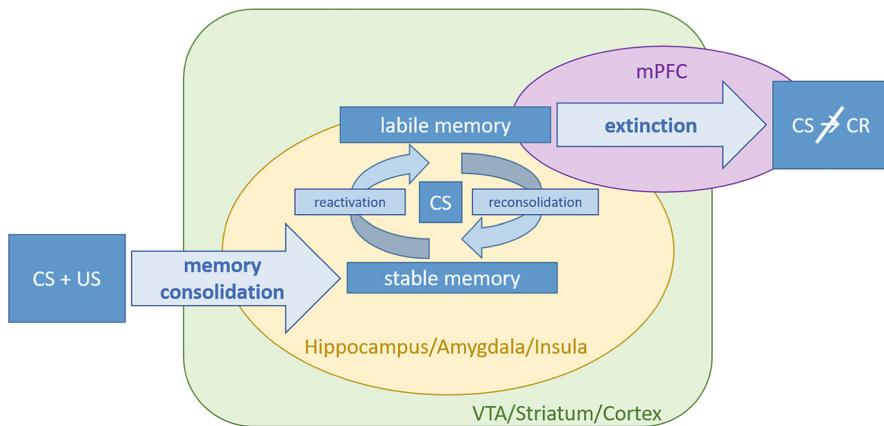


Fig. 1 Schematic depiction of addiction memory processes, associated brain regions and treatment strategies: i] *cue-exposure-based treatments* aim at decoupling the association between a conditioned stimulus (CS) and conditioned reactions (CR), in order to, e.g. reduce the likelihood that alcohol cue-exposure triggers following alcohol use. Conceptually, repeated exposure to the CS (e.g. sight and smell of alcohol) in a controlled setting without following alcohol use (CR) promotes extinction of the CS–CR association; ii) *treatments targeting the reconsolidation of alcohol-memory traces* aim at destabilizing drug-memories. Conceptually, memory traces switch to a labile state, when they are re-activated by e.g. re-exposure to drug cues (CS) and their reconsolidation can be impaired by pharmacological and non-pharmacological interventions. The ventral tegmental area (VTA), the striatum and cortical regions contribute to the formation of drug memories and CS–CR associations. The hippocampus, amygdala and insula are associated with storing drug memories. The medial prefrontal cortex (mPFC) is associated with extinction learning and modulation of CS–CR association (see Text for details)

cravings (Drummond et al. 1990; Monti et al. 1993; Rohsenow et al. 2001; Sitharthan et al. 1997). In these treatments, patients with AUD are exposed to the sight and smell of their preferred beverages in a controlled environment to help them learn to control their conditioned reactions, and thus to avoid behaviours that could lead to relapse. One meta-analysis evaluated the general effectiveness of this procedure positively (Conklin and Tiffany 2002; meta-analysis by Chambliss and Ollendick 2001). The effect sizes for the above-cited studies, regarding a reduced amount of ethanol consumed, including abstinence, vary between $d = 0.17$ (Drummond and Glaudier 1994), $d = 0.54$ (Rohsenow et al. 2001); $d = 0.61$ (Sitharthan et al. 1997) and $d = 0.74$ (Monti et al. 1993; for a review, see Conklin and Tiffany 2002). A recent meta-analysis summarizing the result of seven studies with 447 participants (range 35–195), including the studies above, reported that CET showed no significant average effect on the number of drinking days after 3 months ($g = 0.07$; 95% CI –0.34 to 0.49) and only a small average effect in favour of CET after 6 months ($g = -0.21$; 95%CI –0.48 to 0.06) (Mellentin et al. 2017). Likewise, CET showed no overall effect on drinks per day after either 3 ($g = -0.07$; 95% CI –0.48 to 0.34) or 6 months ($g = -0.16$; 95% CI –0.52 to 0.19>). Furthermore, no significant effect of CET on the number of heavy drinking days was observed after 6 months

($g = -0.02$; 95% CI -0.38 to 0.41). In the single study that assessed the number of heavy drinking days after a 12-month period, the standard mean deviation was reported as -0.22 (95% CI -0.64 – 0.21), indicating a small effect. Concerning secondary outcomes, the meta-analysis reported a small effect in favour of CET on total drinking scores ($g = -0.21$; 95% CI -0.78 to 0.37) and a moderate effect on the latency to relapse ($SMD = -0.68$; 95% CI -1.40 to 0.04), which was however only reported by a single study. Concerning alcohol craving, there was insufficient data to allow the calculation of an average effect size. It should be noted that the overall risk of bias of the included studies was deemed high, which should lead to cautious interpretation of the results. Comparing the effects of different types of CET, the authors report that CET combined with urge-specific coping skills (USCS) may be more effective than conventional approaches. The distinguishing feature of USCS (plus CET) is that USCS are supposed to be used in the presence of alcohol cues, when conditioned responses are elicited, in order to facilitate the extinction of alcohol-associated responses. Indeed, drinking outcomes in a clinical trial with 165 patients, after 6 and 12 months, were significantly associated with urge-specific coping strategies taught in the framework of CET (Dolan et al. 2013). Comparison of CET against different control interventions (i.e. cognitive behavioural therapy [CBT], relaxation techniques [RT] or daily contacts) showed that the effects of CET compared against CBT were smaller, compared to other active comparisons. This however does not come as a surprise, because the efficacy of CBT in treating AUD has been repeatedly demonstrated, sharing several therapeutic elements with CET, while there is more uncertainty about RT (Berglund et al. 2003).

An early study by Monti et al. (1993) reported a significant reduction of cravings after cue-exposure treatment, but only for patients who were initially reacting with an urge to drink alcohol when exposed to the sight and smell of an alcoholic beverage. Similar findings were reported by Scheurich et al. (2004). These results suggest that cue-exposure training may only be an effective treatment for patients who already display cue reactivity before beginning training. In any case, in order to measure the effects of cue-reactivity in humans, one must first define valid read-outs of cue-induced mesolimbic dopaminergic activation. The investigation of neural alcohol cue reactivity drew some attention in this regard, because molecular neuro-imaging studies showed an association between dopamine signals in the mesocorticolimbic system and the fMRI signals, as well as with subjective alcohol craving (Heinz et al. 2004, 2005). In addition, our own workgroup could show that CET reduced neural alcohol cue reactivity in anterior cingulate cortex, the insula in parts of the inferior frontal gyrus (Vollstadt-Klein et al. 2011). Recent studies by our workgroup could also confirm an acceptable reliability and robustness of neural alcohol cue reactivity, captured using fMRI (Bach et al. 2022). Additional imaging studies could repeatedly demonstrate an association between neural alcohol cue reactivity in the striatum and relapse risk (Bach et al. 2020; Reinhard et al. 2015), as well as response to naltrexone treatment (Bach et al. 2021; Mann et al. 2014; Schacht et al. 2017). In addition, studies using real-time fMRI neurofeedback in order to train participants to reduce their neural alcohol cue reactivity showed a significant training effect on striatal and prefrontal brain activation (Kirsch et al.

2016). Taken, together, these findings suggest that neural alcohol cue reactivity might be a read-out that can be used in order to detect the effects of CET and identify suitable patients.

These results taken together suggest that cue-exposure training may represent a viable therapeutic intervention for addiction with small to medium overall effects on drinking outcomes.

5 Novel Treatment Approaches: Virtual Reality Cue-Exposure Therapy

Recently, there has also been interest in whether novel technologies can improve the effects or increase the accessibility of CET. Especially, virtual reality (VR) has been used to create new virtual environments for CET. VR is a versatile tool to create realistic simulations of alcohol cues and drinking situations. The VR environments can be accessed using either goggles or VR-caves, i.e. an immersive virtual reality environment where projectors are directed to the walls of a room-sized cube. Participants can interact with the virtual environment through a range of input devices. In VR environments visual, auditory and various other sensations can be presented to users to enhance immersion. An early study compared the effects of visual, olfactory and auditory alcohol cues against matching neutral cues in a virtual environment on subjective alcohol craving in participants with AUD (Bordnick et al. 2008). Authors reported that all types of alcohol stimuli significantly increased craving compared to neutral cues. Further studies using different cues (e.g. alcohol bottles, bar, party scenario) provided evidence that VR cue exposure elicits craving in individuals with AUD (Bordnick et al. 2008; Kim and Lee 2015; Ryan et al. 2010; Traylor et al. 2011). Several studies have also evaluated the effect of virtual cue-exposure therapy (VR-CET) on alcohol craving in AUD (Choi and Lee 2015; Lee et al. 2009; Son et al. 2015). The study by Lee et al. (2009) reported that Virtual Cue-Exposure Therapy (VR-CET), including relaxation, craving and aversive exposure guided by a therapist, was more effective than CBT in reducing alcohol craving after 10 biweekly sessions. Choi and Lee (2015) could also show that a single VR-CET session, consisting of aversive social situations, significantly reduced alcohol craving in heavy social drinkers compared to light drinkers. There are also reports that VR-CET may attenuate approach bias, indicating the potential of VR-CET to reduce automatic action tendencies towards alcohol stimuli (Kim and Lee 2019). Recent analyses of data from an ongoing clinical trial compared the efficacy of VR-CET against CBT in reducing alcohol craving in a sample of eight patients (Ghiță et al. 2019). The authors reported that both, VR-CET and CBT, significantly reduced craving and anxiety. While these preliminary results have to be confirmed, they support the potential of VR technology in the treatment of AUD. A recent randomized prospective cohort study in 42 outpatients with AUD compared the effects of VR-CET (six sessions) plus treatment as usual (TAU) against treatment

as usual only (Hernández-Serrano et al. 2020). The authors reported a greater craving reduction in the TAU + VR-CET group compared to the TAU group and a significantly higher odds ratio of about 18 for improvement of craving from pre- to post-treatment in the VR-CET + TAU group.

Available preliminary data support the potential of VR-CET for treating patients with AUD. The high degree of immersion and individualization could be factors that promote the efficacy of VR-CET beyond that of classical CET. Still, further investigations are needed to determine the efficacy of VR-CET in AUD and assess the relevance of potential side effects that have to be considered, such as cybersickness, depersonalization, derealization, and dysfunctional re-entry into the real world.

6 Targeting the Reconsolidation of Drug Memories

Preclinical studies suggested that the so-called *reconsolidation* theory might provide the basis for a possible therapeutic intervention at the level of protein biosynthesis and subsequent neuroplasticity.

Gene activation and subsequent protein biosynthesis are necessary to consolidate long-term memory, which is then presumed to remain as a stabilized memory trace. Misanin et al. (1968) challenged this view, proposing that memories become vulnerable to change or loss once they are activated (Misanin et al. 1968). Their work led to the formulation of the reconsolidation hypothesis, which states that reactivation returns already-consolidated memories to a labile state, enabling them to undergo another phase of consolidation, the so-called reconsolidation phase. These reactivated memories are thought to remain unstable for up to 6 h (Walker et al. 2003, Duvarci and Nader 2004), behaving like an adaptive update mechanism, thereby allowing new information to be added (Alberini 2005). During this time window, the destabilized memories are thought to be susceptible to interference, which could potentially impede their ability to reconsolidate. This could open up a powerful avenue for the treatment of psychiatric disorders in which maladaptive memories play a major role, such as addiction. Several preclinical studies have demonstrated memory reconsolidation by using pharmacological blockade of memory reconsolidation. The pharmacological interventions that were used to interfere with memory reconsolidation can be grouped into three categories: protein-synthesis inhibitors, NMDA-receptor modulators and β -adrenergic receptor modulators (for review, see Alberini 2005; Tronson and Taylor 2007; Lee 2009).

6.1 NMDA Receptor Blockade

Blockade of NMDA receptors was the first manipulation reported to interfere with the reconsolidation of alcohol-associated memories. An early study could show that administration of the NMDA receptor antagonist *MK-801* (0.1 mg/kg, ip)

immediately following re-exposure to previously conditioned alcohol cues in rats reduced cue-induced alcohol seeking (von der Goltz et al. 2009). A following study by Wouda et al. (2010) reported that three repeated test sessions (6 days apart), comprising of an administration of MK-801 (0.1 mg/kg) or saline in rats, 20 min after a re-exposure to previously conditioned alcohol cues, only resulted in a trend towards a reduction in alcohol-seeking (Wouda et al. 2010). In a study by Milton et al. (2012), a different administration schedule of MK-801 (0.1 mg/kg, ip), 30 min before, rather than after, the alcohol cue re-exposure yielded similar response rates to alcohol-paired and unpaired cues in rats receiving MK-801, while rats receiving saline showed increased response rates to alcohol-paired cues (Milton et al. 2012). This suggests that NMDA receptor blockade disrupted the reconsolidation of alcohol-cue memories. These results however could not be replicated in a following study by the same workgroup that used a different operant conditioning paradigm. In this study, MK-801 administration before a short non-reinforced lever-responding session failed to reduce alcohol seeking in rats (Puaud et al. 2018). These divergent results might indicate that the reconsolidation of operant (instrumental) memories (Puaud et al. 2018) is less easily disrupted by the administration of NMDA receptor antagonists, compared to classically conditioned memories (Milton et al. 2012). In line with this idea, studies indicated that modification of memories underlying operant behaviours is challenging, but might be feasible through adjustment of memory retrieval procedures (Luo et al. 2015). Further preclinical studies that investigated the NMDA receptor antagonist *memantine* showed that administration of memantine (20 mg/kg, ip) immediately after alcohol cue-memory retrieval and 4 h later resulted in reduced response rates to an alcohol-associated lever (Vengeliene et al. 2015). However, the authors also observed a reduction in alcohol seeking in rats without a prior memory retrieval session. This suggests that memantine affected alcohol seeking irrespective of memory reconsolidation processes.

A study in individuals with heavy alcohol use (not meeting the criteria of an AUD) showed that infusions of ketamine (concentrations were maintained at 350 ng/dl for 30 min using a pharmacokinetic infusion model), following a brief retrieval of maladaptive cue-alcohol memories, significantly reduced the urge to drink alcohol and the number of drinking days per week and volume of alcohol consumed during follow-up (Das et al. 2019). In addition, the blood concentrations of ketamine during the “memory reconsolidation window” predicted the extent of changes following memory retrieval. These findings suggest that NMDA receptor blockade has the capacity to reduce alcohol consumption in humans.

An additional compound which drew some attention is *D-cycloserine* (DCS). DCS is an agonist at the glycine binding site of the NMDA receptor and increases cellular calcium influx, which in turn triggers several intracellular cascades that are critical for memory formation.

An early preclinical study showed that DCS accelerated the reduction of cocaine-induced conditioned place preference in rats (Botreau et al. 2006), suggesting that it might be a useful novel tool to facilitate the effects of extinction training on cue reactivity and cue-induced relapse mechanisms in addiction treatment (Davis et al. 2006). Two following clinical studies have provided evidence that DCS improves

the outcomes of exposure therapy in patients with acrophobia (Ressler et al. 2004) and social anxiety disorder (Hofmann et al. 2006). There is also preclinical evidence in rats to suggest that DCS can facilitate the extinction of conditioned alcohol seeking (Vengeliene et al. 2008). Three RCTs have examined the effects of DCS (50–250 mg) on CET in abstinent patients with AUD (single-dose of 250 mg DCS vs. placebo before the CET session) (Watson et al. 2011), heavy drinkers (single dose of 125 mg vs. placebo before CET session) (Kamboj et al. 2011) and problem drinkers (50 mg DCS vs. placebo three times before each CET session) (Hofmann et al. 2012). None of these trials could detect a significant advantage of DCS plus CET compared to placebo on alcohol craving or secondary outcome measures. These results question the efficacy of DCS, but the high proportion of subjects with little or no response to the cue-exposure sessions could have limited the capacity to detect the effect of DCS. A more recent RCT of our workgroup investigated the effects of DCS vs. placebo, combined with CET (50 mg DCS vs. placebo before each of nine CET sessions, which were spaced over 3 weeks) on mesolimbic cue reactivity, craving and relapse in abstinent alcohol-dependent patients (Kiefer et al. 2015). Following treatment, the CET plus DCS group showed reduced alcohol cue-induced brain activation in the ventral and dorsal striatum compared to the CET plus placebo treatment group. In addition, a higher posttreatment ventral striatal cue reactivity was associated with increased craving and relapse risk during follow-up. These results might indicate that a longer treatment duration is necessary, in order for DCS to exert detectable effects and that DCS-induced effects on addictive phenotypes might be subtle. Another recent placebo-controlled clinical study reported a significant effect of DCS augmentation (50 mg) on alcohol cue-elicited cravings in patients that responded to a previous cue exposure with an increase in craving (i.e. evidence for a positive alcohol cue reactivity) (MacKillop et al. 2015). However, two following clinical studies investigating DCS in cocaine-dependent cigarette smokers reported no significant craving reduction (Yoon et al. 2013) or even an increase in craving for cocaine in patients receiving DCS (Price et al. 2013). It has been argued that these mixed findings might be attributable to issues related to sample size, DCS administration (e.g. timing), and participant characteristics. Specifically, intervals longer than 1 h between DCS administration and cue-exposure sessions seem to attenuate DCS effects. Likewise, application of DCS in non-clinical or mixed samples might have contributed to mixed findings (Myers and Carlezon 2012). It seems important that future studies take these factors into account.

In summary, studies investigating the effects of NMDA receptor antagonism on memory reconsolidation and alcohol response yielded conflicting, yet promising results. This might be due to the fact that successful interventions are highly dependent on the exact timing of memory retrieval and pharmacological intervention. Currently, the availability of esketamine as nasal spray might open up new therapeutic approaches to studying NMDA receptor antagonism in AUD.

6.2 Protein Synthesis Inhibition

The most consistent evidence for the efficacy of pharmacological inhibition of memory reconsolidation was provided by studies investigating different means of protein synthesis inhibition (see (Lee et al. 2017) for review). For example, Nader and colleagues confirmed that after previously conditioned fear memories have been retrieved, these memories can be disrupted with targeted infusions of the protein-synthesis inhibitor *anisomycin* into the lateral and basal nuclei of the amygdala – a site known to play an important role in learning fear (Nader et al. 2000). The study demonstrated that infusing anisomycin shortly after memory reactivation led to amnesia on later tests, while applying anisomycin without first re-exposing the subject to a conditioned cue left memory intact. They therefore concluded that reactivation of a consolidated memory can return it to a labile state from which it must be reconsolidated, as process that, like consolidation, requires new protein synthesis. However, to date, only a few studies specifically investigated the effects of protein synthesis inhibition in the reconsolidation of cue-alcohol memories. For example, Von der Goltz and colleagues provided evidence that the non-selective protein synthesis inhibitor anisomycin, administered intra-cerebroventricularly, disrupted alcohol seeking in an operant self-administration paradigm in Wistar rats, when being administered after memory retrieval (von der Goltz et al. 2009). These effects were still detectable up to 7 days after the intervention. In a following study, administration of anisomycin into the central nucleus of the amygdala (CeA), prior to memory retrieval, reduced alcohol seeking and self-administration (Barak et al. 2013). In the same study, Barak et al. (2013) provided evidence for the importance of the rapamycin complex 1 (mTORC1) pathway in the reconsolidation of alcohol-cue memories and alcohol-seeking behaviour after alcohol priming. mTORC1 controls the translation of a range of dendritic proteins and plays an important role in modulating protein translation, synaptic plasticity and memory formation (Hoeffer and Klann 2010). Barak et al. (2013) could show that the retrieval of alcohol-related memories resulted in the activation of the mTORC1 pathway and increases in synaptic protein concentrations in the prelimbic and orbitofrontal cortices and the CeA (Barak et al. 2013). In their experiments they could show that systemic administration of the mTORC1 inhibitor *rapamycin* (20 mg/kg) in rats, post retrieval (i.e. after re-exposure to the operant context with an oral alcohol prime), interfered with the reconsolidation of alcohol-cue memories, leading to long-lasting (14 days) suppression of relapse to alcohol seeking. The effect of rapamycin on alcohol cue memory reconsolidation was further supported by the work of Lin et al. (2014), which showed that systemic administration of rapamycin (10 mg/kg, ip) after re-exposure to the alcohol-paired environment attenuated alcohol-conditioned place preference for up to 14 days after the injection (Lin et al. 2014). In the study of Barak et al. (2013), it was specifically the local injection of rapamycin in the CeA after memory retrieval that prevented relapse to alcohol seeking and consumption, suggesting that the CeA plays an important role in the reconsolidation of alcohol-cue memories (Barak et al. 2013). The effect of

rapamycin on alcohol-seeking however could only be observed, when rapamycin was administered immediately after the retrieval of alcohol-cue memories, indicating that the efficacy of mTORC1 inhibitors seems to critically depend on the timing of the pharmacological intervention.

6.3 *β-Adrenergic Receptor Blockade*

Several preclinical studies indicated the role of β-adrenergic receptors in memory reconsolidation (Milton et al. 2008). A preclinical study investigating the effects of intracerebral propranolol infusion (2 µg per hemisphere) into the BLA of rats reduced responding for alcohol in the first six test trials, while no significant effect was found in the subsequent 12 trials (Chesworth and Corbit 2018). A recent study could show that administration of the β-adrenergic receptor antagonist *propranolol*, administered in conjunction with memory reactivation in a rat model of AUD, persistently disrupted the capacity of a previously alcohol-associated cue to act as a conditioned reinforcer (Schramm et al. 2016). By contrast, adrenergic stimulation by administration of *dipivefrin*, at reactivation, increased the strength of alcohol-related memories and potentiated alcohol seeking. Another preclinical study failed to show significant effects of an administration of propranolol (10 or 30 mg/kg, ip) on the reconsolidation of alcohol-associated memories when given after retrieval (Font and Cunningham 2012). Also, in a subsequent study, Milton et al. (2012) could not establish a significant effect of an administration of propranolol (10 mg/kg, ip) on alcohol-seeking behaviour, when administrated 30 min before the retrieval of the alcohol-related memories (Milton et al. 2012). In contrary, on the next day after propranolol vs. saline administration, increased alcohol seeking was observed in both experimental groups (Milton et al. 2012). Interestingly, another preclinical study indicated that significant effects of β-adrenergic blockade on alcohol-seeking behaviour in rats were achieved after two and three sessions of propranolol treatment, but not after the first administration (Wouda et al. 2010). This suggests that repeated administration of propranolol is necessary, in order to achieve effects on alcohol-cue memory reconsolidation.

A preliminary randomized double-blind controlled human study in heavy drinkers (not meeting the diagnostic criteria of an AUD) showed significant effects of repeated (six bi-weekly sessions, separated by no less than 48 h) post-retrieval propranolol treatment (1 mg/kg body weight), compared to placebo, on alcohol craving intensity (Lonergan et al. 2016).

6.4 Non-pharmacological Interference with Alcohol-Memory Reconsolidation

Recently, it has been shown that state-dependent transcranial magnetic stimulation (TMS) over the PFC can be used to destabilize fear-memory reconsolidation in anxiety (Borgomaneri et al. 2020). The TMS was state-dependent in the way that it was delivered 10 min after the presentation of a “reminder cue” for previously acquired fear memory contents. TMS trials in addiction used alcohol cue presentation to reactivate addiction memory contents. A first trial reported a significant decrease in craving and drinking measures during treatment, which however did not differ between active or sham stimulation group (Perini et al. 2020). In addition, active TMS significantly modified insular cortex resting state connectivity, suggesting that TMS could modify insula function. A subsequent randomized-controlled TMS trial targeting the mPFC and ACC after alcohol cue-presentation reported significantly lower alcohol craving after treatment and percentage of heavy drinking days during follow-up in the active versus sham control group (Harel et al. 2022). These findings point towards the potential of TMS to modify cue-associated memories and addictive behaviours (Sommer et al. 2022).

6.5 Behavioural Interference with Alcohol-Memory Reconsolidation

Beyond pharmacological interventions, the effects of behavioural interventions on the reconsolidation of alcohol-related memories were tested. In this approach, a behavioural manipulation, performed shortly after memory retrieval, aims to counteract the maladaptive memory and resulting behaviour (Ma et al. 2012; Sartor and Aston-Jones 2014). In 2003, Walker et al. used a finger-tapping paradigm to find that consolidated motor memories, when reactivated, could be returned to a labile state that would again be sensitive to interference. Using interference to block reconsolidation in this way was probably the first convincing demonstration of an erasure of a consolidated memory in humans. Several similar studies followed. Forcato et al. (2007) showed an initially acquired, declarative memory to be impaired when subjects were reminded of the memory material shortly before they learned additional material. Schwabe and Wolf (2010) found evidence that exposing subjects to a stressor directly after memory reactivation could impair how they reconsolidated neutral autobiographical events. The stressor they used was intended to stimulate the release of corticosterone, a glucocorticoid that had previously been shown to block reconsolidation in rodents (e.g. Cai et al. 2006). Interference with memory reconsolidation was also shown in hazardous alcohol drinkers. In these studies retrieval of alcohol-associated memories was performed by presenting participants with a glass of alcohol and then taking it away unexpectedly before the first sip. Two studies in abstinent patients with AUD, using this experimental design,

showed that re-association of alcohol cues with gustatory disgust, immediately after memory retrieval resulted in a reduction in alcohol cue valuation and alcohol craving (Das et al. 2015, 2018). Another study could also show that disgust-based counter-conditioning following memory retrieval led to significant reductions in the amount of alcohol consumed during follow-up (9 months) (Gale et al. 2020).

Another non-pharmacological intervention used to interfere with the reconsolidation of alcohol-related memories is *reappraisal* of the maladaptive memories by active reappraisal. In the study by Hon et al. (2016) authors sought to yield reappraisal by asking participants to identify and describe the maladaptive memories that appeared most relevant to them in a wording that made the maladaptive appraisal personally relevant and then reappraise these memories by generating “arguments” that challenged the maladaptive thoughts (Hon et al. 2016). While this procedure resulted in reduced verbal fluency for positive alcohol-related words, no significant effects could be detected for other outcome measures (i.e. neither for attentional bias, nor for craving, nor for alcohol consumption). Another randomized study compared the effects of a high working memory load before vs. after memory retrieval on interference with the reconsolidation of alcohol-related memories. The results, in contrast to the a priori hypotheses, showed that a high working memory load after memory retrieval did not interfere with memory reconsolidation, while a high working memory load before memory retrieval did and significantly reduced alcohol craving (Kaag et al. 2018). Even though existing data in behavioural interventions to reduce the reconsolidation of alcohol-related memories are somewhat inconsistent, and no recommendations for clinical applications can be made at this stage, they still point to the therapeutic potential of these strategies and further exploration of these interventions seems warranted.

Taken together, the preclinical and clinical behavioural and pharmacological experiments have contributed significantly to our understanding of the neurobiological mechanisms involved in the reconsolidation of alcohol-related memories. The presented findings have important clinical implications, since they suggest that selectively reducing long-lasting, drug-associated memories could become a viable therapeutic option. Disrupting the reconsolidation of drug-related memories may become an effective treatment strategy for reducing the likelihood of relapse in abstinent addicts.

7 Conclusions

Neural changes induced by chronic substance consumption are an important factor underlying the development and persistence of addictive disorders. Implicit learning and memory are both involved in triggering cravings and drug-seeking behaviour, even after years of abstinence. Results showing the involvement of drug-induced LTP and synaptic changes in the mesolimbic system also support the hypothesis of an addiction memory. Future addiction research will have to integrate the growing amount of knowledge concerning drug-induced neuroplasticity into a valid model of

the development of addiction in humans. One of the most important questions facing future researchers is whether addiction memory can be erased using therapeutic interventions. In addition to this need for new pharmacotherapeutic approaches, there is also a need for the development of addiction-specific psychotherapeutic methods which address the implicit contents of addiction memory directly.

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Modulation of Alcohol Use Disorder by Brain Stimulation



Noam Ygael and Abraham Zangen

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Abstract Currently available therapeutic modalities for alcohol use disorder (AUD) produce limited effect sizes or long-term compliance. Recent methods that were developed to modulate brain activity represent potential novel treatment options. Various methods of brain stimulation, when applied repeatedly, can induce long-term neurobiological, behavioral, and cognitive modifications. Recent studies in alcoholic subjects indicate the potential of brain stimulation methods to reduce alcohol craving, consumption, and relapse. Specifically, deep brain stimulation (DBS) of the nucleus accumbens or non-surgical stimulation of the dorsolateral prefrontal cortex (PFC) or medial PFC and anterior cingulate cortex using transcranial magnetic stimulation (TMS) has shown clinical benefit. However, further preclinical and clinical research is needed to establish understanding of mechanisms and the treatment protocols of brain stimulation for AUD. While efforts to design comparable apparatus in rodents continue, preclinical studies can be used to examine targets for DBS protocols, or to administer temporal patterns of pulsus similar to those used for TMS, to more superficial targets through implanted electrodes. The clinical field will benefit from studies with larger sample sizes, higher numbers of stimulation sessions, maintenance sessions, and long follow-up

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periods. The effect of symptoms provocation before and during stimulation should be further studied. Larger studies may have the power to explore predictive factors for the clinical outcome and thereby to optimize patient selection and eventually even develop personalization of the stimulation parameters.

Keywords Alcohol use disorder (AUD) · Deep brain stimulation (DBS) · Transcranial electrical stimulation (tES) · Transcranial magnetic stimulation (rTMS)

1 Preface

Currently available therapeutic modalities for alcohol use disorder (AUD) produce limited effect sizes, particularly when long-term relapse prevention is considered (Kranzler and Soyka 2018; Ray et al. 2021). Following recognition of AUD as a brain disease and advances in understanding of related pathological neural circuitries, methods that were developed to modulate brain activity represent a promising treatment option (Volkow and Boyle 2018). Indeed, brain stimulation procedures that are already being used in clinical setups for various psychiatric and neurological disorders following approval by the FDA and other regulatory bodies can target neural circuitries associated with the pathophysiology of AUD and were shown to affect addictive behaviors. Examples include deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus for Parkinson disease (Aum and Tierney 2018; Wang et al. 2018); repeated transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (PFC), or Deep rTMS of bilateral PFC for major depressive disorder (MDD) (O'Reardon et al. 2007; Levkovitz et al. 2015); Deep rTMS of the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) for obsessive compulsive disorder (OCD) and depression (Carmi et al. 2019; Zangen et al. 2023); and Deep rTMS of bilateral PFC and insula for nicotine dependence (Zangen et al. 2021). In this chapter, we review studies evaluating the potential of brain stimulation methods to affect symptoms of AUD and recommend future directions for development of treatments for AUD using such interventions.

2 Preclinical Studies

Animal models of AUD have been critical for our understanding of the physiological effects of alcohol and contributed substantially to the development of currently available medications for the treatment of AUD (Tunstall et al. 2020). These models mainly include rats exposed to the sucrose- or saccharin-fading procedure, or alcohol-preferring rats selectively bred to consume high quantities of alcohol. While the first study evaluating long-term effects of brain stimulation on addictive behavior and related neurochemical alterations was performed in a rat model for

cocaine self-administration (Levy et al. 2007), only a few studies have explored the effects of brain stimulation over alcohol-related behaviors in preclinical models. The first study evaluating acute effects of brain stimulation on alcohol consumption was published in 2009 by Knapp and colleagues (2009). In this study, Long Evans rats were induced to drink a 10% ethanol solution using a saccharin-fading procedure and implanted with two bipolar stainless steel electrodes into either the shell or the core of the nucleus accumbens (NAc). On test days, rats received DBS (0–150 μ A) for 5 min prior to and during 30 min of being given access to ethanol solutions. DBS of both the shell and the core at 150 μ A reduced ethanol consumption without affecting the consumption of a natural reward (water), which indicates that each of these subregions play roles in processes that mediate ethanol consumption. A study published in the following year demonstrated that NAc-DBS at 200 μ A reduced both alcohol intake and alcohol preference in alcohol-preferring rats, but the authors noted a surprising amount of tissue damage at the tip of the stimulating electrodes (Henderson et al. 2010). Beyond the safety concerns, this suggests that the observed behavioral alterations might have been caused by the local lesion or processes not directly related to the stimulation. Later, Wilden et al. (2014) demonstrated the effects of DBS targeting the NAc shell at 200 μ A to be transient, with reduced consumption only during the first three DBS sessions. Finally, a study with larger sample sizes (Hadar et al. 2016) found that alcohol-related behavior was actually *increased* following DBS targeting the NAc shell. In that study, rats had long-term voluntary access to alcohol that was followed by deprivation for several weeks. Thereafter, chronic-continuous bilateral NAc stimulation started 3 days before the end of the 3 weeks abstinence phase and continued for four post-abstinence days, during which ethanol consumption was measured. During the re-presentation of alcohol, alcohol-deprivation effect was observed as a temporal increase in alcohol intake over baseline, which was greater following active compared to sham DBS. To explain this increase, the authors demonstrated, in different groups of rats, that 24 h of NAc-DBS led to an increase in extracellular NAc dopamine (DA) levels compared to sham stimulation and that intraperitoneal administration of ascending alcohol doses further increases DA levels during active compared to sham DBS. Therefore, DBS in the NAc may increase the rewarding effect of alcohol and thereby may promote relapse behavior.

Overall, these few preclinical studies utilizing DBS to target the NAc showed inconsistent results, but may indicate that while acute DBS of the NAc may reduce alcohol consumption, long-term effect of NAc-DBS following abstinence may actually increase relapse rates.

Only one preclinical brain stimulation study used a non-DBS (non-surgical) method, assessing the effects of transcranial direct current stimulation (tDCS) on alcohol consumption (Santos et al. 2021). In that study, nerve-injured rats with chronic pain showed a progressive increase in alcohol consumption compared to non-injured rats. Eight consecutive days of cortical tDCS (0.5 mA; 20 min per day) induced a reduction in voluntary alcohol consumption that was more pronounced in non-injured rats. The study also found treatment to increase the cerebellar levels of different interleukins and to reduce striatal brain-derived neurotrophic factor levels,

which play an important role in neurogenesis and synaptic plasticity (Wang et al. 2022).

3 Clinical Studies

3.1 Deep Brain Stimulation (DBS)

DBS in humans involves implantation of electrodes into the target brain area, and a pulse generator, usually implanted into the chest, as the power source (Fig. 1). The effects of DBS are not restricted to the main target and also promote excitation of both afferent and efferent axons, synaptic plasticity, and long-term neuronal reorganization (Ashkan et al. 2017). The first report evaluating effects of DBS on alcohol dependency was published in 2007 by Kuhn et al. (2007). The report included a patient receiving NAc-DBS, primarily for treating severe anxiety and depression, but experienced a rapid and drastic reduction of alcohol consumption. Thereafter, results from small case series or case reports suggested a positive outcome of NAc-DBS for AUD (Voges et al. 2013; Ho et al. 2018; Wang et al. 2018; Maatoug et al. 2021). Most patients achieved long-term abstinence from alcohol (with or without occasional lapses), while transient hypomania was reported as an adverse effect. Of note is that long-term clinical outcome with no severe or long-standing side effects was reported for up to 8 years (Müller et al. 2016). Finally, a randomized controlled trial (RCT) of NAc-DBS was conducted on 12 AUD inpatients, wherein the first 6-month

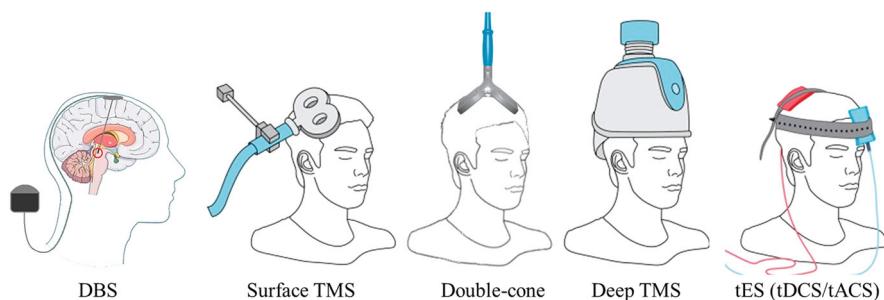


Fig. 1 Brain stimulation techniques. Deep brain stimulation (DBS) involves implantation of electrodes into the target brain area and a pulse generator, usually implanted into the chest, as the power source. Surface transcranial magnetic stimulation (TMS) apparatus includes a stimulator connected to a coil that is placed on the scalp over the target area. The double-cone coil has angled windings that were developed to modulate deeper cortical areas. Deep TMS H-coils are designed to stimulate larger brain volumes and to reach deeper areas in the cortex bilaterally or unilaterally. Transcranial electrical stimulation (tES) involves the delivery of a low-intensity current between a battery-driven stimulator and two electrodes that are placed on the scalp. The two most common tES paradigms are transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). The figure was partially adapted and modified from Ekhtiari et al. (2019) and Szymoniuk et al. (2023)

blind phase was followed by a 12-month unblinded period, in which all patients received active DBS (Bach et al. 2023). Here, no statistically significant difference was found between treatment groups in the primary intention-to-treat analysis, comparing continuous abstinence in the first 6 months. However, the patients receiving active DBS had significantly higher proportion of abstinent days, lower alcohol craving, and anhedonia.

Overall, despite the inconsistent preclinical findings, DBS in humans seems to be an effective treatment option. However, currently available data from all studies and reports include overall less than 40 patients. Finally, NAc-DBS was reported to improve psychometric scores and electrophysiological measures of cognitive control in a case study (Kuhn et al. 2011) and to reduce NAc metabolism, activation, and connectivity in an open labeled study ($n = 6$) (Davidson et al. 2022). However, the significance and relevance of these later results should be verified in sham-controlled studies and larger samples.

3.2 Transcranial Magnetic Stimulation (TMS)

TMS is based on the electromagnetic induction principle, where brief focal electromagnetic pulses penetrate the skull inducing action potentials in neurons, stimulating specific brain regions, and inducing changes in cortical excitability (Ekhtiari et al. 2019). The TMS apparatus includes a stimulator connected to a coil that is placed on the scalp over the target area (in which the effective electromagnetic field is being induced) (Fig. 1). The most common coil is shaped like the number 8 (“figure-of-8 coil”), generating a focal stimulation on the surface of the cortex under the intersection of the “8.” H-coils and the double-cone coil, on the other hand, are designed to stimulate larger brain volumes and to reach deeper areas in the cortex, and are termed Deep TMS coils (Zibman et al. 2019). The double-cone coil, while having a similar shape like the figure-of-8 coil, can reach deeper cortical subregions; however, it causes greater discomfort and local scalp pain. The Deep TMS H-coils produce stimulation of larger cortical areas, reaching even deeper cortical regions, without increasing discomfort and local scalp pain (Zangen et al. 2005; Lu and Ueno 2017). Similar to the figure-of-8 coil, the double-cone coil can be placed to target various brain areas, while each H-coil is usually designed to target specific areas and is less flexible for positioning over different brain targets. For example, the H1-coil is designed to target the LPFC bilaterally, with greater penetration and volume over the left LPFC, while the H7-coil is designed to target the mPFC and ACC, and the H8-coil is designed to target the insula bilaterally (Tendler et al. 2016). Trains of TMS pulses (termed repetitive TMS, rTMS) can induce changes in cortical excitability and are delivered at low frequency (usually 1 Hz) or high frequency (5–20 Hz). High-frequency stimulation is considered to induce increased excitability and to enhance neuroplasticity, while low-frequency stimulation is considered to induce reduction in excitability and so far showed less evidence for long-term

alterations in neuroplasticity; however, these differences between outcomes of stimulation frequencies are not entirely established (Cao et al. 2018).

The effects of stimulation are not restricted just to the main target, due to connectivity between the target area and other brain areas, and may lead to the release of a wide variety of neurotransmitters in cortical and subcortical areas (Diana et al. 2019). For example, rTMS targeting the PFC was shown to increase DA levels in both the PFC and NAc, possibly through activation of pyramidal neurons impinging upon DA-containing neurons in the midbrain (Diana et al. 2019). Moreover, it was shown that secondary activations of mesolimbic areas following PFC stimulation with rTMS in MDD patients are therapeutically relevant (Cuypers and Marsman 2020).

Following earlier studies evaluating effectiveness of high-frequency rTMS treatment over the dorsolateral PFC (DLPFC) in other addictions (Eichhammer et al. 2003; Amiaz et al. 2009), the first study to apply rTMS as a therapeutic intervention for individuals with AUD was a randomized clinical trial (RCT) by Mishra and colleagues (2010). This study compared sham and active high-frequency (10 Hz) rTMS targeting the right DLPFC for 10 daily sessions and found a significant decrease in craving scores that was greater in the active group and lasted for at least 1 month following rTMS treatment. Most of the following TMS studies targeted the right DLPFC as well, with 10 or 20 Hz rTMS for 10 or more daily sessions, using moderate sample sizes (Herremans et al. 2015, 2016; Mishra et al. 2016; Qiao et al. 2016; Wu et al. 2018; Hoven et al. 2023). However, these studies demonstrated no consistent effects of stimulation on alcohol consumption, or similar reduction of craving in both the active and sham groups (Mostafavi et al. 2020). In a study aiming to compare left vs. right DLPFC stimulation (10 rTMS sessions at 10 Hz) in two different groups, a significant reduction in craving scores compared to baseline was noted in both groups, but did not differ between them (Mishra et al. 2015). Two additional small studies that targeted the left DLPFC failed to find significant effects of high-frequency rTMS over craving or alcohol intake (Höppner et al. 2011; Del Felice et al. 2016).

Two crossover rTMS studies examined the acute effects of continuous theta-burst stimulation (cTBS), which involves bursts of 3 pulses at 50 Hz that are repeated every 200 ms for 40 s, providing a total of 600 pulses per train. These studies found that a single session of left ventromedial PFC stimulation ($n = 24$; six trains) did not affect craving, while a single session of right DLPFC stimulation ($n = 20$; one train) impaired inhibitory control and increased alcohol consumption in the Bogus Taste test (Hanlon et al. 2017; McNeill et al. 2018).

The first rTMS study to target deeper and non-DLPFC areas was a case study performed by De Ridder and colleagues, who applied 15 sessions (5/week for 3 weeks) of low-frequency (1 Hz) rTMS over the mPFC-ACC with a double-cone coil on a patient with alcohol dependence. The patient experienced significant reduction of craving for 3 months following treatment (De Ridder et al. 2011). Additional case study applied DBS of the bilateral dorsal ACC that followed 2 weeks of daily rTMS session applied at 1 Hz, with the double-cone coil over the mPFC-ACC (De Ridder et al. 2016). Here, rTMS transiently suppressed alcohol

craving for up to 6 weeks, after which the surgery was performed and the patient remained free of alcohol intake for over 18 months with the chronic DBS applied.

The first study to apply Deep TMS using an H-coil was performed by Rapinesi and colleagues in 2013 and included 3 patients with comorbid dysthymic disorder and AUD (Rapinesi et al. 2013). The protocol included 20 sessions of 20 Hz over the bilateral lateral PFC using the H1-coil, which produces stronger and deeper stimulation over the left PFC relative to the right PFC (Levkovitz et al. 2009). The 3 patients improved on both anxiety-depressive symptoms and alcohol craving, and these positive results in patients with comorbid depression and AUD using the H1-coil were later validated in three different open label small studies (Girardi et al. 2015; Rapinesi et al. 2015, 2018). Later, two small RCTs used Deep TMS H-coils on individuals with AUD as a single indication. In those studies (Ceccanti et al. 2015; Addolorato et al. 2017), stimulation of the lateral PFC using the H1-coil at 10 Hz for 12 sessions ($n = 5$ and 6 in the active and sham control groups, respectively), or the medial PFC using the H7-coil at 20 Hz for 10 sessions ($n = 9$ for the active and sham control groups, respectively), led to a decrease in alcohol craving and consumption.

Two larger RCTs targeted the mPFC-ACC ($N = 51$) using the H7 Deep TMS coil (Harel et al. 2022) or the insula ($N = 56$) using the H8 Deep TMS coil (Perini et al. 2020) with a protocol that included 15 daily sessions of high-frequency (10 Hz) stimulation over 3 weeks and a follow-up of 3 months. In both studies, craving for alcohol was provoked prior to each Deep rTMS session, by pouring the patient's preferred drink into a glass in front of him, and letting the patient smell it. This strategy was based on the assumption that active neuronal circuitries are more liable for changes by stimulation (Isserles et al. 2013; Carmi et al. 2019; Perini et al. 2020; Harel et al. 2022). The study targeting the mPFC-ACC found both craving after treatment and percentage of heavy drinking days during 3 months of follow-up to be significantly lower in the active compared to the sham control group (Harel et al. 2022). The study targeting the insula found no significant difference between the active and sham groups following treatment or during the 3 months of follow-up (Perini et al. 2020).

The first study to assess TMS treatment effect on cognitive functions of AUD patients targeted the right DLPFC at 20 Hz and examined acute modification to behavior in a Go-No/Go task following a single active or sham stimulation session (Herremans et al. 2013). The study, which used a crossover design and included 29 recently detoxified alcohol-dependent patients, found that active but not sham stimulation decreased intra-individual reaction time variability without affecting reaction time or commission of errors. A later study evaluating longer term effects of 4 rTMS sessions targeting the left DLPFC at 10 Hz over 2 weeks found that, compared to sham stimulation ($n = 11$), participants in the active group ($n = 12$) demonstrated better performances in the Stroop and Go-No/Go tasks and an overall reduction of faster EEG frequencies (Del Felice et al. 2016). While this study suggested positive effects of left DLPFC rTMS treatment over inhibitory control and selective attention, the treatment schedule was ineffective in reducing craving and alcohol intake. Finally, Qiao et al. (2016) reported positive effects on memory functions of recently detoxified alcohol-dependent patients, following 20 daily

rTMS sessions targeting the right DLPFC at 10 Hz, in a sham-controlled study ($N = 38$), with effects that correlated with increases in hippocampal metabolites (N-acetyl aspartic acid, choline, and creatine) detected by proton magnetic resonance spectroscopy (Qiao et al. 2016).

Two of the studies presented above suggested that the effects of Deep TMS over alcohol-related behavior may be mediated by modulation of dopaminergic activity. In one study (Ceccanti et al. 2015), multiple sessions of Deep rTMS in abstinent AUD patients were reported to reduce cortisol levels (which usually increase during alcohol withdrawal) and to reduce prolactin levels (which can indicate increased dopaminergic activity). In the other (Addolorato et al. 2017), Deep TMS of the lateral PFC has reduced the availability of the DA transporter (DAT) in the caudate and putamen in AUD patients. Finally, active Deep TMS treatment targeting the mPFC/ACC induced reduction in resting-state functional connectivity between the dorsal ACC and the caudate, as well as reduced connectivity between the mPFC and the subgenual ACC (Harel et al. 2022). In addition, active Deep TMS treatment targeting the insula induced a significant group effect in connectivity at follow-up between the right posterior insula (PI) and the left precuneus and between the left PI and right cingulate (Perini et al. 2020). However, no direct correlation was observed between these changes in brain connectivity and the clinical outcomes. Of note is that a follow-up paper to Harel et al. (2022) demonstrated that the progression of white matter alterations during early abstinence from alcohol was selectively arrested in the stimulated brain region by active but not sham Deep TMS (Selim et al. 2024). This study thus suggests that the therapeutic efficacy of Deep TMS is, at least in part, related to the recovery of white matter microstructure and points to myelin plasticity as a possible mediator.

3.3 Transcranial Electrical Stimulation (tES)

tES technique involves the delivery of a low-intensity current (1–2 mA) between a battery-driven stimulator and two electrodes (anode and cathode; 20–35 cm² each) that are placed on the scalp (Fig. 1). The current passes through the scalp and induces changes in the electrical activity and response threshold of the neurons, as well as synaptic efficiencies (Fertonani and Miniussi 2017). However, unlike TMS, these methods do not produce suprathreshold pulses which directly induce action potentials in large populations of neurons at the target area. The two most common tES paradigms are tDCS and transcranial alternating current stimulation (tACS) (Ekhtiasi et al. 2019), although only the former was examined as a potential treatment for alcohol dependence.

The first clinical study to investigate the efficacy of tDCS for the treatment of AUD was done by Boggio and colleagues (2008), with a setup that included anode over the left DLPFC and cathode over the right DLPFC, or vice versa (2 mA for 20 min). The study used a crossover design, where each participant ($n = 13$) underwent 3 acute stimulation sessions (48-h inter-session interval) using the two

active protocols and one sham protocol and found that both active protocols significantly reduced craving compared to sham stimulation. Most of the following studies used anode over the left DLPFC and current intensity of 2 mA, with the cathode mostly placed over the right supradeltoid, but included moderate sample sizes and/or low number of sessions (≤ 5) (Mostafavi et al. 2020). These studies failed to demonstrate significant tDCS effects on symptoms of AUD, although some studies reported small reductions in alcohol craving and consumption induced by the treatment (Kim and Kang 2020; Mostafavi et al. 2020). One RCT included 60 subjects and 10 stimulation sessions of anode over the left DLPFC and cathode over the right DLPFC (twice per day, 13 min duration each, separated by 20 min, on five consecutive days) and measured relapse rates 1 and 4 months following the intervention. While overall relapse rates were lower following active stimulation, the difference between groups was not statistically significant, unless considering women subjects only (Camchong et al. 2023). Two other RCTs by Klauss et al. (2014, 2018) included medium sample sizes ($N = 45$ and 33, respectively) applying 10 sessions of cathode over the left DLPFC and anode over the right DLPFC with current intensity of 2 mA. The main finding in these studies was reduced relapse in the active group compared to the sham group when measured 3 and 6 months after the end of treatment.

Only one tES study targeted the non-DLPFC brain area, the right inferior frontal gyrus (IFG; 1 mA for 10 min), and examined performance following a single session in two different versions of the alcohol implicit association test (IAT), one with approach and avoidance words (motivation IAT) and one with positive words and negative words (affective IAT). The study found no evidence for tDCS-induced changes in alcohol craving or biases of hazardous drinkers following acute stimulation (den Uyl et al. 2015).

The first study to explore neurobiological effects of tDCS in AUD was conducted by Nakamura-Palacios et al. and examined the effect of acute left DLPFC tDCS over cue-induced event-related potentials (ERPs) in 49 alcoholic subjects during the subacute abstinence period (Nakamura-Palacios et al. 2012). In this study, active tDCS (anode over F3 and cathode over the contralateral supradeltoid area; 1 mA for 10 min) induced an increase in the mean amplitude of frontal P3 following exposure to alcohol cues, but not natural cues, with the more pronounced changes observed in the most severe alcoholics. The authors suggested that such tDCS-induced local increase in frontal activity in response to drug cues may have a beneficial clinical impact. Indeed, across studies, patients with AUD displayed smaller P3 amplitudes (resulting in less differentiation between relevant versus irrelevant stimuli) compared to controls (Rohde et al. 2020). In another study (Camchong et al. 2023) mentioned above, active tDCS (anode over F3 and cathode over F4; twice per day for 5 days, 2 mA for 13 min) increased the average strength of connectivity from the left DLPFC to the incentive salience and negative emotionality networks. Moreover, the change in connectivity between the left DLPFC and the incentive salience network was associated with a statistically significant increase in the odds of remaining abstinent during the 4-month follow-up period, with increased connectivity associated with greater chance of abstinence. Finally, Holla et al. (2020)

observed an increased global efficiency of brain networks following active tDCS (cathode over F3 and anode over F4; once daily for 5 consecutive days, 2 mA for 20 min) that was significantly associated with a reduced likelihood of early lapse (Holla et al. 2020).

4 Safety and Tolerance

Only a limited number of subjects have undergone DBS for AUD, but the procedure seems safe and well tolerated, with only mild to moderate adverse events and no reports of serious adverse events resulting in lasting disability or death. Conversely, several hundred AUD patients already underwent non-invasive brain stimulation (NIBS) for AUD using rTMS, Deep rTMS, or tDCS. Overall, NIBS was well tolerated by most patients, with discomfort at the site of stimulation and transient headaches as the most common adverse effects (Mostafavi et al. 2020; Sorkhou et al. 2022). However, dropout rates tended to be high when long-term follow-up periods were included. For example, while only one of 45 patients was lost to a 1-month follow-up in the study by Mishra et al. (2010), 16 out of 18 patients were lost during a 6-months follow-up period in the study by Ceccanti et al. (2015).

5 Discussion

While AUD treatment is yet to be optimized, this chapter indicates that adding brain stimulation to standard treatment can positively affect the outcome. Various methods of brain stimulation can induce long-term behavioral, cognitive, and biological modifications, including reduced alcohol craving, consumption, and relapse. Initial studies demonstrate that NAc-DBS or noninvasive stimulation of the DLPFC or mPFC-ACC has clinical potential. The latter was also highlighted by recent studies on brain lesions disrupting the addiction map, which suggested the fronto-polar cortex as a promising target for noninvasive brain stimulation in addiction, including AUD (Joutsa et al. 2022; Soleimani et al. 2023). However, further preclinical and clinical research is needed to establish understanding of mechanisms and the clinical utility of brain stimulation for AUD.

Admittedly, while brain stimulation studies in AUD are accumulating, the current data is still limited and includes variable techniques and stimulation parameters. One reason for the limited availability of preclinical data in noninvasive techniques is that, despite many efforts (e.g., Macedo et al. 2016; Koponen et al. 2020; Sánchez et al. 2020), there are no comparable coils for TMS or electrodes for tES that accurately model the human condition in small animals. Most often when studying animals using these methods, a much larger volume of brain tissue is affected, thereby not mimicking human conditions receiving standard stimulation protocols. While efforts to design comparable apparatus continue, preclinical studies can be

used to examine targets for DBS protocols, and to administer rTMS- or tES-like parameters of stimulation to more superficial targets through implanted electrodes (e.g., Levy et al. 2007).

Due to the burden, risk, and cost of neurosurgery including not only anesthesia and hospitalization, but also long-term maintenance of the apparatus, DBS is not expected to be commonly used in the clinical treatment of AUD, but be reserved for the most severe cases (Maatoug et al. 2021). Also, it has been repeatedly proven difficult to recruit addicted patients to studies using this intervention which require multiple treatment sessions over weeks. One reason could be the strongly fluctuating motivation for treatment (Luigjes et al. 2015). As noted by Bach et al. (2023), the available data underscore the importance of carefully balancing the risks of DBS against the risks of uncontrolled alcohol use in treatment-resistant AUD. These limitations make NIBS a more preferable choice, as these methods are not only safe and well tolerable in AUD (Sorkhou et al. 2022) but can also induce neuronal modifications relevant to the pathophysiology of AUD (Ekhtiari et al. 2019). Multiple sessions of NIBS have the potential to induce long-term beneficial effects in AUD patients by facilitation of neuroplasticity and modulations in functionally associated neural circuits (Ghin et al. 2022).

The most recent meta-analysis of NIBS studies in AUD patients suggests that suprathreshold rTMS may be superior to tDCS in reducing alcohol craving but that additional research is needed to identify optimal stimulation parameters for both techniques (Sorkhou et al. 2022). Indeed, most trials included low sample sizes, small numbers of stimulation sessions, short follow-up periods, or an open label design. Yet, those that applied a greater number of sessions produced more positive outcomes, which is in line with a meta-analysis that found positive linear association between the number of stimulation sessions and craving reduction in drug addiction (Song et al. 2019). In addition, gray matter volume in common TMS brain targets was found to be reduced in participants with AUD compared to healthy controls (McCalley and Hanlon 2021). Given previous studies indicating that TMS-evoked changes are dependent on gray matter volume, McCalley and Hanlon concluded that stimulation protocols may require higher doses to sufficiently modulate these brain targets (McCalley and Hanlon 2021). Clearly, the clinical field will benefit from RCTs with large sample sizes and long follow-up of participants (at least 6 months). In addition, data in this chapter as well as brain stimulation studies in MDD patients suggest that more stimulation sessions are more likely to induce long-term effects. Due to the difficulties in the conductance of large sample studies and long-term follow-up, it is recommended to join efforts in multi-site studies rather than to perform small-scale single-site studies that involve different stimulation parameters and outcome measures. Large-scale studies using uniform stimulation protocols may also have the power to explore predictive factors (demographic, clinical, behavioral, or various biomarkers) for the clinical outcome, and thereby to optimize patient selection, and eventually even develop personalization of the stimulation parameters. In addition, objective measures of alcohol metabolites in urine or blood samples should be used to verify the efficacy of the treatment in comparison to currently available treatments. Finally, variables such as scalp-to-cortex distance, gray matter

volume in the stimulated region, and white matter integrity may affect the clinical outcome and thus should be addressed (Philip et al. 2020; McCalley and Hanlon 2021).

One factor that may promote positive clinical outcome in rTMS studies is the use of symptoms provocation before and during stimulation. Provocation, such as the presence of the preferred alcoholic drink, can activate relevant neuronal circuitry and by that to make it more susceptible to modifications (Dudai 2004, 2006). For example, exposure to alcohol cues can promote retrieval of memories related to alcohol seeking and taking, which are then more amenable to modification during the reconsolidation phase (Milton 2013; Borgomaneri et al. 2020; Barak and Goltseker 2023). At the same time, provocation can also serve as a form of exposure therapy (Isserles et al. 2021), where the preferred patient's drink can be poured into a glass in front of the patient and smelled, repeatedly in each treatment session, but cannot be consumed. Indeed, there are indications that provocation prior to each stimulation session can promote the anti-addictive effects of brain stimulation (e.g., Dinur-Klein et al. 2014), and is gradually implemented into a greater number of stimulation protocols, including for the treatment of AUD (e.g., Isserles et al. 2013; Carmi et al. 2019; Perini et al. 2020; Harel et al. 2022). This may not be the case in tES protocols, as those that involved the presentation of alcohol-related cues in various tasks during stimulation provided weak or no evidence of a positive effect on alcohol-related outcomes (Philip et al. 2020). However, an RCT conducted on inpatients, which included alcohol cue inhibitory control training (ICT), found that abstinence rates were highest following tDCS combined with ICT (Dubuson et al. 2021). That study included a 2 (active vs. sham tDCS) \times 2 (alcohol cue vs. neutral ICT) factorial design, with a stimulation protocol of 5 daily sessions of simultaneously combined tDCS (2 mA; anode over the right DLFPC and the cathode over the left DLFPC) and ICT.

Additional factor that can promote positive effects is the use of post-session behavioral training, as it was suggested that brain stimulation opens a “plasticity window” that lasts for several minutes beyond the time of treatment (Wilson et al. 2018). This window is short-lived and protocol-dependent but is still sufficient for the delivery of specially designed behavioral intervention or motivational talks, or the completion of a cognitive function-oriented behavioral task.

Finally, the administration of maintenance stimulation sessions (e.g., once weekly) may increase or sustain the effects achieved during the acute treatment phase. Indeed, pre-session provocation, post-session motivational talk, and maintenance sessions were incorporated in the recently FDA-approved Deep rTMS protocol for nicotine dependence (Zangen et al. 2021).

As in the case of nicotine, the context in which the individual attempts abstinence from alcohol is highly challenging. Moderate alcohol consumption is a legitimate behavior in many cultures, and there is a widespread availability of drinks, drinking opportunities, and alcohol-related stimuli. Repeated exposure to alcohol cues can trigger craving and seeking behavior and eventually lead to complete relapse (Milton 2013; LeCocq et al. 2020). Thus, brain stimulation protocols are suggested to be a part of more holistic therapeutic programs, which also include behavioral therapy,

supporting groups, and the use of established pharmacological interventions when needed.

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Role of the Microbiome and the Gut-Brain Axis in Alcohol Use Disorder: Potential Implication for Treatment Development



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Abstract The gut microbiota is constituted by trillions of microorganisms colonizing the human intestine. Studies conducted in patients with alcohol use disorder (AUD) have shown altered microbial composition related to bacteria, viruses, and fungi.

This review describes the communication pathways between the gut and the brain, including the ones related to the bacterial metabolites, the inflammatory cytokines, and the vagus nerve. We described in more detail the gut-derived metabolites that have been shown to be implicated in AUD or that could potentially be involved in the development of AUD due to their immune and/or neuroactive

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properties, including tryptophan-derivatives, tyrosine-derivatives, short chain fatty acids.

Finally, we discussed the potential beneficial effects of microbiome-based therapies for AUD such as probiotics, prebiotics, postbiotic, and phage therapy.

Keywords Fecal microbiota transplantation · Gut microbiota · Gut-brain axis · Inflammation · Metabolomics · Prebiotics · Probiotics

Abbreviations

4-EPS	4-Ethylphenylsulfate
AhR	Aryl hydrocarbon receptor
AUD	Alcohol use disorder
BBB	Blood brain barrier
BHB	β -hydroxybutyrate
CNS	Central nervous system
CT	Controls
FA	Fractional anisotropy
FMT	Fecal microbiota transplantation
GABA	Gamma-aminobutyric acid
HDAC	Histone deacetylase
IL	Interleukin
ITS	Internal transcribed spacer
LBP	LPS-binding protein
MCT	Monocarboxylate transporter
MRI	Magnetic resonance imaging
NMDA	N-methyl-D-aspartic acid
rDNA	Ribosomal DNA
SCFA	Short chain fatty acids
TLR	Toll-like receptor

1 Introduction

The gut microbiota is a complex ecosystem with huge impact on host's health (Nicholson et al. 2012). The microorganisms living in the gastrointestinal tract, comprising bacteria, viruses, fungi, and archaea, have numerous functionalities such as regulation of the immune system, involvement in many metabolic responses (including absorption of nutrients and minerals, synthesis of vitamins, breakdown of toxic components), and regulation of the nervous system with consequences for brain functions and behavior (Cryan and Dinan 2012). Consequently, unbalance of this ecosystem is usually associated with diseases including inflammatory diseases,

obesity, diabetes, liver diseases, and neurologic or psychiatric disorders (Nicholson et al. 2012; Cryan et al. 2019). The factors that can significantly affect the gut microbiota include dietary habits, lifestyle factors (like stress or sleep patterns), medications used, age, and sex (Zhernakova et al. 2016; Quigley 2017; David et al. 2014).

Alcohol use disorder (AUD) is a chronic relapsing psychiatric disease associated with metabolic, immune, cognitive, mood, and social disturbances. Alcohol abuse leads to several nutritional deficiencies and it is one of the main causes of malnutrition in Western countries (Amadieu et al. 2021). Since nutrition is a major factor shaping the gut microbiota, it is of interest to interrogate the gut microbiota composition of AUD patients. Furthermore, due to the large psychosocial distress of those patients, this clinical population represents an interesting target to investigate the gut-brain relationship.

In this review, we discuss the microbial alterations observed in AUD patients and describe the potential mechanisms by which the microbes could influence brain functions and behavior. We summarize the gut-brain communication pathways that have been described in the scientific literature, which are mainly related to the gut-derived metabolites, to the inflammatory cytokines and to the vagus nerve. While a large amount of data arises from animal experiments, we chose to highlight clinical data when possible. Finally, we discuss the potential benefits of microbiota-based therapies for the improvement of AUD.

2 The Gut Microbiota Composition in AUD Patients

A recent systematic review examined the effect of alcohol consumption on the gut microbiome, including AUD individuals with and without alcoholic liver diseases (Litwinowicz et al. 2020). Seventeen studies were included in this review and only results (related to bacterial changes) confirmed in at least two studies were included. At the phylum level, Bacteroidetes had a lower relative abundance and Proteobacteria (a highly pro-inflammatory phylum) a higher relative abundance in individuals with AUD than in healthy controls. At the family level, the relative abundance of Enterobacteriaceae was increased and Ruminococcaceae reduced. At the genus level, *Ruminococcus*, *Collinsella*, *Prevotella*, *Clostridium*, *Faecalibacterium*, *Paraprevotella*, *Bacteroides*, *Parabacteroides*, *Alistipes*, and *Akkermansia* had lower relative abundances in individuals with AUD. Results regarding *Bifidobacterium* were mixed, with some studies reporting a lower relative abundance in AUD individuals while other reported a higher abundance.

Overall, the results of existing studies are conflicting with little overlap asking for larger and more carefully designed studies. Also, the differences in the methodologies (related to DNA extraction, 16S rDNA sequencing, bioinformatics pipelines) across studies and that are in constant evolution could participate in the heterogeneity of the results. Furthermore, adjustment for confounders including lifestyle factors, nutrition, and medications used is needed. Indeed, drugs commonly used

in AUD patients such as proton pump inhibitors and antidepressants have been shown to largely modify the gut microbiota (Zhernakova et al. 2016; Letchumanan et al. 2021). Also, the status of the liver should be taken into consideration. Specific bacterial changes also characterized subjects presenting with progressive alcoholic liver disease (Maccioni et al. 2020), as well as cirrhotic patients (Addolorato et al. 2020). The team of Bernd Schnabl has carefully investigated the microbial composition of patients with alcoholic hepatitis. They found that the abundance of *Enterococcus faecalis* was 2,700-fold higher in the feces of alcoholic subjects compared to healthy controls, and about 80% of alcoholic hepatitis patients were *E. faecalis* positive in feces (Duan et al. 2019). Interestingly, this bacterium produces an exotoxin, called cytolsin, which is found to be a good predictor of mortality due to liver failure. Indeed, 89% of cytolsin-positive patient with alcoholic hepatitis died within 3 months after hospital admission compared to <4% of cytolsin-negative patients. Also, colonization of germ-free mice with feces from cytolsin-positive patients developed more severe ethanol-induced liver injury, inflammation, steatosis, and fibrosis and have a reduced survival time compared with germ-free mice colonized with feces from cytolsin-negative patients. Those results provide evidence that cytolsin promotes ethanol-induced liver damage (Duan et al. 2019).

In our lab, where we conducted studies in AUD patients that were selected not to present with severe liver disease, we found that only a subset of patients (around 40%) have alterations of the gut microbiota (Leclercq et al. 2014a). The dysbiotic group of alcoholic patients was characterized by decreased Ruminococcaceae and increased Lachnospiraceae families. Among the Ruminococcaceae's family, the genera *Ruminococcus* and *Subdoligranulum* were almost absent in dysbiotic patients, and the level of *Faecalibacterium prausnitzii*, a bacterium with anti-inflammatory properties (Sokol et al. 2008), was 10,000 times lower compared to healthy controls. Interestingly, intestinal dysbiosis of AUD patients was associated with a large increase in intestinal permeability, also called leaky gut (Leclercq et al. 2014a).

While the first decade of gut microbiome research has mainly focused on DNA-based 16S rRNA gene sequencing and shotgun metagenomic sequencing which elucidate the bacterial composition and gene content, more attention is recently given to fungi (amplicon sequencing based on 18S rRNA and ITS) and viruses (Gao et al. 2021a). The human mycobiome diversity is relatively low compared with bacterial communities and is dominated by yeast such as *Candida*, *Saccharomyces*, and *Malassezia*. Dysbiosis of intestinal fungi has been reported in alcoholic patients with an overgrowth of *Candida* (Yang et al. 2017). On the other hand, viruses are key constituents of the gut ecosystem and contribute greatly to its evolution and homeostasis. Viromic sequencing has also been performed in a population of patients with alcoholic hepatitis using metagenomic sequencing. Higher viral diversity was found in fecal samples of alcoholic patients compared to controls (Jiang et al. 2020).

3 The Gut Microbiome-Brain Axis in Patients with Alcohol Use Disorder

The first study investigating the gut-brain axis in AUD patients was published in 2014. The authors showed that the patients characterized by alterations of the gut microbiota had higher scores of depression, anxiety, and alcohol craving compared to AUD patients with no altered microbial composition. In a later study (Leclercq et al. 2020), the authors showed that the leaky gut and the dysbiosis of the microbiota were also associated with altered sociability.

In recent studies (Radjabzadeh et al. 2022; Bosch et al. 2022) assessing the effect of gut microbiota composition on depression scores in more than 2,500 individuals, increased Lachnospiraceae and decreased Ruminococcaceae were consistently associated with depression across ethnicities. *Subdoligranulum*, a butyrate-producing bacteria, was also consistently found to be depleted in individuals with generalized anxiety disorder and depression in several studies (Simpson et al. 2021). Those bacterial changes were also observed in the subset of dysbiotic alcoholic patients presenting with more severe psychological symptoms, suggesting that the gut microbiota might contribute to the development of psychological alterations associated with AUD, including depression, anxiety, and alcohol craving.

In order to demonstrate the causal role of the gut microbiota in the development of the behavioral and neurobiological alterations associated with AUD, we performed a fecal microbiota transplantation experiment (Leclercq et al. 2020). Briefly, mice were first treated with a cocktail of antibiotics to deplete their microbiota. Then, the first group of mice (AUD-recipient) were transplanted with the dysbiotic microbiota of AUD patients, and the second group of mice (CT-recipient) were transferred with the gut microbiota of healthy subjects. Both groups were tested for behavior and different brain areas were collected at the end of the experiment. We found that AUD-recipient mice displayed reduced social behavior, increased depression-like behavior, and increased blood stress marker, corticosterone, compared to CT-recipient mice, while anxiety-like behavior was similar in both groups. Interestingly, mice inoculated with the AUD microbiota exhibited changes in brain functions such as reduced myelination, disturbances of GABA and glutamate neurotransmission in the frontal cortex, and increased inflammatory markers in the striatum. We then investigated the metabolic pathways that could drive the changes in behavior and brain functions. We found that increased ethanol production by the gut microorganisms and reduced β-hydroxybutyrate (BHB) levels, a ketone body produced by the liver known for its multiple neuroprotective, anticonvulsant, and anti-inflammatory properties, could contribute to the brain alterations. Those pre-clinical findings were confirmed in a cohort of AUD patients where lower blood BHB levels were associated with higher psychological distress, including social impairment, depression, and alcohol craving. To test the implication of BHB in myelination, we conducted an MRI study to extract the fractional anisotropy (FA) maps, a reflect of brain myelination (Pérez-Cervera et al. 2023; De Santis et al. 2019; Spindler et al. 2022), and found that plasma BHB levels were

significantly and positively correlated with FA in two areas of the white matter (Leclercq et al. 2020).

In conclusion, this was the first study showing that the transplantation of a human AUD microbiota to mice recapitulated some of the neurobiological and behavioral alterations associated with addiction, including depression, higher stress level, and social impairments and elucidating the potential mechanisms underlying the gut-brain relationships. Social deficits are also essential features of AUD patients and are related to difficulties in interpreting the emotions of others, sensitivity to social rejection (Maurage et al. 2012), and difficulties in taking into account the perspectives of others (Maurage et al. 2015), which results in high rates of relapses after alcohol withdrawal (Zywiak et al. 2003). Interestingly, while the link between gut microbiome and social behavior has been demonstrated in multiple animal models (Sherwin et al. 2019), our clinical data reported a link between leaky gut, gut dysbiosis, and social impairments in humans, suggesting a role for specific metabolites (Leclercq et al. 2020).

The metabolic pathway is a major communication pathway linking the gut and the brain. Here below, we described a non-exhaustive list of gut-derived metabolites that could potentially contribute to alcohol addiction or to the behavioral alterations associated with AUD, with a special focus on depression and sociability. After that, in the next section, we briefly reviewed the other gut-brain pathways related to inflammation and to the vagus nerve (see Fig. 1).

3.1 Microbial Metabolites Potentially Contributing to Alcohol Use Disorder

Presence or absence of specific microbial taxa has been associated with health or disease outcomes. However, given the redundancies of microbiome pathways, the functions of the microbiota, rather than their mere presence, are more likely to be the major determinants of their impact on human health. Functionality of the microbiome can be evaluated by measuring the metabolites produced by the gut bacteria via metabolomics studies. Metabolomics is an omics approach that makes possible the study of the metabolic changes in the body by measuring small molecules (i.e., metabolites) (Voutilainen and Kärkkäinen 2019). Unlike the genome, the metabolome directly represents the functional changes in cellular metabolism, and therefore provides a view about the current physiological state. In the human blood circulation, metabolites arise from different origins, including the diet, the gut microorganisms, the host, or other exogenous sources. At the crossroads between the gut microbiota and the host, microbial products from the intestine travel through the portal vein and the liver where they are metabolized into bioactive mediators and continue their journey in the systemic blood where they can eventually reach the brain to exert neuroactive effects.

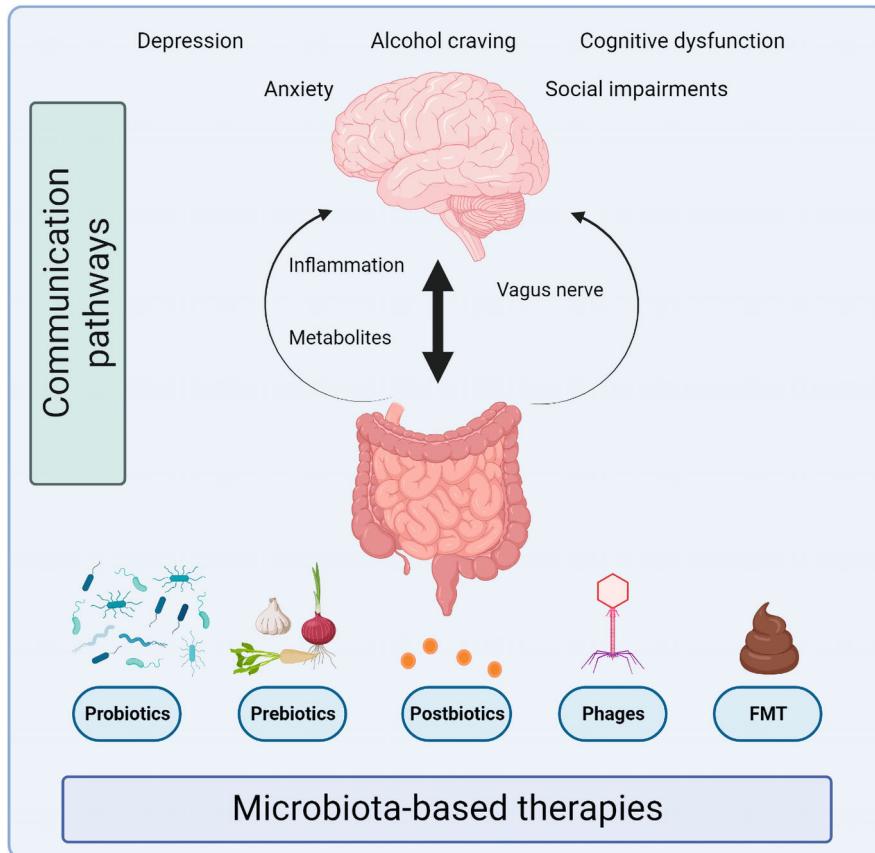


Fig. 1 Gut-brain communication pathways and microbiota-based interventional approaches that could be used in AUD patients to improve emotional, cognitive, and social impairments. FMT: fecal microbiota transplantation. Figure created with BioRender

Here, we reviewed the gut-derived metabolites that have been shown to be implicated in AUD or that could potentially be involved in the development of AUD due to their immune and neuroactive properties.

3.1.1 Neurotransmitters

The gut bacteria are able to synthesize neurotransmitters including dopamine, norepinephrine, glutamate, and GABA. The vast majority (>90%) of serotonin in the human body is produced by enterochromaffin cells of the gut under the influence of bacteria (Reigstad et al. 2015; Yano et al. 2015; Wikoff et al. 2009). Although this may not directly affect brain neurotransmitters levels since neurotransmitters

produced at the gut level may not cross the blood brain barrier (BBB), they likely influence the communication between bacteria and the motility of the gastrointestinal tract through an effect on the enteric nervous system.

3.1.2 Tryptophan Metabolites Including Indole-Derivatives and Kynurenone

Tryptophan is an essential amino acid whose degradation can occur through human or microbial pathways. Tryptophan metabolism is greatly influenced by alcohol consumption and has been widely studied in psychiatry since tryptophan is the precursor of serotonin. In fact, tryptophan can be absorbed in the intestine and enter the host serotonergic and kynurenone pathways, or it can be converted to indole and its derivatives by gut microorganisms.

Indole-derivatives are ligands for aryl hydrocarbon receptor (AhR) and can accumulate in the brain (Jaglin et al. 2018). AhR signaling pathways have been recently associated with intestinal immune responses and neuronal signaling (Barroso et al. 2021). They are therefore potent mediators of gut-brain communication. Fecal metabolic profiling has confirmed low level of indole-derivatives in AUD patients (Leclercq et al. 2014a; Hendrikx et al. 2018).

Intestinal levels of indole-3-acetic acid are reduced in patients with alcoholic hepatitis and in mice fed ethanol (Hendrikx et al. 2018). Supplementation of ethanol fed mice with indole-3-acetic acid attenuated liver damage and restored the expression of IL-22 and Reg3g implicated in the gut barrier function, through AhR activation (Hendrikx et al. 2018). Also, amelioration of anxiety-like behavior in a humanized mouse model of irritable bowel syndrome was suggested to be mediated by indole-3-acetic acid (Constante et al. 2021).

The role of indoxyl sulfate, another AhR ligand, remains controversial. It has been shown to promote oxidative stress and neuroinflammation in some studies, while in a mouse model of multiple sclerosis, indoxyl sulfate suppressed CNS inflammation (Rothhammer et al. 2016, 2018).

Kynurenone metabolites have gained considerable attention since they are at the interface between intestinal bacteria, host immune response, and brain functions. In situations of stimulated inflammation, the enzyme indoleamine 2,3 dioxygenase is activated and due to this activation, the tryptophan metabolism switches from serotonin to kynurenone pathway. By-products of the kynurenone pathway, such as kynurenic acid (neuroprotective) and quinolinic acid (neurotoxic), modulate glutamatergic neurotransmission, and their blood levels have been associated with alcohol craving and cognitive function in AUD patients (Leclercq et al. 2021). Interestingly, those metabolites were also correlated with specific gut bacteria including *Subdoligranulum*, *Faecalibacterium prausnitzii*, *Akkermansia*, and *Prevotella*, a butyrate-producing bacterium, suggesting that the gut microbiota may influence the circulating levels of neuroactive metabolites. While current pharmacological drugs targeting the NMDA receptors showed only modest efficacy and are accompanied by multiple side effects (Jonas et al. 2014), an indirect

approach targeting glutamatergic neurotransmission through the modulation of the kynurenine pathways might represent an interesting alternative for modulating alcohol-related behavior.

3.1.3 Tyrosine-Derivatives

In a maternal immune activation experiment, a mice model of autism spectrum disorder, Hsiao et al. (Hsiao et al. 2013) showed that serum levels of 4-ethylphenylsulfate (4-EPS), a tyrosine-derivative and a metabolite modulated by gut bacteria such as *Bacteroides fragilis*, could contribute to the behavioral alterations related to autism. Later, it was shown that 4-EPS interfered with oligodendrocyte maturation, myelination, and brain activity patterns in the limbic system (Needham et al. 2022). p-Cresol (or 4-methyl phenol) is another tyrosine-derivative metabolite produced by certain bacteria that is able to reduce the amount of myelin produced by brain cells and reduced social behavior (Gacias et al. 2016). The gut-host co-metabolite p-cresol glucuronide has been shown to improve, *in vivo*, the BBB integrity by acting as a TLR4 antagonist (Stachulski et al. 2022). Interestingly, the fecal levels of p-cresol were found to be modulated by alcohol consumption (Leclercq et al. 2014a).

3.1.4 Short Chain Fatty Acids

Short chain fatty acids (SCFAs) are produced by gut bacteria during the fermentation of nondigestible polysaccharides such as dietary fibers and are considered key mediators of the gut-brain axis due to their immune and neuroactive properties. Acetate (C2), propionate (C3), and butyrate (C4) are the most abundant SCFAs in the human body. Following their production in the colon, they are rapidly absorbed by colonocytes via active transport mediated by monocarboxylate transporters (MCTs), and then, they enter the citric acid cycle in the mitochondria to generate ATP and energy for the cells. Butyrate is produced by specific bacteria, called butyrate-producing bacteria (e.g., *Faecalibacterium prausnitzii*, *Roseburia*, *Subdoligranulum*, etc.) and has a key role in the protection of tight junction proteins of the gut barrier, thereby preventing the translocation of microbial toxins and exerting a protective effect for the liver (Roychowdhury et al. 2019). SCFAs that are not metabolized in the colonocytes are transported in the portal circulation and are used as energy source for the hepatocytes. Consequently, only a minor fraction of colon-derived SCFAs reaches the systemic circulation (Boets et al. 2017).

In vitro and animal studies have shown that SCFAs can cross the BBB and reach the brain likely through the MCTs abundantly expressed in the endothelial cells. In preclinical studies, SCFAs have been involved in numerous brain functions including neuroprotection, neurotransmission, and integrity of the BBB (Dalile et al. 2019; Braniste et al. 2014). In addition, SCFAs regulate gene expression by inhibiting histone deacetylases (HDACs), thereby promoting hyperacetylation of histones,

which have been shown to be protective for the pathophysiology of depression, autism spectrum disorders, and addiction (Volmar and Wahlestedt 2015; You et al. 2014; Kratsman et al. 2016). Studies in mice have shown that systemic administration of sodium butyrate combined with fluoxetine (a selective serotonin reuptake inhibitor antidepressant) significantly reduced depression-like behavior compared to fluoxetine alone, while histone hyperacetylation was observed in the hippocampus and frontal cortex (Schroeder et al. 2007). Also, intraperitoneal injection of sodium butyrate for 10 days attenuated the social deficits in a mouse model of autism (Kratsman et al. 2016).

However, in humans, the brain uptake of SCFAs appears to be minimal and it is currently unclear whether butyrate at physiological concentrations induces HDAC inhibition. This implies that the effects of SCFAs may rather result from peripheral signaling instead of direct uptake to the brain as seen in animal models. The effects of SCFAs on the brain could be driven by their effects on systemic inflammation which can modulate neuroinflammation (Hoogland et al. 2015). Preclinical evidence suggests that the gut microbiota might affect systemic inflammation and central neuroimmune function, with SCFAs being candidate mediators of these effects (Dalile et al. 2019). In humans, a meta-analysis (McLoughlin et al. 2017) supports the systemic anti-inflammatory effects of prebiotic and symbiotic supplementation, which are known to promote SCFAs production. However, whether those gut-targeted interventions result in decrease neuroinflammation is currently unknown but PET imaging studies could fill this gap of knowledge.

3.2 *Inflammatory Pathways Contributing to Alcohol Use Disorder*

AUD patients are characterized by a chronic systemic low-grade inflammation as witnessed by elevated plasma levels of TNF α , IL-1 β , IL-6, IL-8, IL-10, and hsCRP (Leclercq et al. 2012, 2014b). Ethanol is likely not sufficient to induce a peripheral inflammatory response in AUD patients, as elevated circulating cytokines are also found in detoxified patients. This suggests that other stimuli might challenge the immune system, such as the gut which is a source of pro-inflammatory agents.

By yet incompletely understood mechanisms, chronic alcohol abuse increases intestinal permeability, leading to the translocation of bacterial components such as lipopolysaccharides and peptidoglycans derived from the cell wall of Gram-negative and Gram-positive bacteria, respectively, candidalysin, cytolysin, β -glucan from the gut lumen to the systemic circulation (Gao et al. 2021b). These gut-derived bacterial products are recognized by Toll-like receptors of the immune cells circulating in the blood or residing in target organs, which consequently synthesize and release pro-inflammatory cytokines. Circulating cytokines are considered important mediators of the gut–brain communication, as they can reach the central nervous system

and induce neuroinflammation that is associated with change in mood, cognition, and drinking behavior (Leclercq et al. 2017).

3.3 The Vagal Communication

The vagus nerve is composed of up to 80% of afferent fibers that are not in direct contact with the gut microbiota or luminal content but can be stimulated by neurotransmitters and gut microbial metabolites including serotonin (Ye et al. 2021), SCFAs (Muller et al. 2020), and indoles (Jaglin et al. 2018) through diffusion across the intestinal barrier.

A hallmark study conducted by Bravo et al (Bravo et al. 2011) showed that oral administration of *Lactobacillus rhamnosus* JB1 to mice reduced depression-like behavior, anxiety-like behavior, and stress level and modified glutamate, GABA, and N-acetyl aspartate in several brain areas (Janik et al. 2016). Noteworthily, the behavioral effects of the bacterium were not observed in vagotomized animals, indicating that the vagus nerve is the main route of communication linking the bacterial strain to the brain.

In the context of AUD, Ezquer et al. (Ezquer et al. 2021) showed that, in rats selectively bred for their high ethanol intake, innate gut microbiota profile (rich in Proteobacteria, for instance) influences voluntary alcohol consumption and that, interestingly, subdiaphragmatic vagotomy led to an overall 80% reduction in voluntary ethanol intake compared with sham-operated animals.

4 Promises of Microbiome-Based Therapies for Alcohol Use Disorder

Strategies targeting the gut microbiota, including probiotics, prebiotics, and fecal microbiota transplantations (FMT) have been evaluated in AUD patients. Other strategies, including postbiotics and phage therapy, have never been tested in AUD patients but preclinical results highlight their potential beneficial effect for alcohol addiction (Fig. 1).

4.1 Probiotics

Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Hill et al. 2014).

Kirpish et al. (Kirpich et al. 2008) have shown that short-term oral supplementation with *Bifidobacterium bifidum* and *Lactobacillus plantarum* 8PA3 was

associated with greater improvement in alcohol-induced liver injury than standard therapy alone.

In an open-label study (Stadlbauer et al. 2008), patients with alcoholic cirrhosis received *Lactobacillus casei Shirota* for 4 weeks. Probiotics restored neutrophil phagocytic capacity, possibly by changing IL10 secretion and TLR4 expression.

However, currently, no study has evaluated the effects of probiotics on the behavioral dimensions of AUD.

4.2 Prebiotics

A prebiotic is defined as “a substrate that is selectively utilized by host microorganisms conferring a health benefit” (Gibson et al. 2017). Prebiotics act as substrates for bacteria in the colon which in turn ferment them into SCFAs.

We have performed the first randomized, double-blind, placebo-controlled study to test the effect of a prebiotic fiber supplementation on gut microbiota, immune markers, liver function, and behavior of AUD patients (Amadieu et al. 2022a; Amadieu et al. 2022b). The prebiotic inulin, a polysaccharide that is indigestible by the gut human enzymes but accessible to fermentation by the gut microorganisms, was given during a 3-week detoxification program at the hospital. Biological measurements and psychological assessments were performed before and after the intervention. Inulin induced changes in the gut microbiota composition such as an increase in *Bifidobacterium* and decrease in *Bacteroides* abundance. All patients showed an improvement in depression, anxiety, and alcohol craving scores during alcohol withdrawal regardless of the intervention group. Interestingly, only patients treated with inulin significantly improved the sociability score and had an increased serum level of brain-derived neurotrophic factor (Amadieu et al. 2022a). We then tried to elucidate the mechanisms by which the prebiotic could modulate social behavior. We did not find any improvement of systemic inflammatory markers and liver function suggesting that, in this study, inflammatory cytokines did not contribute to social behavior (Amadieu et al. 2022b). Consequently, we are currently performing blood metabolomics analysis in order to identify which gut-derived metabolites with potential neuroactive properties could contribute to the improvement of sociability score upon inulin exposure.

4.3 Fecal Microbiota Transplantation

FMT from healthy donors to patients has been used to change the gut microbiota of the recipient and represents an untargeted therapeutic approach.

The first FMT experiment in AUD patients was performed in 2017 in steroid-ineligible patients with severe alcohol hepatitis and showed improved liver disease and survival at 1 year (Philips et al. 2017). Then, in a randomized clinical trial of

FMT for AUD-related cirrhosis patients, Bajaj et al. (Bajaj et al. 2020) showed that patients receiving FMT had improved cognition and psychosocial quality of life compared to the placebo group. Serum inflammation (IL-6) and LPS-binding protein (LBP) were reduced while butyrate and fecal Ruminococcaceae were increased compared to baseline in the FMT group but not in the placebo group. A recent systematic review including 4 human studies showed that FMT overall led to an improvement in neurocognitive function in patients with hepatic encephalopathy (Madsen et al. 2021).

One major concern regarding FMT is the risk of infection, since AUD patients can have increased intestinal permeability and immune dysfunction. Also, selection of safe donors for FMT is quite complex, particularly given the potential transfer of multidrug-resistant bacteria. Since the definition of a “healthy” gut microbiota has not been determined yet, stool donors should be screened for several criteria. For instance, obesity (body mass index $>30 \text{ kg/m}^2$), active cigarette smoking, gastrointestinal, autoimmune, atopic, allergic, metabolic, neurologic, and psychiatric conditions, as well as abnormal serologic laboratory tests are exclusion criteria. Recent data from a stool bank estimate the donor eligibility rate at 3%, highlighting that healthy donors are not easy to find (Kassam et al. 2019).

4.4 Postbiotics

While microbially generated metabolites have been related to the development of metabolic, immune, and psychosocial disturbances related to AUD, they can also serve as therapeutic opportunities. The microbial metabolites were previously included in the broad-spectrum definition of postbiotics, but this has been changed by a panel of experts in 2021. The current definition of postbiotic is “preparation of inanimate microorganisms and/or their components that confers a health benefit on the host” (Salminen et al. 2021). This includes deliberately inactivated microbial cells with or without metabolites or cell components that contribute to demonstrate health benefits.

In the context of addiction, depletion of the gut microbiota by antibiotics showed enhanced sensitivity to cocaine reward in mice while administration of SCFAs normalized the reward response (Kiraly et al. 2016). Only one randomized, placebo-controlled trial has been performed to investigate the neuroactive effect of SCFAs supplementation. Authors demonstrated that 1-week colonic SCFA-mixture delivery significantly attenuates the cortisol response to psychosocial stress in healthy men (Dalile et al. 2020).

4.5 Phage Therapy

Alcoholic hepatitis is the most severe form of alcohol-related liver disease, with 75% of patients dying within 90 days of diagnosis (Maddrey et al. 1978; Thursz et al. 2015). Therapy with corticosteroids has limited efficiency (Thursz et al. 2015) and liver transplantation is not available for all patients. Therefore, new approaches that target the gut microbiota could be of importance for those patients. Phage-based treatment is a potential interesting tool to edit very precisely the gut microbiota. Previous work has demonstrated the key role of cytolytic *E. faecalis* in ethanol-induced liver damage and mortality in patients with alcoholic hepatitis (Duan et al. 2019). Therefore, eradication of those specific bacterial strains that produce cytolysin might result in better outcome compared to current treatments of alcoholic hepatitis. Phages or bacteriophages are viruses infecting bacteria in a highly-strain specific manner. In a preclinical study, mice were colonized with feces from cytolysin-positive patients and then administered with a bacteriophage cocktail containing phages against cytolytic *E. faecalis*. The treatment with phages reduced the fecal amount of *Enterococcus* without affecting the overall composition of the gut microbiota and interestingly, it abolished ethanol-induced liver injury (Duan et al. 2019). A clinical trial is now required to validate the human relevance of those findings.

5 Conclusion

The fields of microbiology and neuroscience in modern medicine have largely developed in recent years, but following distinct trajectories. However, accumulating evidence demonstrated that the gut microbiota can greatly influence all aspects of physiology including brain functions and behavior (Cryan and Dinan 2012). It should be emphasized that the majority of the gut microbiota-brain axis studies have been performed in rodent models. While modelling complex human psychiatric disorders such as alcohol addiction in animals is challenging, it should be noted that important discrepancies between rodent and human microbiota do exist (Nguyen et al. 2015). This review has therefore put the focus on human studies, whenever possible.

Characterization of the human alcoholic gut microbiota composition is challenging. Results of existing studies are conflicting likely due to many confounding factors that influence the microbial composition, including lifestyle factors, diet, and drugs used. Therefore, combining metagenomics and metabolomics approaches in well-defined AUD population could be a better way to uncover the intricate communication within the gut-brain axis. Some bacterial metabolites have been proposed in this review to contribute to the physiopathology of AUD. The role of other microbiota-derived metabolites with neuroactive properties in other pathological contexts has been reviewed elsewhere (Ahmed et al. 2022).

We believe that modulating certain type of neuroactive metabolites, by acting on nutrition and gut microbiota, represents an interesting strategy to manage neuropsychiatric diseases such as alcohol addiction. It appears probable that, in the future, a detailed analysis of the patient's microbiome and metabolome will be performed, in relation to discrete behavioral impairments, to determine which personalized microbiota-centered therapies might be the most useful to restore microbe-host homeostasis (Bajaj et al. 2022).

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