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Review article

# Neurobiological mechanisms of control in alcohol use disorder – Moving towards mechanism-based non-invasive brain stimulation treatments

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## ABSTRACT

Alcohol use disorder (AUD) is characterized by excessive habitual drinking and loss of control over alcohol intake despite negative consequences. Both of these aspects foster uncontrolled drinking and high relapse rates in AUD patients. Yet, common interventions mostly focus on the phenomenological level, and prioritize the reduction of craving and withdrawal symptoms. Our review provides a mechanistic understanding of AUD and suggests alternative therapeutic approaches targeting the mechanisms underlying dysfunctional alcohol-related behaviours. Specifically, we explain how repeated drinking fosters the development of rigid drinking habits and is associated with diminished cognitive control. These behavioural and cognitive effects are then functionally related to the neurobiochemical effects of alcohol abuse. We further explain how alterations in fronto-striatal network activity may constitute the neurobiological correlates of these alcohol-related dysfunctions. Finally, we discuss limitations in current pharmacological AUD therapies and suggest non-invasive brain stimulation (like TMS and tDCS interventions) as a potential addition/alternative for modulating the activation of both cortical and subcortical areas to help re-establish the functional balance between controlled and automatic behaviour.

## 1. Introduction

Alcohol use disorder (AUD) is a chronic relapsing disorder that affects millions of people each year. In 2016 alone, alcohol consumption was estimated to be the primary cause of almost 300,000 deaths and 7.6 million years of life lost (YLL) due to premature mortality in European countries (WHO, 2018, 2019). Common causes associated with alcohol-related deaths are cardiovascular and gastrointestinal diseases, diabetes, cancer, and injuries (Rehm and Shield, 2014). AUD does not only affect those who meet the diagnostic criteria, but it also places a major social and economic burden on the patients' relatives and on general public health services. Over the years, different strategies, such as prevention programmes, increased taxes on alcoholic beverages, and stricter policies on alcohol-related advertising, have been introduced to limit high consumption of alcoholic beverages among the general population. Despite the huge worldwide social costs of alcohol abuse, only a minority of AUD patients receive any treatment or professional help. In the US, for example, only about 20 % of AUD patients receive such services (Grant et al., 2015). Furthermore, only a minority (an estimated

33 %) of the individuals who have been directed to professional help actually receive the care recommended by clinical practice guidelines (Hepner et al., 2019). Oftentimes, AUD patients also experience other comorbid substances abuse or other clinical conditions, such as depression, anxiety, and personality disorders. This makes AUD symptoms hard to contextualize and treat (Grant et al., 2015). Lastly, individuals with AUD can often be under the influence of alcohol for the majority of their waking time. As a consequence, AUD can negatively impact work as well as personal and social life obligations.

AUD is characterized by a strong desire to drink and by a loss of control over consumption despite negative consequences (Schuckit, 2009). Such drinking behaviour is often driven by consolidated habits and automatic stimulus-responses (S-R) associations. In certain circumstances, alcohol-related stimuli can strongly trigger drinking behaviours like alcohol seeking and drinking (Everitt and Robbins, 2016; Koob and Volkow, 2016; McKim et al., 2016; O'Tousa and Grahame, 2014). Most importantly, AUD is characterized by impaired cognitive control functions. This compromises the selection and execution of goal-directed actions in conflicting contexts and the ability to inhibit

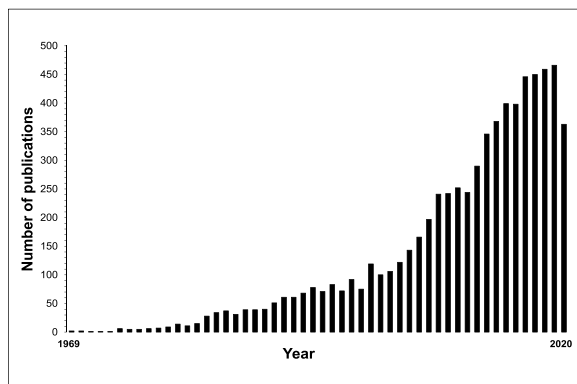
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**Fig. 1.** The graph shows the number of publications per year from 1969 until 2020 obtained for the search terms “alcohol use disorder” OR “alcoholism” AND “cognitive control”. The constant increase in publications combining these terms demonstrates the growing interest in the role played by cognitive control in pathological AUD behaviour. Source: <https://pubmed.ncbi.nlm.nih.gov/>.

prepotent responses. Importantly, habitual responses and top-down cognitive control are not independent from each other. It has been argued that they represent different ends of a behavioural spectrum from more automatic to more controlled, or maybe even different phases of action planning (Hommel, 2019). Further evidence for such notions is provided by the observation that they seem to arise from interrelated neural circuits that compete for limited cognitive and neural resources (i.e., meta-control) to access information processing. Instead of investigating control and habits as two independent aspects of AUD, we should therefore focus on the imbalance between controlled and (long-term) goal-directed behaviour on the one hand versus habitual behaviour that might be serving more short-term goals on the other hand (De Houwer, 2019; Hogarth, 2020; Kruglanski and Szumowska, 2020). Although the acute and long-term neurochemical and neurophysiological effects of alcohol in functionally associated (sub)cortical brain circuits have previously been investigated (Barker et al., 2015; Corbit and Janak, 2016; Koob and Volkow, 2016; Sjoerds et al., 2013), the neurobiological mechanisms underlying this imbalance are still disputed (Fig. 1) (Barker and Taylor, 2014; Everitt and Robbins, 2005; Volkow and Morales, 2015).

Despite the substantial progress made in AUD treatment, relapse rates have remained very high. Even individuals who successfully complete a therapeutic programme often fail to maintain abstinence for longer periods thereafter (Garbusow et al., 2014b; Naqvi and Morgenstern, 2015). Pharmacological therapies are the most common form of intervention and mainly focus on reducing craving and withdrawal symptoms. However, therapeutic programmes designed to target possible neurobiological correlates of the mechanisms that maintain the balance between cognitive control and automatism have received rather limited attention. In recent years, non-invasive brain stimulation techniques, such as transcranial electrical current stimulations (TES) and transcranial magnetic stimulation (TMS) have been applied to modulate the activity of cortical and subcortical areas and consequently induce behavioural modifications. Both TES and TMS have been shown to produce short- and long-term neural plasticity changes (Chan et al., 2021; Duffau, 2006; Farahani et al., 2021; Klomjai et al., 2015), which provides a theoretical basis for their use in therapeutic interventions (Lefaucheur et al., 2020, 2017). However, only a limited number of studies have applied these techniques in AUD. This is at least partly due to a lack of mechanistic understanding of the functional processes that need to be targeted in order to regain control over drug intake (Heinz et al., 2020).

Against this background, the goal of this review is to provide a comprehensive mechanism-based understanding of AUD, where

symptoms (such as craving and relapsing) reflect pathological alterations in the underlying imbalance between controlled and habitual behaviour. After summarizing the cognitive and neurobiological aspects of this imbalance, we define the basis for a novel TMS- and TES- based approach intended to modulate the neurobiological mechanisms underlying the imbalance between increased habit-driven behaviour and loss of control over alcohol intake. Based on this, we propose a change in the focus of AUD interventions from direct action on the symptoms towards neuromodulation of the mechanisms that actually drive the pathological behaviour. This mechanism-based approach may help to compensate or maybe even overcome the limitations that currently characterize AUD treatments.

## 2. AUD as an imbalance between controlled and habitual behaviour

The compulsive and impulsive nature of pathological behaviour in AUD has been suggested to arise from a combination of increased tendencies to rely on habitual behaviour and of impaired cognitive control system guiding behavioural responses. Protracted consumption of alcohol, like other drugs, leads to the consolidation of automatic S-R associations and harmful habits that can become activated by environmental stimuli, which have previously been associated with this substance (Barker and Taylor, 2014). Even more importantly, alcohol has detrimental effects on executive functions, particularly on cognitive control that sustains effortful goal-directed behaviours by modifying or inhibiting impulsive / automatic response tendencies (Diamond, 2013; Miyake et al., 2000; Wilcox et al., 2014). In the following paragraphs, we discuss how both of these aspects (i.e., shifts in controlled and automatic processes), could conjointly foster the development and maintenance of AUD. Specifically, cognitive control deficits may increase the risk of relapse, whereas strong alcohol-associated automatisms may maintain uncontrolled consumption. A deeper understanding of the consequences of these factors may play a strategic role in the development of alternative therapeutic interventions aimed at regaining control over alcohol intake to increase the chances that patients succeed to remain abstinent.

### 2.1. From occasional to chronic drinking

One of the main characteristics of AUD is the transition from occasional drinking to drinking-related behaviours that have become consolidated into harmful habits (Corbit et al., 2012; Corbit and Janak, 2016; McKim et al., 2016). In both humans and non-human animals, behaviour (or actions) can be generated in a controlled goal-directed manner or driven by habits and automatic S-R associations. Goal-directed actions are characterized by a relationship between stimulus, response, and outcome (S-R-O association). In this relationship, a behaviour is carried out after weighing value of the outcome against the cost of that particular behaviour (Eder and Dignath, 2019; Shenhav et al., 2013). If an outcome devaluation occurs due to attenuation or disruption of the relationship between response and outcome, goal-directed behaviour will either be reduced or interrupted. In recreational and occasional drinking, alcohol is commonly consumed for its hedonic effects, such as alcohol-related euphoria and facilitation of social interactions. Additionally, alcohol may sometimes be consumed to cope with anxiety, stress, or depression (Book and Randall, 2002; Field and Powell, 2007; Holahan et al., 2003). In those scenarios, alcohol intoxication is mostly the result of goal-directed behaviours and consumption is relatively flexible and controlled. However, repeated alcohol consumption strengthens the relationship between alcohol-related stimuli and alcohol-seeking behaviour, most likely due to an interaction of Pavlovian and instrumental learning (Everitt and Robbins, 2016; Garbusow et al., 2016; Koob and Le Moal, 2005). So while consumption is initially driven by S-R-O associations, it often gradually becomes less and less dependent on the outcome (e.g., outcome devaluation). This way, S-R associations eventually establish

themselves as consolidated habits, thus replacing initially goal-directed behaviours. Per se, habitual behaviour is often very useful as it helps to save cognitive resources in action selection and action execution (Bensmann et al., 2020; Diamond, 2013; Stock et al., 2019). When a devaluation of the outcome occurs, cognitive control functions can normally redirect or inhibit automatic responses. In drug and alcohol-related contexts, however, habitual behaviour eventually becomes insensitive to changes in the outcome value. In this scenario, consumption is perpetuated regardless of its actual consequences and thus no longer driven by its expected rewards (Corbit and Janak, 2016). The progression to a condition in which alcohol is no longer consumed for its positive rewards and cognitive functions can no longer exert flexible control over a habit-based behaviour decisively marks the development of AUD. For these reasons, the disconnection of habitual responses from outcome devaluation and resistance to extinction are considered defining features of the compulsive nature of AUD (McKim et al., 2016). Yet, it should be noted that these assumptions are still subject to an ongoing debate, as it has also been argued that regular drug users might not show a greater propensity towards habitual behaviour in general and that increased economic demand / drug value might sustain consumption instead (Hogarth, 2020). In line with this view, it could be argued that instead of being detached from all outcomes, persistent drinking might be caused by a focus on the reward obtained from short-term improvements in negative affect and withdrawal symptoms at the expense of long-term costs, probably due to steep outcome devaluation functions. However, the fact that patients who are treated with drugs that eliminate the positive effects of alcohol consumption (like disulfiram or naltrexone) still frequently relapse (Soyka and Rosner, 2021; Zindel and Kranzler, 2014) refutes the idea that a mere shift in goals can serve as the sole explanation for continued alcohol consumption in AUD. Against this background, we maintain the notion that changes in habitual behaviour are likely to contribute to pathological behaviour in AUD, although we recognize that the detrimental effects on cognitive control and executive functions are better supported and less vigorously disputed.

Studies have extensively investigated the mechanisms by which repeated exposure to alcohol promotes the formation of dysfunctional habits and by which alcohol-related stimuli drive the development and perpetuation of pathological behaviour in AUD. In particular, there has been much interest in how alcohol-related cues may trigger alcohol seeking and drinking behaviours (Everitt and Robbins, 2005; Garbusow et al., 2016; Heinz et al., 2020; Sommer et al., 2017). When contextual stimuli (e.g., the view of a bar or alcohol advertisement) are consistently paired with alcohol consumption, the behavioural response (i.e., drinking) becomes strongly associated with the rewarding effect of that substance, thus ultimately triggering consumption and increasing the chances of relapses in AUD (Barker and Taylor, 2014). High craving and a high number of relapses in AUD could be explained by such contextual cues that become alcohol-related stimuli through Pavlovian conditioning and then act as reminders of alcohol consumption (Barker and Taylor, 2014). To investigate this, several experimental paradigms have been employed in animal and human studies to assess the impact of alcohol-related cues on individuals with AUD. One of the most efficient approaches is the Pavlovian to Instrumental Transfer (PIT) paradigm (Corbit and Janak, 2016; Garbusow et al., 2014a, ; Garbusow et al., 2016; Sommer et al., 2017). Overall, several studies using this experimental approach (Corbit and Janak, 2007; Garbusow et al., 2016, 2014a; Sommer et al., 2017) have supported the assumption that, by regularly pairing alcohol-related stimuli with drinking responses, behaviour eventually becomes strongly automatized and guided by harmful drinking habits. This condition is further exacerbated by the progressive inability to operate proper control over these dysfunctional behaviours. In this regard, the shift towards less controlled, more habit-based behaviour in AUD patients is supported by the detrimental effects of alcohol on cognitive control functions (Stavro et al., 2013; Wilcox et al., 2014). These top-down functions are indispensable for guiding behaviour and controlling automatic response tendencies by

analysing and processing ongoing mental and environmental information. Against this background, we will summarize the evidence for adverse alcohol effects on cognitive control functions, particularly on the inhibition of impulsive behaviour, below.

## 2.2. Detrimental effects of alcohol on cognitive control

Cognitive control is a general term often used for cognitive functions dedicated to inhibiting, supervising, and updating surrounding information in order to control thoughts and engage in appropriate behaviour. Cognitive control aids decision-making processes and goal-directed actions, and inhibits or modifies habitual and automatic responses in contexts where they would be inappropriate or ill-advised (Diamond, 2013; Shenhav et al., 2017, 2013). How acute intoxication (Bartholow et al., 2018; Bensmann et al., 2020; Chmielewski et al., 2018b; Stock et al., 2017, 2016b, 2016c) and chronic alcohol abuse (Bernardin et al., 2014; Brion et al., 2017; Kuźma et al., 2014; Le Berre et al., 2017; Wilcox et al., 2014) affect top-down cognitive control functions has been extensively reviewed. Cognitive control functions are generally responsible for keeping habitual behaviour "in check" by selecting and executing an appropriate response in case of conflicting conditions or when there is no prior experience with a given scenario. Controlled and habitual processing may be conceptualized as two ends of a broader neural network that compete for access to neural and cognitive resources in order to maintain balanced behaviour – a concept that has been defined as meta-control (Beste et al., 2018b; Goschke and Bolte, 2014; Hommel, 2015; Hommel and Wiers, 2017). Meta-control is assumed to emerge from distributed neural networks involving brain systems associated with emotional processing of reward stimuli, salience signalling, and cognitive control abilities determining comprehensive neural resource processing (Goschke, 2013, 2003). Against this background, AUD-typical behaviour may be rooted in a pathological shift from cognitive and neural resources driving top-down control functions to more automatic processes (Goschke, 2014). Intact cognitive control abilities are indispensable for flexible behaviour and refraining from the execution of prepotent response tendencies. Inhibition, shifting between task or mental sets, and monitoring / updating working memory have been identified as functionally distinct, yet related sub-domains of cognitive control (Miyake et al., 2000). Inhibition can further be subdivided into inhibitory and interference control. Inhibitory control (or behavioural inhibition) encompasses different processes involved in the suppression of prepotent responses, action control or action cancellation (Chmielewski et al., 2018a; Chmielewski and Beste, 2017; Mückschel et al., 2017; Stock et al., 2016b; Verbruggen et al., 2019). Interference control (or cognitive inhibition) encompasses the suppression of irrelevant mental and attentional processes or resistance to interfering stimuli or information (Bari and Robbins, 2013; Diamond, 2013; Miyake et al., 2000). Shifting between tasks or updating mental sets involves the ability to disengage from old or inappropriate tasks in order to engage in new or more relevant ones instead. However, inhibition is also thought to play a central role for these two functions. Updating may require ignoring or suppressing irrelevant information, while shifting may require suppression of an old mental set in order to switch to new sets (Miyake et al., 2000; Ridderinkhof et al., 2004a, b; Rubia et al., 2001; Zhang et al., 2016). Even though functional impairments have been found across several cognitive control domains, inhibition is thought to be most crucially involved in the pathologically impulsive and compulsive nature of AUD (Burchi et al., 2019; de Wit, 2009; Wilcox et al., 2014). In AUD, the shift from goal-directed consumption to maladaptive habits strengthens over time, and progressive impairments in cognitive control functions reduce the probability of remaining abstinent (Heinz et al., 2020). Although it is still debatable whether impairments in cognitive control may be a vulnerability factor rather than the consequence of heavy drinking, evidence strongly supports their role in explaining the high relapse rates among AUD patients (Mackiewicz Seghete et al., 2013; Naqvi and Morgenstern, 2015; Pfefferbaum et al.,

1998; Saunders et al., 2008). At the functional level, deficits in response inhibition may undermine the ability to confront contextual alcohol-related stimuli and to suppress the drive towards alcohol drinking (Day et al., 2015). In addition to that, compromised interference control may reduce the possibility of engaging an alternative course of actions and adopting corrective coping strategies when facing alcohol-related cues. Although impairments in cognitive control functions are associated with chronic drinking, it is also well-known that acute alcohol intoxication has an exceptionally strong detrimental effect on top-down control processes and - comparatively - little effects on habits and automatisms (Bensmann et al., 2020; de Wit, 2009; Stock et al., 2014, 2019; Stock et al., 2016d).

Acute alcohol consumption has repeatedly been shown to have strong negative effects on response inhibition, especially when higher levels of top-down control are required (Chmielewski et al., 2018b; Gan et al., 2014; Loeber and Duka, 2009; Stock et al., 2016d). Overall, evidence indicates that the negative effects of alcohol intoxication are much more pronounced when responses require a high level of cognitive control than when they are solely driven by automatic S-R bindings (Bensmann et al., 2020). Matching this, AUD patients are characterized by low inhibitory control as compared to healthy controls (Ames et al., 2014; Kamarajan et al., 2005; Noel et al., 2007; Kamarajan et al., 2005). Furthermore, the ability to withhold or cancel an impulsive response has been found to be particularly weak in individuals with AUD when alcohol-related stimuli are used to test their performance (Noel et al., 2007). This supports the assumption of specific inhibitory control biases in case of alcohol-related cues, which are probably related to the higher salience and stronger S-R associations of these stimuli (Corbit and Janak, 2016; Garbusow et al., 2014a, 2016; Sommer et al., 2017). In line with this, AUD patients have been shown to be prone to a strong imbalance towards automatic behaviour, which is sustained by reduced inhibitory control (Goudriaan et al., 2006; Joos et al., 2013; Maurage et al., 2011; Rubio et al., 2008).

With respect to interference control (Chmielewski and Beste, 2019; Stock et al., 2016a), acute alcohol intoxication has repeatedly been shown to have negative effects on performance, especially when increased cognitive control is required (Bartholow et al., 2003; Marinkovic, 2013; Marinkovic and Azma, 2010; Stock et al., 2017). Yet, it should be noted that findings on interference control have been more heterogeneous, as some studies reported increased interference effects during acute alcohol intoxication (Bartholow et al., 2018; Curtin and Fairchild, 2003; Rose and Duka, 2007; Rosen et al., 2016), while others failed to replicate this finding (Bombeke et al., 2013; Duka and Townshend, 2004; Marinkovic et al., 2012). The chronic effects of alcohol on interference control have also been less consistent than those on inhibitory control and response inhibition, as the performance of AUD patients is not always reported to be worse than that of healthy controls (Brion et al., 2018; Chanraud et al., 2007; Joos et al., 2013; Padilla et al., 2011; Pitel et al., 2009). For example, Padilla et al. (2011) found no association between the number of drinking years and reduced interference control, while Brion et al. (2018) found that compared to healthy controls, AUD patients exhibited lower response inhibition in higher (flanker) conflict conditions and a higher sensitivity to the interference of incongruent flanker stimuli. Mixed results have also been found when AUD patients are confronted with a Stroop task (Chanraud et al., 2007; Dao-Castellana et al., 1998; Joos et al., 2013; Tedstone and Coyle, 2004). Joos et al. (2013) found that patients with early AUD onset (< 25 years old) had better interference control performance than those with a late AUD onset (> 25 years old). Similar investigations showed that interference control in AUD patients was characterized by slower responses and higher error rates (Dao-Castellana et al., 1998; Noel et al., 2013; Tedstone and Coyle, 2004). A recent mega-analysis (Liu et al., 2019), which analysed data from several studies assessing the integrity of inhibitory control functions in substance and polysubstance use, found no significant relation between alcohol use and response inhibition impairments. However, it should be noted that this analysis only

included individuals with light to heavy substance use, but no persons who received any form of treatment for substance use disorder or who were currently maintaining abstinence. Based on this, the authors concluded that the relationship between alcohol and inhibition deficits might not be linear, so that functionally relevant deficits might only be found in more severe cases of AUD.

Overall, the lack of consistency among these studies may be attributed to variability in consumption levels between samples as well as variation in experimental designs. Different experimental paradigms may assess different facets of cognitive control processes, thereby complicating the generalization of these findings outside the specific function being examined. Against this background, the role of pre-morbid cognitive deficits might be particularly important when considering cognitive control deficits in AUD.

### 2.3. Premorbid cognitive control deficits

It has remained an open question whether impairments in cognitive control functions are a mere consequence of chronic alcohol intake, or a pre-morbid factor that could increase the risk of developing AUD later in life. Several studies investigated whether impairments in inhibitory and interference control can be used as markers to identify the risk of developing AUD in non-clinical samples (Crean et al., 2002; Nigg et al., 2006; Saunders et al., 2008; Silveri et al., 2011). An interesting aspect of the association between cognitive control deficits and AUD is that the age at which addicted behaviour starts seems to be a contributing factor. Evidence shows that subjects with an early onset of addiction (< 25 years old) have significantly lower response inhibition (but not lower interference control) than healthy controls, supporting the hypothesis that response inhibition is one of the first components of executive control functions to be affected in AUD (Joos et al., 2013). Furthermore, performance in response inhibition tasks has been demonstrated to already be impaired in subjects categorized as heavy drinkers (Montgomery et al., 2012; Rubio et al., 2008). Rubio et al. (2008) investigated several neuropsychological functions at baseline and after 4 years follow-up in a sample of more than 400 individuals who has been diagnosed as heavy drinkers but had not received previous treatments. As predicted, heavy drinkers performed worse than the control group in most of the cognitive tasks. Interestingly, the authors also found a significant correlation between response inhibition impairments and alcohol consumption at the follow-up assessment.

Overall, these results highlight that heavy drinking at a young age may impair the normal development of cognitive control abilities and promote the progression from occasional consumption to AUD (Nigg et al., 2006; Norman et al., 2011; Ridderinkhof, 2002; Wetherill et al., 2013). Another important conclusion that can be drawn from these findings is that lower cognitive control performance in laboratory or experimental tasks may be considered a predictive factor for developing AUD later in life. However, further evidence is needed to clearly identify the extent to which cognitive control impairments are a "pre-morbid" risk factor for developing substance use disorder (Heinz et al., 2020). Understanding the mechanisms underlying dysfunctional inhibition is therefore vital for designing new interventions to help regain control over alcohol abuse. In this regard, it is crucial to consider that cognitive control deficits may strongly contribute to the imbalance between habitual and controlled behaviour in AUD, and are thus critical for the development and perpetuation of the drinking disorder. As outlined above, both acute and chronic alcohol consumption support a shift towards more impulsive behaviour, which is aggravated by impaired cognitive control processes. Cognitive control dysfunctions undermine the possibility of inhibiting incessant automatisms and pursuing alternative non-harmful behaviours. For example, lower cognitive control in acute alcohol intoxication could lead to a failure in restraining impulsive behaviour. This likely increases drinking frequency in at-risk individuals, thus ultimately increasing the risk of relapse and favouring uncontrolled consumption. Similarly, chronic consumption may pave

the way for a dysfunctional cognitive control system and strengthen the degree to which harmful habits and compulsion may drive behaviour. From this perspective, a recovery of cognitive control and a reinstatement in the functional balance between habitual and cognitive control systems may play a key role in regaining control over drinking. Against this background, it is important to identify the neurobiological mechanisms responsible for the shift from top-down controlled behaviour towards the increased reliance on consolidated habits and automatisms. Next, we outline how the detrimental effects of alcohol on cognitive control, particularly inhibition, can be attributed to acute and long-term neurobiochemical and neuroanatomical alterations in cortical and subcortical circuits that constitute the neural network maintaining the balance between controlled and habitual behaviour (Everitt and Robbins, 2005; Koob and Volkow, 2016; Volkow et al., 2012).

### 3. Neurobiology of alcohol

Acute alcohol intoxication causes transient changes in brain chemistry and is responsible for short-term neurophysiological changes in brain activity (Bjork and Gilman, 2014). Repeated alcohol exposure produces long-term neurobiological alterations in a number of brain circuits and several neurotransmitter systems (Barker et al., 2015; Koob and Volkow, 2016; Volkow et al., 2012; Volkow and Morales, 2015). Both the short-term and long-term effects of alcohol affect cortical and subcortical circuits known to be involved in maintaining an appropriate balance between cognitive control and automaticity resources (Beste et al., 2018b; Hommel and Wiers, 2017). However, the extent of these effects is still being debated. The mechanisms responsible for long-term effects of alcohol abuse on the brain probably rely on some form of homeostatic neuroadaptation, which are at least partly associated with the development of alcohol tolerance. Homeostatic neuroadaptation can be defined as a corrective response to deviations from the normal range of functioning in a given system (Ramsay and Woods, 2014). In case of chronic alcohol abuse, this mechanism re-balances the acute substance-induced neurochemical changes to restore the normal cellular function (e.g., by rebalancing the expression of a given neurotransmitter or receptor). Yet, this can easily result in an over-corrective response (Lovinger, 1997; Lovinger and Roberto, 2010), especially when there is a certain degree of variability in intoxication levels. One of the main problems in alcohol abuse is that such long-term neural adaptations strengthen over time. After developing tolerance for the substance, there will be a constant need for alcohol consumption in order to reduce craving and withdrawal symptoms, as well as an increasing risk of relapse and aversive long-term physiological/ psychological consequences (Koob and Le Moal, 2005).

Although the neurobiological consequences of alcohol have been studied extensively, the fact that ethanol affects a wide range of neurotransmitter systems and brain regions makes it an inherently challenging endeavour to precisely target its pharmacodynamics. Above, we described how acute and chronic alcohol effects yield similar consequences at the behavioural level of cognitive control impairments and increased automaticity. The following section will elaborate the detrimental consequences of alcohol from a neurobiological perspective. We will elucidate the neurobiochemical and neuroanatomical alterations that occur in several brain regions and how they can ultimately be associated with dysfunctional cognitive control and behaviour in AUD. First, we review the evidence for acute and chronic alcohol effects on several neurotransmitter systems and how they influence cognitive control and automatic behaviour. Subsequently, we describe how neurochemical alterations caused by alcohol impact the activity of cortical and subcortical circuits linked to pathological behaviour in AUD. In particular, we outline how a shift of activity within the striatum and associated functional neuroanatomical loops (Chudasama and Robbins, 2006) may promote the formation of habitual behaviour and, thereby, be responsible for the increased compulsivity in AUD (Everitt and Robbins, 2005). Furthermore, we review the evidence indicating

that activity changes in frontal cortical regions can be related to impaired response inhibition and interference control functions (Wilcox et al., 2014).

#### 3.1. Neurotransmitter systems affected by alcohol

##### 3.1.1. GABA and glutamate

Acute and chronic alcohol consumption interfere with the neural excitability equilibrium by modulating both glutamate and  $\gamma$ -aminobutyric acid (GABA) (Chandrasekar, 2013; Clapp et al., 2008; Koob, 2004). Glutamate is the principal excitatory neurotransmitter in the central nervous system and crucial for modulating synaptic strength in learning and memory functions (Heaney and Kinney, 2016; Kolasinski et al., 2019). GABA is the primary inhibitory neurotransmitter of the brain and plays an important role in learning and control functions (Heaney and Kinney, 2016; Hermans et al., 2018; Kolasinski et al., 2019). GABAergic and glutamatergic activity in basal ganglia nuclei (e.g., the striatum) and in cortical regions have been shown to modulate response selection, response inhibition, and conflict monitoring functions (Beste et al., 2012, 2008; Haag et al., 2015; Quetscher et al., 2015). In healthy individuals, these two neurotransmitter systems are usually in reciprocal balance, but both acute and chronic alcohol consumption have large effects on their activity. Acute alcohol intoxication induces a reduction in the efficiency of glutamate receptor *N*-methyl-D-aspartate (NMDA), thus hampering glutamatergic transmission. It also acts as an indirect GABA agonist, increasing the release of GABA, and thus enhancing neural inhibition (Koob, 2004). These transient molecular alterations are responsible for some of the common behavioural responses to acute alcohol intoxication, such as lower anxiety and higher sedation. Functions associated with learning, memory (Lovinger et al., 1989; White et al., 2000) and cognitive control (Cheng et al., 2018; Cuzon Carlson, 2018; Zorumski et al., 2014) are also affected by this. In chronic alcohol consumption, the system responds with upregulation of NMDA receptor activity to compensate for the frequent alcohol-induced glutamatergic inhibition (Griffin et al., 2014; Qiang and Ticku, 2005). Concomitantly, prolonged alcohol consumption induces downregulation of GABA<sub>A</sub> receptors in response to the prevalent GABAergic overstimulation (Adermark et al., 2013; Lewohl et al., 1997). These modulatory changes can be found in both cortical and subcortical regions (Koob, 2004; Zorumski et al., 2014). Importantly, reduced striatal GABAergic neurotransmission may negatively affect response selection and learning of new S-R mappings (Cuzon Carlson, 2018). With respect to clinical symptoms, the combination of NMDA receptor upregulation and GABA<sub>A</sub> receptor downregulation eventually induces hyper-excitability, which can trigger acute withdrawal-associated symptoms, such as agitation, dysphoria anxiety, and increased risk of experiencing a seizure episode when AUD patients interrupt alcohol consumption after prolonged excessive use (Most et al., 2014). The associated hyper-glutamatergic status, and especially the excessively stimulated NMDA receptors, are furthermore likely to substantially contribute to cellular degeneration (i.e., excitotoxicity) (Hoffman, 1995).

##### 3.1.2. Dopamine

Dopamine plays a pivotal role in mediating reward effects and reinforcement learning. As such, dopamine is deeply involved in the reinforcing aspects of alcohol and the shift from occasional recreational drinking to AUD (Arias-Carrión et al., 2010; Phillips et al., 2008; Volkow et al., 1996). Furthermore, dopamine regulates the balance between the prefrontal cortex (PFC) and basal ganglia circuits associated with motor and cognitive control functions, learning, and reward prediction errors (Albrecht et al., 2014; Bari et al., 2009; Bensmann et al., 2019; Beste et al., 2018a, 2016; Eagle et al., 2011; Holroyd and Coles, 2002; Schultz, 1998; Ullsperger et al., 2014). Alterations in the dopaminergic activity of the PFC and subcortical structures could therefore be linked to AUD-associated impairments in these functions (Trantham-Davidson

and Chandler, 2015; Volkow et al., 1996). Acute alcohol intoxication has a direct effect on the dopaminergic system, as ethanol enhances dopaminergic activity in the ventral tegmental area (VTA) (Brodie and Appel, 1998; Leurquin-Sterk et al., 2018; Lyness and Smith, 1992; Weiss et al., 1996; Yoshimoto et al., 2000), which results in higher dopamine release in the nucleus accumbens (NAc) and PFC (Robinson et al., 2009). This means that alcohol intoxication increases dopamine release in several PFC regions that are involved in addiction-associated reward processing, but also in decision-making and cognitive control functions (Leurquin-Sterk et al., 2018). Acute alcohol intoxication also enhances dopamine release in ventral portions of the striatum, which has been linked to increased attentional and emotional processing of alcohol-associated stimuli (Chastain, 2006; Diana et al., 1993). As a result of compensatory adaptations, patients with a history of alcohol abuse demonstrate several changes in the dopamine system, such as a downregulation of dopamine-related activation and a reduction in dopaminergic D<sub>2</sub> receptor availability in the ventral striatum (Hietala et al., 1994; Volkow et al., 1996). This "hypo-dopaminergic state" (Siciliano et al., 2018) has been associated with a reduced effectiveness of alternate rewards in producing satisfactory gratification during alcohol abstinence. Furthermore, chronic alcohol exposure has been shown to reduce dopamine D<sub>2</sub> receptor function in both pyramidal neurons and interneurons of the rat PFC (Trantham-Davidson et al., 2014). Such a reduction in dopaminergic PFC activity in chronic drinkers may be associated with reduced cognitive faculties, ultimately leading to lower cognitive flexibility and increased impulsivity due to impaired inhibitory control (Trantham-Davidson et al., 2014; Trantham-Davidson and Chandler, 2015; Volkow et al., 1996).

### 3.1.3. Endogenous opioids

Evidence also suggests an involvement of the endogenous opioid system in the aforementioned alterations of dopaminergic circuits. Alcohol stimulates the release of particular endogenous opioids in select brain areas (Jarjour et al., 2009; Lam et al., 2008; Marinelli et al., 2003; Mitchell et al., 2012).  $\beta$ -endorphin has been found to interact with  $\mu$ - and  $\delta$ -opioid receptors located in the VTA and NAc, which could increase dopamine levels and therefore be directly involved in reward and reinforcement of a potential compulsive behaviour (Gianoulakis, 2001; Mitchell et al., 2012). One study also found that alcohol interacts with PFC regulation of the endogenous opioid system in processing alcohol-associated rewards and increased impulsivity (Mitchell et al., 2012). These findings are supported by the fact that naltrexone, a pharmacological endogenous opioid antagonist used in AUD therapy, seems to have some beneficial effect in decreasing response conflicts and impulsivity (Mitchell et al., 2007). The interaction of alcohol with the endogenous opioid system also contributes to its analgesic effects, as acute alcohol intoxication can increase pain tolerance (Perrino et al., 2008). Importantly, the analgesic properties of alcohol may contribute to promoting drinking and facilitating relapses. Therefore, it is not surprising that individuals with AUD frequently report chronic pain, and it could also explain why some drinkers report pain as a main factor to justify their consumption (Robins et al., 2019; Witkiewitz and Vowles, 2018).

### 3.1.4. Serotonin

Serotonin is associated with a wide range of functions, such as learning, attention memory, and the regulation of emotional states (Lovinger, 1997; Puglisi-Allegra and Andolina, 2015; Puig and Gullledge, 2011; Zhang and Stackman, 2015). Serotonin has also been linked to cognitive control functions and impulsive behaviour (Beste et al., 2010b, a; Eagle et al., 2008, 2009; Evers et al., 2007; Strobel et al., 2007), and serotonergic depletion has been suggested to result in increased automatic response tendencies. In this regard, serotonergic activity seems to be involved in action restraint (i.e., during Go/NoGo tasks), but it does not seem to affect response cancellation (i.e., during Stop-signal tasks) (Clarke et al., 2004; Eagle et al., 2009, 2008). Serotonin also has an

anxiolytic effect and plays an important role in shaping social behaviour, regulating emotion control and aggression (Faccidomo et al., 2008; Kiser et al., 2012; Takahashi et al., 2010). Both human and animal studies (LeMarquand et al., 1994a, 1994b) have found that acute alcohol intake can increase serotonergic concentrations and 5-HT receptor activity, thus resulting in an over-stimulation of the serotonergic system (Lovinger and Peoples, 1993; Lovinger and Zhou, 1994). In chronic alcohol consumption, a negative correlation between serotonergic neurotransmission and years of alcohol abuse has been demonstrated (Berggren et al., 2002). Particularly the early stages of abstinence are marked by a reduction in serotonin transporter availability, which has been associated with higher levels of anxiety and depression (Heinz et al., 1998). The serotonergic depletion in chronic alcohol drinkers has furthermore been associated with increased aggressive behaviour (Bushman and Cooper, 1990; Chermack and Giancola, 1997; Heinz et al., 2011), which is probably due to reduced cognitive control functions and social information processing (Giancola, 2000). Interestingly, the depletion of tryptophan (a precursor of serotonin) in healthy subjects with a genetic predisposition for AUD has been found to impair behavioural inhibition, as compared to controls (Crean et al., 2002). These findings highlight the role of serotonin in inhibition functions, particularly in individuals who have a predisposition for developing AUD.

### 3.1.5. More than the sum of its parts: combined effects

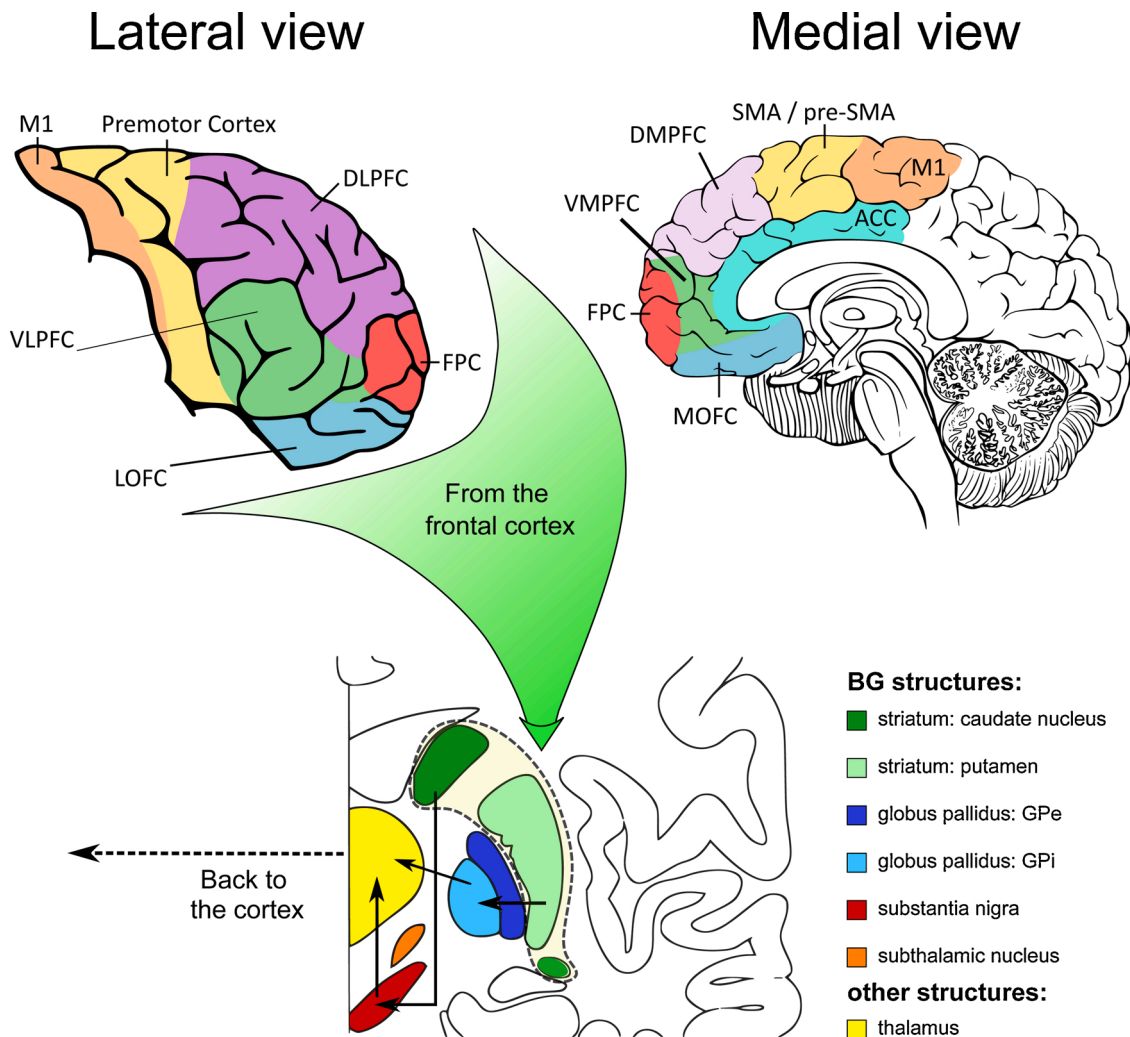
In summary, both acute and chronic alcohol consumption have profound effects across several classes of neurotransmitters, receptors, and other molecules. Detrimental alcohol effects on cognitive functions (like increased impulsive behaviour) often arise from the conjoint modulation of several neurotransmitter systems. Alcohol intoxication-induced increases in GABAergic activity may play a role in increased impulsivity, whereas the concomitant increase in dopamine release affects fronto-striatal reward circuits and increases the selection of alcohol-related behaviours. On the other hand, repeated alcohol exposure eventually results in long-term neuroplasticity changes characterized by over-compensatory regulation of the normal neurotransmitter activity and neurotoxicity. These alterations are involved, to varying degrees, in long-term impairments of cognitive control functions and increased impulsivity in AUD. Chronic changes at the neurochemical level can then affect entire neural networks that would normally help to maintain the balance between controlled and habitual behaviour. In particular, alterations in fronto-striatal activity have been associated with the transition from occasional to habitual consumption, which is characterized by impulsive behaviour and impaired inhibition.

## 3.2. Alcohol effects on habit and cognitive control circuits

Repeated alcohol intake can cause long-lasting changes in several cortical and subcortical areas associated with the progressive shift from controlled to compulsive alcohol consumption (Harper et al., 1988; Harper and Kril, 1989; Pfefferbaum et al., 2010). Pathological behaviour in AUD can ultimately be attributed to neurobiological changes in fronto-cortical structures, which are essential for cognitive flexibility, and to changes in basal ganglia nuclei, which are involved in reward processing and the formation of automatic S-R associations (Barker et al., 2015; Everitt and Robbins, 2005; Gremel and Costa, 2013; Gremel and Lovinger, 2017; Koob and Volkow, 2016; Sjoerds et al., 2013).

### 3.2.1. Goal-based and habit-based (striatal) circuits

AUD is characterized by a progressive shift from hedonic occasional consumption to a dysfunctional drinking habit where consumption is perpetuated despite negative consequences. Goal-directed behaviours involve the activity of fronto-ventral striatum circuits processing reward predictions (i.e., difference between expected and experienced outcome) and reinforcement learning behaviours. Assimilation of S-R associations and habit formation activate other neural networks,



**Fig. 2.** Visual representation of the fronto-striatal direct pathway of behavioural control. The top-left part of the figure shows the lateral view, while the top-right part of the figure shows the medial view of the right frontal cortex. The bottom part of the figure illustrates a coronal section of the right basal ganglia. Frontal areas can be divided into: the primary motor cortex (M1), the supplementary motor cortex (SMA), the pre-SMA, the dorsolateral prefrontal cortex (DLPFC), the dorso-medial prefrontal cortex (DMPFC), the ventrolateral prefrontal cortex (VLPFC), the ventromedial prefrontal cortex (VMPFC), the fronto-polar cortex (FPC), the lateral orbitofrontal cortex (LOFC) and the medial orbitofrontal cortex (MOFC). The green arrow indicates excitatory glutamergic projections from the frontal cortex to the striatum (nucleus caudatus and putamen). The striatum plays an important role in the integration of emotional, cognitive and motivational information that drives action selection and execution. The caudate nucleus of the striatum and the putamen send inhibitory projections to the substantia nigra and the internal segment of the globus pallidus (GPi). Both the GPi and the substantia nigra have inhibitory GABAergic effects on the ventral anterior (VA) and ventral lateral (VL) nuclei of the thalamus. Therefore, increased striatal output reduces GABAergic modulation of the thalamus, ultimately increasing thalamic activity and the resulting input back into the cortex, allowing voluntary action selection and execution.

including dorsolateral regions of the striatum (Everitt and Robbins, 2005). In healthy individuals, these circuits are functionally balanced, usually resulting in sufficient inhibitory control of automatic response tendencies. In contrast to this, AUD seems to be associated with a shift of activity from a ventral to a more dorsal portion of the striatum (Grüsser et al., 2004; Sjoerds et al., 2013; Vollstadt-Klein et al., 2010). Even though the precise role of different portions of the striatum in modulating cognitive flexibility is still debated (Darvas and Palmiter, 2011), this shift has been suggested to increase behavioural automaticity in response to drug-related stimuli, as well as reduce cognitive flexibility and sensibility towards outcome devaluation (Grüsser et al., 2004; Heinz et al., 2007; Vollstadt-Klein et al., 2010). Matching this, Vollstadt-Klein et al. (2010) demonstrated that heavy drinkers had greater activation of the dorsal striatum during alcohol-related stimulus processing, while light drinkers had greater activation in the ventral striatum and the prefrontal areas, including the right medial and middle frontal gyrus and the left superior and medial frontal gyrus. Supporting evidence was also

found in a later study investigating the balance between goal-directed and habitual actions (Sjoerds et al., 2013): Compared to a control group, AUD patients had decreased activation of the ventromedial prefrontal cortex (VMPFC) and the anterior putamen (which are involved in goal-directed actions), and increased activation of the posterior putamen (which is more involved in habitual responses). Overall, these studies provide evidence for a shift in neural activity from ventral to more dorsal/posterior regions of the striatum. This change has been suggested to be an indicator of AUD development/progression, increased consolidation of rigid habits, and increased sensibility to alcohol-related cues. This change might however also indicate a shift in neural resources in an attempt to respond to the increased demands of habit-driven behaviours. Once consolidated, alterations in frontal-striatal circuits may constitute the neurobiological foundations of the increased tendency towards automatic responses and lower control in AUD. From this perspective, understanding the neurobiological mechanisms underlying pathological AUD behaviour may help to



understand how the altered balance between controlled and habitual behaviour influences the patients' impulsive drinking behaviour and the inability to remain abstinent.

### 3.2.2. The role of prefrontal regions in cognitive control

Diminished behavioural control in AUD is thought to arise from long-term neurophysiological changes in different regions of the PFC and basal ganglia (Koob and Volkow, 2016; Wilcox et al., 2014). Lower cognitive control and a stronger tendency to rely on habitual behaviour have been associated with a transition from a fronto-cortical to a more striatal regulation of drug taking behaviour (Everitt and Robbins, 2005). The PFC is the central hub of executive control functions, including behavioural inhibition (Bari and Robbins, 2013). The PFC can be sub-divided into the medial PFC (MPFC), dorsolateral PFC (DLPFC), and orbitofrontal cortex (OFC) (Fig. 2). The MPFC projects to the pre-supplementary motor cortex (pre-SMA) and both the rostral and dorsal portion of the anterior cingulate cortex (ACC). The DLPFC projects to the SMA, motor cortex, dorsal striatum thalamus, and parietal cortex. Finally, the OFC, which projects to the anterior temporal, ventral temporo-occipital cortex, and medial DLPFC, can be divided into the lateral OFC (which responds to negative reinforcement) and the medial OFC (which responds to positive rewards and reinforcement) (Chudasama and Robbins, 2006; Middleton and Strick, 2000; Ridderinkhof et al., 2004a, b). Cortical areas involved in inhibitory control are the SMA, pre-SMA, pre-motor cortex, motor cortex, parietal cortex, ventrolateral PFC (VLPFC), and insula (Aron, 2011; Bari and Robbins, 2013; Drummond et al., 2017; Mostofsky et al., 2003; Ridderinkhof et al., 2004a; Rubia et al., 2001; Rushworth et al., 2004; Simmonds et al., 2008; Swick et al., 2008; Vahid et al., 2018). The right VLPFC and the inferior frontal gyrus (IFG), may be particularly relevant for response cancellation (Simmonds et al., 2008). The DLPFC has also been linked to inhibitory control, especially in action selection and motor planning. However, some studies suggested that the DLPFC is more involved in the surveillance of task rules, and working memory demands seem to directly influence its activation level (Garavan et al., 2006; Mostofsky et al., 2003; Simmonds et al., 2008). Medial frontal areas, and the ACC in particular, have been associated with response selection, error detection, conflict monitoring, conflict anticipation, and the need for mental effort (Botvinick, 2007; Botvinick et al., 1999, 2004; Botvinick and Cohen, 2014; Ridderinkhof et al., 2004a). Furthermore, the ACC has been proposed to be particularly involved in motor response inhibition, promoting correct responses and suppressing incorrect responses (Paus et al., 1993; Rubia et al., 2001). In summary, efficient cognitive control depends on the interplay of different cognitive processes and the brain regions that they are driven by. Healthy individuals can efficiently recruit frontal control circuits to achieve successful inhibition of pre-potent responses and control over interfering information. In contrast, impaired cognitive control functions are strongly associated with neurobiological alterations of these circuits in both acute alcohol intoxication and AUD (Bjork and Gilman, 2014; Stavro et al., 2013; Wilcox et al., 2014).

Several long-term neurophysiological alterations caused by chronic alcohol consumption have been associated with impaired cognitive control functions. In AUD patients, cognitive control demands seem to activate different brain circuits than in healthy controls. For example, AUD patients showed weaker activation of fronto-parietal regions during response inhibition than healthy controls (Kamarajan et al., 2005). Compared to healthy subjects, AUD patients also exhibit a lower temporo-parietal N400 amplitude. This component has been associated with processing incongruent semantic information, thus further supporting the hypothesis of weakened control over interfering information in AUD (Nixon et al., 2002). Further indications of dysfunctional cognitive control networks in AUD have been derived from fMRI and positron emission tomography (PET) studies (Ames et al., 2014; Claus et al., 2013; Dao-Castellana et al., 1998; Li et al., 2009; Schulte et al., 2012). For example, Li et al. (2009) found reduced activation of the

DLPFC in AUD patients during response cancellation and in post-error behavioural adjustment. In addition, neural responses in brain circuits processing response inhibition and error monitoring (including the right insula, inferior frontal gyrus, pregenual ACC, and inferior frontal lobe) have been found to negatively correlate with AUD severity (Claus et al., 2013). When asked to suppress interfering information, AUD patients exhibited lower activation in the mediofrontal PFC and DLPFC, as compared to healthy controls (Dao-Castellana et al., 1998). Specifically, the slower processing of interfering information corresponded to lower activation in mediofrontal areas, whereas a higher number of committed errors was associated with lower activation in the left DLPFC. Reduced activation in the posterior cingulate cortex (PCC) (thought to reflect a reduced reserve of network resources to properly operate response switching) and greater activation of midbrain regions during response repetition (associated with the impaired regulation of midbrain responsiveness to repetition learning) have also been reported in AUD (Schulte et al., 2012).

Studies assessing cortical and subcortical changes in AUD patients have also demonstrated that alterations in cortico-cortical and subcortical functional connectivity are also associated with impaired cognitive control functions (Camchong et al., 2013; Courtney et al., 2013; Lee et al., 2013; Müller-Oehring et al., 2013; Park et al., 2010). AUD severity has been shown to be associated with impaired functional connectivity during response inhibition, involving the dorsal striatum (putamen) and prefrontal regions, such as the left anterior insula, bilateral IFG, OFC, and ACC (Courtney et al., 2013). In addition, AUD patients presented with lower cortico-cortical functional connectivity between the middle cingulate, posterior cingulate, and medial PFC (a network associated with top-down control functions), but increased midbrain-orbitofrontal cortical functional connectivity (associated with bottom-up automatic attention functions and S-R learning) when top-down control task demand was high (Schulte et al., 2012). AUD patients also exhibit impaired functional connectivity between the medial OFC and striatal system when they are required to inhibit the compulsivity predisposition of habitual responses (Lee et al., 2013). Similarly, reduced DLPFC-striatum connectivity in AUD has been associated with lower error prediction signalling (reflecting the difference between expected and experienced outcomes) and the ability to update the value of optional responses (Park et al., 2010). Weakened connectivity between the cortical and subcortical regions in AUD is also the direct consequence of structural and functional alteration of white matter fibres, which are responsible for the correct integration of distant neural activity (Harper et al., 1988). The disrupted integrity of white matter tracts in perpetuated alcohol abuse has been explained by demyelination and axonal damage (De Santis et al., 2019; Monnig et al., 2014; Pfefferbaum et al., 2010; Sorg et al., 2015; Zou et al., 2018). In this regard, microstructural differences emerging in early abstinence have been found in the corpus callosum, fornix, and fronto-striatal tracts (De Santis et al., 2019; Sorg et al., 2015). Chronic alcohol consumption effects on white matter are particularly accentuated in fronto-striatal and motivational reward systems. For example, a negative correlation has been reported between white matter integrity and responsiveness to alcohol cues. In detail, lower white matter integrity has been shown to correspond to higher activation by alcohol cues in the medial frontal gyrus, cingulate gyrus, preceuneus, parahippocampal gyrus, fusiform gyrus, insula, thalamus, putamen, caudate, and cerebellum (Monnig et al., 2014). Overall, this and other evidence (Sorg et al., 2012; Zou et al., 2018) suggests that estimates of white matter loss (as compared to healthy controls) could be used to predict the risk of relapse and to evaluate residual inhibitory control abilities in AUD patients.

Although there are some discrepancies (mostly attributable to the variety of cognitive control functions, different task demands, and experimental designs) regarding the brain areas showing altered activity in AUD, the general consensus is that impaired inhibitory control is tightly associated with alterations in fronto-striatal neural networks. Compared to healthy controls, individuals with AUD show diminished

activity in prefrontal areas and impaired connectivity between the DLPFC, VMPFC, OFC, ACC, PCC, IFG, and the striatum, but increased activity and connectivity between portions of the basal ganglia (dorsolateral striatum), limbic system (amygdala), and medial OFC (Aron et al., 2007a, b). Neurochemical and neuroanatomical alterations in brain circuitry constitute the neural correlates of pathological behaviours characterized by lower control over automatized harmful habits and increased sensitivity towards alcohol-related cues. Thus, the functional connections between biological and behavioural factors of cognitive control and automaticity in AUD should be exploited to design new, and hopefully efficacious interventions directed to regain control over drinking behaviour and alcohol intake.

#### 4. Treatment strategies in AUD

In the previous sections, we described how the imbalance between behavioural control and automaticity mediates uncontrolled alcohol intake and relapse among AUD patients. Furthermore, we summarized how these pathological behaviours can be attributed to biochemical changes occurring in the activity of different neurotransmitter systems that functionally modulate cortico-subcortical networks. In AUD, pharmacological interventions are commonly prescribed with the intent to directly reduce craving and withdrawal-associated symptoms. However, this approach largely neglects the potential benefits of directly targeting the neurobiological mechanisms underlying the (im)balance between controlled and automatic behaviour (Colzato et al., 2020). Yet, mechanism-based approaches might hold the promise of additional benefits for AUD patients. Innovative neuromodulatory techniques, such as non-invasive brain stimulation, can induce long-term modifications of impaired synaptic activity and functional connectivity. Against this background, the following section will summarize the mechanisms of action of current pharmacological therapies and their (limited) effects on cognitive functions in AUD. Furthermore, we will outline current knowledge on alternative interventions in AUD using non-invasive brain stimulation with the ultimate aim to propose an alternative mechanism-based therapeutic approach that might help to re-establish a functional balance between control and automaticity.

##### 4.1. Current therapies for AUD

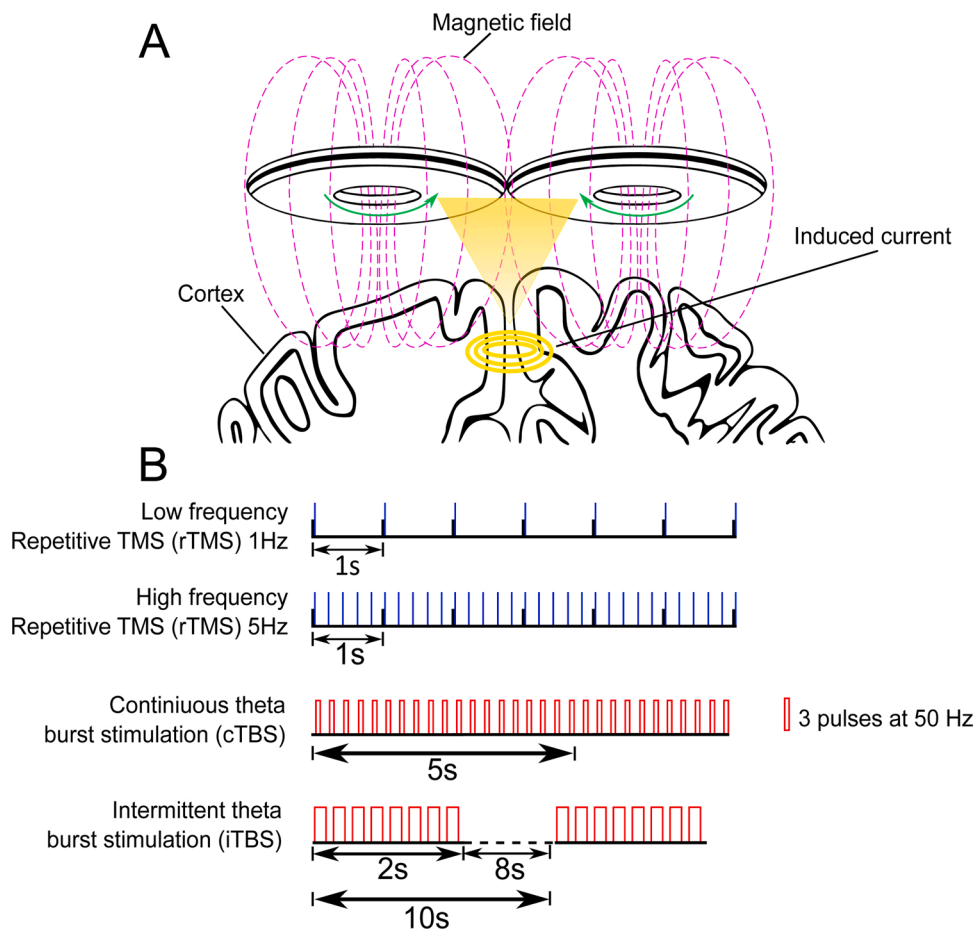
A combination of pharmacological treatments and psychological or social therapy is the most recommended intervention to treat AUD (Kranzler and Soyka, 2018; Liang and Olsen, 2014; Lingford-Hughes et al., 2012; Mann et al., 2017).

Depending on the aim of the treatment, different pharmacological therapies can be used. Common pharmacological treatments include naltrexone, disulfiram, acamprosate, and benzodiazepines, which aim to help AUD patients remain abstinent, reduce relapse rates, and treat withdrawal symptoms. A few systematic reviews have described limited effects of some of these medications on cognitive control functions (Butler and Le Foll, 2019; Pujol et al., 2018). The pharmacological mechanism of naltrexone is based on a reduction of mesolimbic opioidergic activity, which modulates the rewarding effects of dopamine release. Therefore, depletion of the reward effect associated with alcohol intoxication is expected to reduce consumption in AUD patients treated with naltrexone (Font et al., 2013; Gianoulakis, 2001). The effects of naltrexone on cognitive control are still debated. Studies on rats have shown that naltrexone has limited or no effects on inhibitory control, but effects seem to be task-dependent (Ciano and Foll, 2016; Kieres et al., 2004; Oberlin et al., 2010). Similarly, one study in human participants found that naltrexone reduced impulsive choice, but the effects depended on the participants' baseline impulsivity traits (Mitchell et al., 2007). The pharmacological action of disulfiram is the inhibition of aldehyde dehydrogenase, which metabolizes the highly toxic alcohol metabolite acetaldehyde. When alcohol is consumed during disulfiram treatment, this results in an increased concentration of acetaldehyde.

This leads to aversive side effects like nausea, vomiting, sweating, flushing and, in rare cases, serious side effects such as cardiovascular collapse. Human studies have shown that disulfiram does not seem to affect executive functions (Gilman et al., 1996; Peeke et al., 1979) and has a limited effect on improving inhibitory control in rats with initially poor decision-making functions (Di Ciano et al., 2018). Other pharmacological therapies are used to treat alcohol withdrawal symptoms. For example, acamprosate is used to re-establish the equilibrium between excitatory and inhibitory neurotransmitter activity in abstinent chronic drinkers. It acts as an NMDA receptor and metabotropic glutamate receptor 5 (mGlu5) antagonist, and some evidence indicates that it may also have an indirect effect on GABA<sub>A</sub> receptor transmission (Kalk and Lingford-Hughes, 2014; Plosker, 2015). Acamprosate is considered helpful in AUD treatment because it potentially reduces the negative consequences of alcohol withdrawal, such as hyperactivity and anxiety. Even though acamprosate mainly acts on NMDA activity, which is important for memory and learning, the limited number of available studies revealed no conclusive effects on cognitive control functions (Hu et al., 2015; Ralevski et al., 2011). Benzodiazepines, such as diazepam and lorazepam, have also been recommended for treating alcohol withdrawal symptoms (Amato et al., 2011). Benzodiazepines are pure GABA<sub>A</sub> agonists that help reduce symptoms associated with low GABAergic activity during alcohol withdrawal. The effects of benzodiazepines on cognitive control functions are also still debated. Generally, it has been assumed that benzodiazepines should have a detrimental effect on cognitive control functions due to their inhibitory effects on PFC activity. However, the currently available studies do not yet sufficiently substantiate such a conclusion (Rush et al., 1993; Wilcox et al., 2015).

Even though several studies demonstrated beneficial effects in patients with mild AUD, meta-analyses and evidence-based guidelines still maintain an open discussion about the efficacy of pharmacological-based interventions (Kranzler and Soyka, 2018; Lingford-Hughes et al., 2012). An additional complication in current treatment strategies is the variability of general guidelines and treatment programmes among hospitals and detoxification centres. Against this background, it is not surprising that recent studies have called for improvements in the quality of provide treatments (Hepner et al., 2019; Stock, 2017). One potential problem could be associated with the difficulties of reconciling standard treatments with the latest findings from alcohol and addiction research (Stock, 2017). For example, acamprosate exhibited lower efficiency in US-based studies than in European studies (Lingford-Hughes et al., 2012). Likewise, the efficiency of disulfiram has been questioned because it does not affect the craving process and the risk of serious adverse effects for patients who relapse while on medication (e.g., tachycardia and hypotension) has raised concerns about its safety (Liang and Olsen, 2014; Skinner et al., 2014). Side effects of benzodiazepines, such as their addictive potential and the potent depressant effect on the central nervous system, have also limited their use in controlled settings.

More importantly, current pharmacological approaches mainly focus on reducing craving and/or the reinforcing effects of alcohol. Yet, they have little to no proven benefit in restoring the balance between cognitive control and automatic behaviour caused by neurobiochemical and neuroanatomical alterations in fronto-striatal circuits. In order to develop efficacious interventions, there has recently been increasing interest in additional or alternative therapeutic approaches based on an understanding of behavioural and neurophysiological mechanisms that contribute to losing control over alcohol intake (Heinz et al., 2020; Naqvi and Morgenstern, 2015; Stock, 2017). The possibility of using pharmacological or brain stimulation techniques to directly target neurobiological and behavioural mechanisms underlying the automaticity-control imbalance has recently gained interest in addiction research (Burchi et al., 2019; Wilcox et al., 2014). Some studies have already assessed the efficacy of alternative pharmacological approaches in reducing impulsive behaviour or in increasing cortical activation. For example, a 12-week therapy with topiramate, an anticonvulsant usually



**Fig. 3.** Visual representation of the TMS technique and common repetitive TMS (rTMS) protocols. A) A 8-figure shape TMS coil generates a magnetic field that induces a resulting electric field within the cortex. This manipulation produces a localized neural membrane depolarization and generates action potentials. B) Illustration of the different TMS protocols. In order from top to bottom: high frequency rTMS (hf-rTMS), low-frequency rTMS (lf-rTMS), continuous Theta Burst Stimulation (cTBS), and intermittent Theta Burst Stimulation (iTBS).

prescribed for disorders characterized by impulsivity symptoms, has shown a reduction in drink consumption and decreased impulsive behaviour in detoxified AUD patients (Rubio et al., 2009). The use of central nervous system stimulants (e.g., modafinil), nicotine agonists, dopaminergic agonists, and antipsychotics, has also been tested for cognitive control enhancement in AUD (Litten et al., 2013; Moallem and Ray, 2012; Naranjo et al., 1997; Plebani et al., 2013; Schmaal et al., 2013). Overall, these studies have shown some promising results, but more research is needed to demonstrate the efficacy and safety of these drugs in AUD patients.

Lastly, framing AUD as a pathological condition driven by a strong automatization tendencies and reduced cognitive control has also promoted the conceptualization of new interventions (Copersino, 2017). For example, cognitive bias modification (CBM), which was initially developed to investigate the role of cognitive biases in psychological disorders (Amir et al., 2009; Fadardi and Cox, 2009; Wiers et al., 2011), has been developed and promoted as a form of intervention to directly address detrimental cognitive biases that characterize AUD patients (Batschelet et al., 2020; Copersino, 2017; Eberl et al., 2014). Two main forms of CBM are approach bias modification (ApBM) and attentional bias modification (AtBM) training. Both are designed to establish an automatic avoidance response towards alcohol-related stimuli. In short, ApBM requires subjects to push a lever or a joystick forwards (as form of approach behaviour) when presented with soft drinks, but to pull it away from alcohol related stimuli (avoidance behaviour). AtBM requires subjects to divert their attention away from alcohol-related pictures and instead direct their attention to visual control pictures instead. A recent systematic review (Batschelet et al., 2020) concluded that there is some proof for ApBM to be clinically effective in reducing alcohol relapse rate, while there are still inconclusive results regarding the effectiveness of

the AtBM.

#### 4.2. Non-invasive brain stimulation (NIBS) interventions in AUD

An interesting alternative approach that has received increasing interest in addiction research is the possibility of directly modulating the activity of cortical and subcortical circuits using non-invasive electrical and magnetic stimulation. Several studies examined the efficacy of NIBS techniques, particularly TES and TMS protocols, as interventions in substance use disorders (Bollen et al., 2021; Diana et al., 2019, 2017; Hanlon et al., 2018; Lupi et al., 2017). Unlike some of the currently applied pharmacological therapies (like disulfiram), extensive evidence shows that non-invasive brain stimulations very rarely causes dangerous side effects (i.e., seizures) (Rossi et al., 2009; Taylor et al., 2018). Additionally, NIBS has the potential to induce long-term beneficial effects in AUD patients by producing long-term neuroplasticity changes and modulating the activity of functionally associated neural circuits. In the following, we outline the known neurobiological and behavioural effects of NIBS in AUD and summarize the efficacy of current NIBS-based interventions as well as possible alternative applications in modulating neural circuits associated with the pathological control-automaticity imbalance in AUD.

##### 4.2.1. Transcranial magnetic stimulation (TMS)

TMS is a NIBS technique used to induce short- and long-term changes in brain activity and thereby modulate behaviour (Miniussi et al., 2013). In the last 20 years, different TMS protocols have been applied to investigate their possible therapeutic efficacy in several clinical conditions. TMS interventions have been carried out in depression, motor stroke, pain disabilities, Parkinson's disease, and various psychiatric

conditions, such as post-traumatic stress disorder (PTSD) and schizophrenia. A recent evidence-based guideline indicates that therapeutic TMS protocols are "definitively efficacious" in improving depression, neuropathic pain, and motor stroke, further suggesting its "probable efficacy" in Parkinson's, multiple sclerosis, and PTSD (Lefaucheur et al., 2020). The effectiveness of TMS treatments has been shown to last up to several months after the end of the stimulation, most probably due to long-term potentiation (LTP) and long-term depression (LTD) of synaptic activity (Duffau, 2006). TMS-induced changes in synaptic strength could modulate the functional connectivity between stimulated areas and associated neural networks, which may induce beneficial adjustments of altered neural activity (Duffau, 2006; Lee et al., 2003).

However, the underlying mechanisms that could explain the long-term therapeutic effects of TMS have yet to be fully elucidated (Müller-Dahlhaus and Vlachos, 2013). Furthermore, the efficacy of this technique in various clinical settings (including addiction research) is still being debated due to the great variability in terms of stimulation protocols, study designs, and sample sizes across different research groups (Diana et al., 2017; Hanlon et al., 2018). Despite these open questions, promising TMS-based effects on conditions such as depression and neuropathic pain should encourage further investigations of this technique in a broad number of clinical conditions.

**4.2.1.1. Methods and proposed mechanisms of action of TMS.** TMS delivers a strong and focused brief magnetic field (i.e., pulse) through a solenoid (i.e., coil) placed over the scalp (Fig. 3A). This brief intense pulse generates a transitory electric field in the cerebral cortex beneath the scalp. The transient electrical impulse causes depolarization of the neural membrane that, if applied repetitively, can either induce neural excitation or neural inhibition; and both of these effects can outlast the stimulation period (Rossi et al., 2009). Critical parameters of experimental TMS paradigms are the frequency at which the pulses are delivered and the intensity of the magnetic field. The depth and focality of the electric field also depend on the shape of the coil used for stimulation. For example, the 8-shaped coil, which is one of the most used coil shapes, can reach a depth of 1–2 cm and a focality of 5–10 cm<sup>2</sup> (Deng et al., 2013). In contrast to this, the H-shaped coil has been used to target deeper brain areas, and its use is often referred to as a deep TMS (dTMS) protocol. This particular coil shape is designed as a circular crown composed of multiple copper windings running tangentially over the scalp (Levkovitz et al., 2015). It delivers simultaneous bilateral pulses over the cortex, thereby reaching greater depth (4–6 cm). However, the ability to stimulate deeper structures with the H-shaped coil comes at the cost of reduced electrical field focality (Deng et al., 2013; Roth et al., 2007).

TMS can be delivered as a single pulse at a time, as double pulses at variable inter-pulse intervals, or in trains of repetitive pulses (Fig. 3B). Repetitive TMS (rTMS) is currently one of the most commonly applied protocols because it can induce LTP and LTD effects. rTMS delivers trains of closely spaced pulses. Depending on the frequency of these pulses, it can cause excitatory ( $\geq 1$  Hz) or inhibitory ( $\leq 1$  Hz) effects on neural activity (Thut and Pascual-Leone, 2010). Theta burst TMS (TBS), which is another rTMS protocol, delivers a short train of three pulses at high frequency (50 Hz), which are repeated at theta frequency (i.e., 5 Hz). TBS can be delivered continuously (i.e., 600 pulses in 40 s) or in an intermittent manner, where five trains are delivered with intermittent 8-second pauses. While continuous TBS (cTBS) has been found to induce long-term inhibitory effects, intermittent TBS (iTBS) seems to increase neural excitability (Huang et al., 2007, 2005). Although the effects of TMS at the neural level have been widely studied, there are still uncertainties about its mechanisms of action.

The current understanding is that a single TMS pulse induces an electric field, which temporally alters cortical excitability by causing a fast and transitional activation of voltage-gated sodium channels, modulating the neural membrane potential and eliciting neural firing. In

contrast to this, the application of several magnetic pulses via rTMS can induce neurophysiological effects that outlast the stimulation period. Due to the mechanisms of LTP and LTD, rTMS can prompt synaptic plasticity-like processes and alter neurotransmitter activity in certain cortical sites (Duffau, 2006; Klomjai et al., 2015): Both animal (Erhardt et al., 2004; Kanno et al., 2003; Keck et al., 2002; Zangen and Hyodo, 2002) and human studies (Cho and Strafella, 2009; Ko et al., 2008; Strafella et al., 2001, 2003) demonstrated the effects of rTMS on dopamine release in subcortical areas. In human study participants, the application of excitatory rTMS over the left DLPFC and primary motor cortex has been shown to increase the release of extracellular dopamine in the dorsal caudate nucleus (Strafella et al., 2001), ACC, OFC (Cho and Strafella, 2009), and ventrolateral putamen (Strafella et al., 2003). Given that rTMS does not allow to directly modulate subcortical regions, the modulation of glutamatergic cortico-striatal axons originating in the DLPFC has been suggested to explain its indirect effects on the dopaminergic system (Michael et al., 2003) and dopamine release in the striatum (Strafella et al., 2003, 2001). On the other hand, the long-term effects of TBS may rely on partially different mechanisms of action in the "classic" high and low frequency rTMS. Notably, both cTBS and iTBS seem to induce LTD and LTP effects even though both are delivered at the same frequency (50 Hz). TBS seems to influence both glutamatergic and GABAergic neurotransmission, but the two different TBS protocols might have differential modulatory effects GABAergic activity. In particular, the excitatory effect of iTBS may be the consequence of suppression of GABA interneuron activity, while the inhibitory effects of cTBS may be the result of increased GABAergic inhibitory interneuron activity (Harrington and Hammond-Tooke, 2015; Li et al., 2019; Stagg et al., 2009b; Vidal-Pineiro et al., 2015). And while more evidence is needed to further substantiate this assumption, a few studies have shown that TBS may also influence dopaminergic activity in striatal structures (Brunelin et al., 2011; Ko et al., 2008).

**4.2.1.2. TMS neuromodulatory effects in AUD.** To date, literature on the neurophysiological consequences of and possible mechanisms of action of the long-term beneficial effects of rTMS applications in AUD is still scarce. A few studies demonstrated that rTMS could be used to modulate neurotransmitter systems, specifically dopaminergic activity, in AUD patients. Multiple sessions of deep rTMS were reported to reduce cortisol and prolactin levels in abstinent AUD patients (Ceccanti et al., 2015). Cortisol levels are usually increased during alcohol withdrawal and convey stress. Prolactin can be used as a marker of dopaminergic activity. Specifically, higher prolactin concentrations negatively correlate with diminished dopaminergic activity during withdrawal periods. Multiple excitatory rTMS sessions have been shown to induce changes in the availability of the dopamine transporter (DAT), which is typically increased in withdrawing AUD patients (Addolorato et al., 2017). Single photon emission computed tomography (SPECT) before and after 12 sessions of dTMS at 10 Hz over the frontal cortex demonstrated a post-stimulation reduction (i.e., a normalization) in DAT availability in the caudate and putamen. Even though more evidence is needed, these results suggest that it is possible to alter dopaminergic activity of AUD patients in sub-cortical areas that are distant from the stimulation site via rTMS.

Other studies used rTMS and TBS protocols to modulate neural activation in cortical circuits known to be important for reward and motivational processes and to regulate craving symptoms (De Ridder et al., 2011; Herremans et al., 2016; Jansen et al., 2015; Wu et al., 2018). In an early case study, De Ridder et al. (2011) examined the effects of inhibitory 1 Hz rTMS delivered bilaterally over the medial frontal cortex daily for 3 weeks in a hospitalized AUD patient. After the stimulation treatment, the patient reported reduced cravings and showed a reduction in resting-state beta and gamma activity in the dorsal ACC (dACC) and posterior cingulate cortex (PCC) for up to 3 months post-TMS treatment. A later randomized controlled study found that in a group

of AUD patients, one session of 10 Hz rTMS over the right DLPFC increased resting state functional connectivity of the fronto-parietal cognitive control network (including the ACC, IFC, DLPFC, and PCC), but did not induce any significant changes in the orbitofrontal-striatum motivational network (Jansen et al., 2015). Herremans et al. (2016) investigated the possibility of inducing long-term baseline changes in the cortical activation of AUD patients. In this open-label study, 14 sessions of 20 Hz rTMS over the right DLPFC were delivered over the course of 3 days. Before and after the stimulation protocol, the BOLD signal was recorded during an alcohol cue-exposure paradigm. The stimulation protocol modulated dACC activity depending on the baseline activation values: After the rTMS intervention, the neural activation increased in the dACC of patients characterized by a lower initial baseline activation. On the other hand, the rTMS intervention resulted in decreased dACC activation in patients with high baseline activity. Using a similar stimulation paradigm as Herremans et al. (2016), a subsequent study from the same research group investigated the possibility of rTMS causing grey matter volume changes in the frontal, temporal, and parietal areas of AUD patients (Wu et al., 2018). But while they found a correlation between low grey matter volume and relapse, the rTMS intervention did not alter grey matter volume.

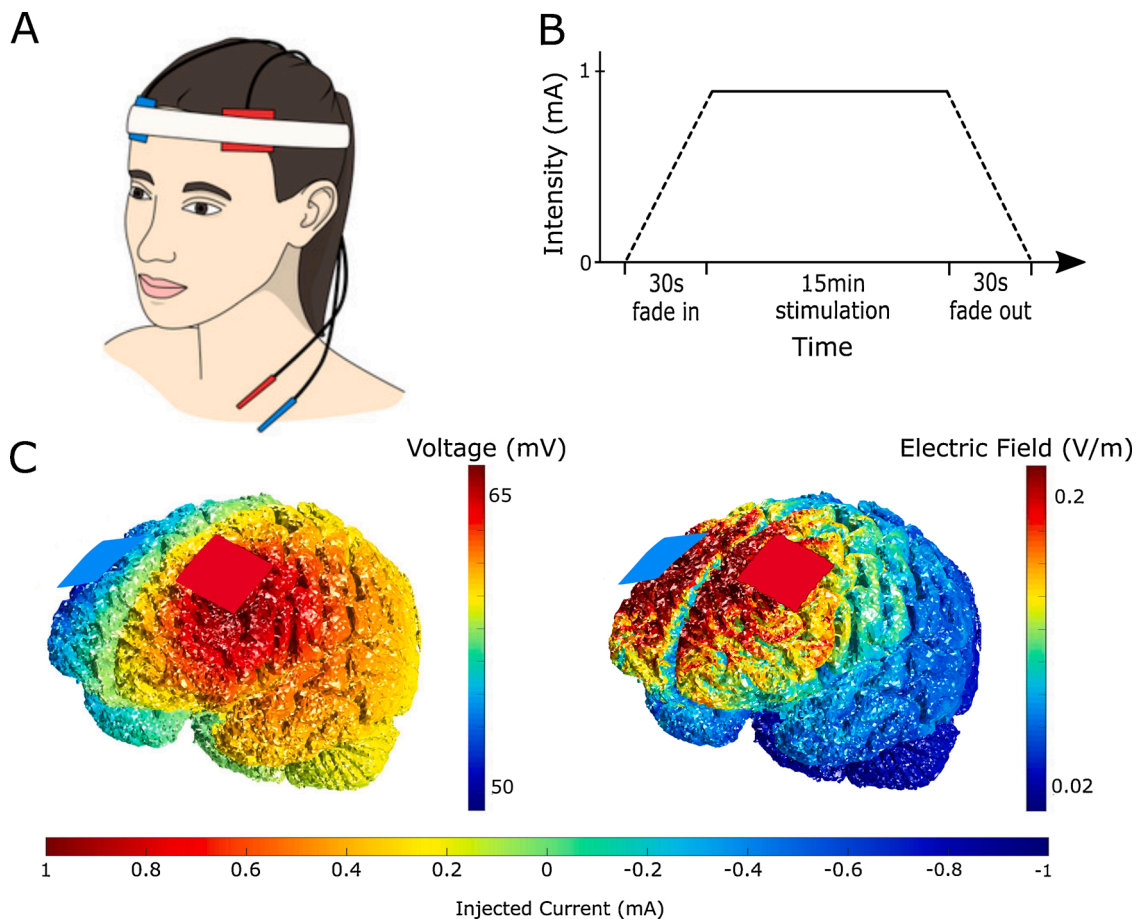
The effects of TBS protocols on cortical and subcortical brain activity in AUD patients are still unclear. One study demonstrated that cTBS over the fronto-polar cortex of AUD patients induced LTD-like effects in the cortical and subcortical nuclei of the limbic area (Hanlon et al., 2017). Specifically, 3600 cTBS pulses over the left frontal pole dampened BOLD activation in brain regions associated with reward and cue processing, including the parahippocampal gyrus, anterior insula, OFC, and the temporal pole (compared to baseline measures), and the left postcentral gyrus and posterior insula, the OFC, anterior insula, and left IFG (compared to the control condition). Using the same stimulation paradigm, this research group also investigated the LTD-like effects of cTBS on brain responses in an alcohol-related stimulus cue-reactivity fMRI task (Kearney-Ramos et al., 2018). The authors hypothesized that after cTBS, functional connectivity between the VMPFC and regions involved in salience and cue responses would decrease during alcohol-related cue processing (compared to neutral cues). In line with their predictions, cTBS reduced functional connectivity between the left VMPFC and several subcortical structures (including the bilateral putamen, bilateral caudate, left insula, and ventral striatum) during alcohol-cue processing.

Overall, the studies outlined above provide significant evidence for the assumption that neurostimulation protocols like rTMS and TBS can prompt neurophysiological changes in cortical and subcortical structures in AUD patients, especially when multisession stimulation regimens are applied. Furthermore, they show that the activity of several neurotransmitter systems (e.g., the glutamatergic, GABAergic, and dopaminergic systems) can be modulated in AUD. Even though further evidence is needed to confirm the underlying neurophysiological mechanisms of action, it seems to be feasible to implement TMS-based treatments that specifically target fronto-striatal circuits underlying the development and consolidation of pathological drinking behaviour.

**4.2.1.3. TMS-based therapeutic applications in AUD.** Most of the therapeutic investigations employing a TMS paradigm in AUD patients assessed the effects of high frequency rTMS on craving symptoms and the relapse rate (Girardi et al., 2015; Herremans et al., 2016; Mishra et al., 2015, 2010; Rapinesi et al., 2015; Wu et al., 2018). This approach probably relies on excitatory rTMS to modulate the activity of cortico-subcortical areas associated with lower frontal control and downregulation of dopaminergic activity in the ventral striatum. Most of these studies focused on the stimulation of a cortical site like the DLPFC. Excitatory rTMS over the DLPFC likely increases subcortical dopaminergic activity (Cho and Strafella, 2009; Strafella et al., 2001, 2003). Based on this mechanism, the restoration of normal dopaminergic activity in order to reduce craving symptoms or re-sensitization to

alternative rewards could be used as a potential therapeutic approach (Diana et al., 1993). Even though a single session of excitatory rTMS has proven ineffective in reducing craving symptoms (Herremans et al., 2012; Jansen et al., 2019), there is some evidence for its efficacy when multiple sessions of rTMS are carried out over the course of several days. Principal differences in the stimulation protocols of these interventions are the targeted area (i.e., mainly left, right, or bilateral DLPFC) and the type of stimulation protocol. Stimulation of the right DLPFC using a 20 Hz rTMS protocol has shown mixed result for reducing craving symptoms. An open-label study of 15 sessions of 20 Hz rTMS over the right DLPFC reported reduced craving levels (Herremans et al., 2015). However, subsequent studies using a similar paradigm failed to demonstrate a clear reduction in craving measures after the stimulation treatments (Herremans et al., 2016; Wu et al., 2018). Moreover, implementing a multisession rTMS protocol at 10 Hz over the right DLPC showed that stimulation was effective in reducing craving scores in a group of abstinent AUD patients (Mishra et al., 2010). Other studies also targeted the left DLPFC at both 20 Hz (Hoppner et al., 2011) and 10 Hz (Del Felice et al., 2016). Yet, the interventions appeared to be ineffective in those two studies, as neither found reduced cravings or alcohol intake. In contrast to this, deep rTMS protocols were proven to be efficacious in reducing craving symptoms, even though the duration of the beneficial effects remains unclear. Two studies from the same research group evaluated a treatment of 20 deep rTMS sessions at 20 Hz in AUD patients with or without a depression diagnosis. Depression and craving levels were evaluated before and after the treatment (Girardi et al., 2015; Rapinesi et al., 2015). In both studies, a decrease in craving levels and an improvement in depressive symptoms were found. Interestingly, the beneficial effects of the rTMS lasted up to 6 months. In addition, a 12-session deep rTMS protocol at 10 Hz delivered bilaterally over the DLPFC also had some effects on drinking behaviour in a group of AUD patients: After the stimulation period, AUD patients showed a significant increase in the number of abstinent days as well as a reduction in the number of drinking days, the number of drinks per drinking days, and total drinks. However, these improvements were not associated with reduced craving symptoms after 1 month of treatment, thus challenging the long-term effect of this specific stimulation protocol (Addolorato et al., 2017). Another study investigated potential differences between the stimulation of the right vs. left DLPFC in reducing cravings (Mishra et al., 2015). The results showed that compared to baseline, multiple sessions of 10 Hz rTMS immediately reduced craving levels, and no difference was found between the stimulation of the right vs. left DLPFC. Yet, the absence of a sham condition and the small sample size ( $n = 10$  for each group) may limit the interpretation of these findings. Finally, a double-blind study examined the effects of deep rTMS at 20 Hz over the dorsal MPFC (Ceccanti et al., 2015). The stimulation site was chosen based on previous studies that had found a grey matter loss in the MPFC of ( $n = 45$ ) abstinent AUD patients (Rando et al., 2011). Ceccanti et al. (2015) interviewed AUD patients about the average number of drinks consumed each day, the number of alcoholic drinks, and days of maximum alcohol intake at the first and last rTMS session, as well as each month for a follow-up of 6 months. Overall, the rTMS treatment induced a decrease in alcohol consumption and the number of drinking days. Reduced cravings were also reported in the post-stimulation period (up to the 2-month follow-up).

These findings suggest that multisession rTMS interventions targeting the frontal cortex may reduce craving symptoms in AUD patients. However, several methodological limitations should be taken into account: For example, studies have frequently investigated relatively small samples (e.g., between 10 and 20 participants per group), which may reduce the robustness and replicability of the results. Another important concern is the use of surveys for the self-evaluation of craving symptoms and alcohol consumption, as this form of assessment can lead to misjudgements and response biases. These limitations and the variability in stimulation paradigms (e.g., the number of stimulation sessions, number of stimulation trains and target sites) make it difficult to gain a better



**Fig. 4.** Visual representation of tDCS and its effects on the cortex. A) Bilateral montage with the cathodal electrode (blue) placed over the left DLPFC and anodal electrode (red) over the right DLPFC. B) Illustration of a typical course of electrical current during an experiment. C) Model of current flow for bilateral DLPFC montage at 1 mA of injected current. The model shows the current flow in the cortex as index of voltage (mV) (left) and electric field (V/m) (right). Obtained with ROAST toolbox (Huang et al., 2019, 2016) for Matlab (Version R2020b; The MathWorks Inc., MA, United States).

understanding of the therapeutic value of this technique in reducing cravings in AUD. Nevertheless, the initial positive outcomes and evidence-based effectiveness in other psychiatric disorders, such as depression and PTSD, suggest that the potential therapeutic benefits of rTMS should be further investigated in AUD.

#### 4.2.2. Transcranial electrical stimulation (tES)

tES is administered with a battery-powered device that delivers a low intensity (1–2 mA) electrical current through one or more electrodes placed over the scalp for several minutes (Fig. 4). Different electrical stimulation protocols can be used. The most widely known protocols are transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). Comparatively new protocols, such as random noise stimulation (tRNS) have only been investigated in the last decade (Antal and Herrmann, 2016; Ghin et al., 2018, 2021; Pavan et al., 2019). In the last twenty years, the behavioural, physiological and clinical effects of applying an electrical current to the brain have been extensively studied (Lefaucheur et al., 2017; Nitsche et al., 2008). So far, tDCS is the most commonly used and studied type of non-invasive TES. For rDCS, a direct current is delivered through two or more electrodes. This type of stimulation has been widely used in clinical settings. While its efficacy has been proposed for some neurological and psychiatric disorders (Fregni et al., 2020), the efficacy of tDCS for substance addiction is still under investigation (Bollen et al., 2021; Fregni et al., 2020; Lefaucheur et al., 2017). TDCS simultaneously delivers an anodal (positive charge) and a cathodal (negative charge) current. Commonly used stimulation protocols apply two stimulation electrodes. The

electrode delivering the polarity of interest (active electrode) is usually placed over the target area, while the second “reference” electrode is placed over a control area (that is ideally not associated with the task or cognitive function of interest). Early on, it was discovered that the effects of the direct current over the cortex depend on its polarity. For example, Bindman et al. (1964) found that in the cerebral cortex of anesthetized rodents, anodal stimulation increased the spontaneous firing rate of active neurons close to the electrode, while cathodal stimulation decreased the neural firing rate. Overall, it has been proposed that anodal stimulation depolarizes the resting membrane potential (thus increasing firing rate), while cathodal stimulation hyperpolarizes it (thus decreasing firing rate) (Fig. 4C). While it has been proposed that the stimulation of deep brain structures can lead to opposite outcomes (Purpura and McMurtry, 1965), physiological results seemed to confirm this modulatory effects over the motor cortex in human studies (for a review see Nitsche et al., 2008).

**4.2.2.1. Method and proposed mechanism of action of tES.** One of the proposed mechanisms of tDCS is the modulation of the neural firing rate via changes in neural resting membrane potentials. This effect might be based on the ability of tDCS to modulate the intracellular concentration of calcium ions (Ca<sup>2+</sup>; Bikson et al., 2004). This is of particular relevance, since increments in Ca<sup>2+</sup> concentration can promote short and long-term plasticity (Greer and Greenberg, 2008). Furthermore, pharmacological evidence shows that blocking voltage-dependent sodium (Na<sup>+</sup>) and Ca<sup>2+</sup>-channels seems to eliminate the excitatory effects of anodal tDCS (atDCS), but not the inhibitory cathodal effects (Nitsche

et al., 2003). Interestingly, it has been found that NMDA receptors are not responsible for short-term tDCS effects, but they seem to play a critical role in the formation of post-stimulation after-effects. Supporting this, it has been found that the partial NMDA receptor agonist d-cycloserine may prolong the excitatory effects of anodal tDCS (Nitsche, 2004; Nitsche et al., 2004). Additionally, GABA also seems to play a role in tDCS mechanisms of action. For example, evidence shows that anodal tDCS can reduce GABA concentrations, while cathodal tDCS (ctDCS) decreased glutamatergic neuronal activity with a correlated reduction in GABA concentration (Stagg et al., 2009a). Future investigations on the therapeutic applications of tDCS in clinical conditions might derive support from recent findings showing that tDCS delivered over the frontal cortex induced a release of extracellular dopamine in the striatum (Bunai et al., 2021; Fonteneau et al., 2018).

**4.2.2.2. tES neuromodulatory effects in AUD.** While there is extensive literature on the short and long-term physiological consequences of tDCS in both healthy and clinical populations, only very few studies investigated the potential effects of tES in AUD patients. Given this lack of studies in the field, understanding the behavioural and neurophysiological basis of tDCS effects, as well as their relation is of particular relevance in order to gain mechanistic insights and design potentially efficient therapeutic protocols. In this regard, one early study demonstrated that atDCS stimulation of the left DLPFC modulated the frontal P3 component in response to drinking-related vs. neutral auditory stimuli (Nakamura-Palacios et al., 2012). A subsequent study (da Silva et al., 2013) delivered multiple tDCS sessions over the DLPFC during a cue-reactivity paradigm. Subjects were asked to respond to alcohol-related stimuli, but refrain from responding to neutral cues. Results showed that irrespective of stimulus condition, the tDCS treatment reduced neural activation in various PFC areas. Using a bilateral stimulation protocol over the DLPFC (ctDCS-left and atDCS-right DLPFC), Nakamura-Palacios et al. (2016) investigated PFC activation in AUD patients. They enrolled participants from a previous study (Klauss et al., 2014), who underwent five consecutive days of tDCS or sham (control condition) treatment during a cue-reactivity paradigm. The results showed that tDCS increased activation in the vmPFC and middle temporal gyrus in response to alcohol-related stimuli, while the sham group only showed an increased activation in the middle temporal gyrus from pre to post treatment. The authors suggested that the tDCS treatment might have modulated PFC activity because of their involvement in processing drug-related stimuli and therefore in aiding increased self-control over drug seeking behaviour. Although this study is of particular interest, it needs to be noted that these results were obtained from a relatively small sample ( $n = 22$ ), the majority of which ( $n = 14$  participants) was assigned to the active tDCS stimulation group, thus leaving only  $n = 8$  participants in the sham stimulation group. Additionally, the statistical analyses for the 6-month follow-up were only conducted on participants from the sham group who had relapsed, and on participants from the tDCS group who had remained abstinent. A more recent study examined the effects of 8 sessions of atDCS over the right IFG on the late positive potential (LPP), which reflects affective processing of salient stimuli (Brown et al., 2020). They found that the LPP amplitude decreased over time and that this was positively correlated with a reduction in craving. Yet, this was not modulated by the stimulation. Finally, another recent study assessed the effects of multiple sessions of bilateral tDCS on detoxified AUD patients via fMRI resting-state activity (Holla et al., 2020). Results showed that tDCS increased functional connectivity in prefrontal networks. In particular, the tDCS treatment increased the ability to integrate global information (global efficiency), which was correlated with the ability to remain abstinent. At the same time, tDCS treatment reduced the presence of interconnected brain regions processing similar information (global clustering), which was correlated with a decrease in behavioural impulsivity. Overall, these studies demonstrated that tDCS delivered to

the PFC might allow to induce some long-term modification of neural activity. However, there are limitations to some of the studies (e.g., small sample sizes), so that more studies are required to fully elucidate short-term and long-term neurophysiological effects of tDCS, and whether those correlate with behavioural modification after tDCS-based (AUD) treatments.

**4.2.2.3. tES-based therapeutic applications in AUD.** Up to date, several studies have examined the clinical application of tDCS in AUD patients. Most of these studies investigated potential short-term and long-term changes of critical symptoms such as craving, drinking amounts, and the ability to remain abstinent. An early study examined the effects of bilateral tDCS over the DLPFC in AUD patients (Boggio et al., 2008). Interestingly, the experimental procedure included two reverse stimulation montages, where anodal and cathodal stimulation were applied to the left and right DLPFC, respectively. Results showed that both montage conditions reduced craving symptoms. The authors suggested that the lack of differences between the two stimulation protocols could be explained as a general tDCS-induced interference in craving-relevant brain circuits. Based on these positive findings, following studies mostly examined the effects of different stimulation protocols over the DLPFC, with only two studies examining the effects of tDCS over the right IFG (Brown et al., 2020; den Uyl et al., 2015). Aside from the stimulation target area, the main differences among studies are the number of stimulation sessions, the inclusion of cognitive tasks, and pre- vs. post-stimulation evaluations of craving and other relevant measures (e.g., relapses or the frequency of consumption). One early study assessed the effects of a single atDCS stimulation session over the left DLPFC in 49 AUD patients (Nakamura-Palacios et al., 2012). Results showed that this single stimulation did not induce any significant pre- vs. post treatment differences in craving symptoms (as measured with the obsessive compulsive drinking scale / OCDS), or in frontal functions (as measured with the frontal assessment battery / FAB). A subsequent study (den Uyl et al., 2015), also investigated the effects of one atDCS session delivered either over the left DLPFC or the right IFG. Craving estimates were measured using an implicit association task (IAT) and alcohol approach/avoidance questionnaire. Overall, results showed that tDCS had limited effects in reducing post-stimulation craving measures, but only when stimulation was applied over the left DLPFC. The limited effectiveness of tDCS was somewhat supported by a later study, in which a single stimulation session of tDCS delivered over the DLPFC in recently detoxified AUD patients did not induce any significant reductions in craving (Wietschorke et al., 2016). Overall, more evidence is needed, but there seems to be a rather limited efficacy of a single tDCS session in producing substantial changes in craving symptoms and/or cognitive functions in AUD patients.

On the other hand, studies employing therapeutic protocols with multiple stimulation sessions have shown, although not definitively, some efficacy in reducing craving symptoms. The first study investigated the effects of multiple stimulation sessions in Lesch IV AUD patients (da Silva et al., 2013). Anodal stimulation was delivered over the left DLPFC for 5 sessions with one session per week. Results showed that the stimulation protocol reduced craving and depression symptoms, but was ineffective at inducing any changes in anxiety, quality of life, or executive function measures. Albeit promising, this study suffered from a small sample size (13 participants, divided into an active and a control stimulation group). Furthermore, the patients in the active tDCS treatment group surprisingly relapsed more often than those in the control treatment group (which the authors however attributed to baseline differences in drinking amounts between the two groups). A subsequent study applied a speed-up multi-session treatment (5 sessions on 5 consecutive days) using a bilateral montage (left-cathodal; right-anodal) over the DLPFC and a stimulation intensity of 2 mA (Klauss et al., 2014). Pre-post measurements showed that the stimulation protocol was not effective in reducing craving, frontal functions, anxiety, or depressive

status. However, it is worth noting that at 6-month follow-up, participants in the tDCS group showed significantly less relapses than the sham group. In a subsequent double-blind, randomized, sham-controlled clinical trial, the same research group (Klauss et al., 2018) applied the same experimental paradigm (Klauss et al., 2014), but increased the number of stimulation sessions to 10. During the trial, craving symptoms decreased in both groups, but a pre-post treatment difference was only evident in the tDCS group. At the 3-month follow up, the relapse rate between groups showed opposite trends, with roughly 70 % of the sham group patients experiencing relapses and 70 % of the tDCS group patients remaining abstinent. Other studies combined multisession stimulation treatment with task interventions as well as cognitive and mindfulness therapies (Brown et al., 2020; den Uyl et al., 2017, 2018; Witkiewitz et al., 2019). One research group combined alcohol approach retraining as a form of CBM training and anodal stimulation over the left DLPFC for a total of 4 sessions (den Uyl et al., 2017). 91 AUD patients were randomly assigned to one of three experimental groups. While alcohol approach bias rates decreased over the study, this was not related to the experimental conditions. Furthermore, pre-post treatment examinations revealed no effects related to the CBM training or the tDCS on craving and follow-up relapse rates. Another subsequent study from the same research group (den Uyl et al., 2018) investigated the combination of a similar stimulation protocol (atDCS) over the DLPFC and an ABM paradigm delivered over four sessions. Results showed that the attentional bias to alcohol was reduced when tDCS was combined with the ABM training, but not when tDCS or ABM were applied separately. Furthermore, no significant differences in craving symptoms or relapse rate were found. A recent study from the same research group (Witkiewitz et al., 2019) combined mindfulness-based relapse prevention and tDCS therapy sessions once a week over the course of eight weeks. Differently from most of previous studies, stimulation was delivered over the right IFG (and not over the DLPFC). Results showed that, even though the amount of consumption and craving decreased over time, this was not associated with the stimulation condition (active vs sham).

#### 4.3. A therapeutic mechanism-based approach for NIBS-based interventions in AUD

Therapeutic interventions based on rTMS or tES mainly explored the effectivity of high-frequency stimulation protocols in reducing general craving symptoms of AUD patients. The aim of these interventions has been to regulate craving by targeting the prefrontal-striatal pathway and restoring functional prefrontal inhibitory control over the ventral striatum. As described in the previous sections, this approach is based on the assumption that the frontal cortices have a regulatory role and are a neural hub of cognitive control exerted over subcortical regions implicated in motivational and reward processing (Everitt and Robbins, 2005). While craving and relapse may reflect the pathological imbalance between controlled and automatic behaviour, limiting the scope of therapeutic applications to the reduction of craving symptoms without gaining a mechanistic understanding of impaired cognitive control functions may have limited the efficacy of these approaches. Therefore, we think that more research should be conducted in order to understand how non-invasive brain stimulation techniques, such as rTMS and tDCS, can be used to modulate cognitive control functions and yield beneficial restorative effects on the imbalance between automatic response tendencies and controlled behaviour. In other words, we would like to advocate a shift from a symptom-based to a mechanism-based therapeutic approaches for future neuromodulatory interventions.

While most of the currently available NIBS research has heavily focussed on the DLPFC as a primary stimulation site in AUD patients (Del Felice et al., 2016; Dormal et al., 2020; Herremans et al., 2013; Holla et al., 2020; McNeill et al., 2018; Weidler et al., 2020), it should be acknowledged that research in healthy individuals has also yielded several other brain areas associated with cognitive control processes and their role in regulating the balance between controlled and automatic

behaviour.

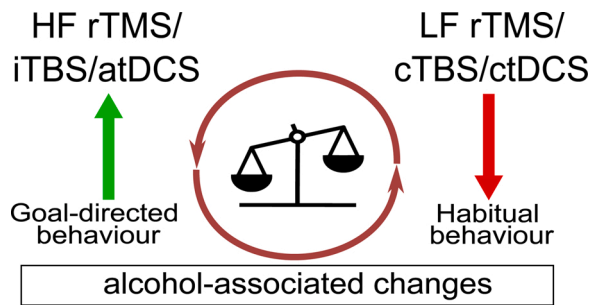
TMS studies on cognitive control functions in healthy subjects investigated the role of the DLPFC, as well as other cortical areas associated with inhibitory control and automaticity, such as the IFG and pre-SMA (Chambers et al., 2006, 2007; Li et al., 2017; Lowe et al., 2014; Sandrini et al., 2008; Verbruggen et al., 2010; Yang et al., 2018). Single sessions of cTBS over the left DLPFC have been shown to efficaciously reduce interference control process, while leaving response inhibition unchanged (Lowe et al., 2014). Inhibition of the IFG via rTMS and cTBS protocols may weaken response inhibition and reduce the ability to stop action execution (Chambers et al., 2007, 2006; Verbruggen et al., 2010). Furthermore, cTBS-induced suppression of neural activity in the IFG weakened goal-directed behaviour and concurrently increased habitual response tendencies (Bogdanov et al., 2018). In healthy participants, dampening rIFG activity via inhibitory cTBS seems to yield consistent results, and single sessions of excitatory neuromodulation of the same area do not lead to significant changes in response inhibition and response selection processes (Yang et al., 2018).

Furthermore, one recent meta-analysis (Schroeder et al., 2020) showed that a single session of tDCS may induce small, but significant, effects on response inhibition. Of note, this study found that the target area is an important contributing factor to the stimulation outcome. More precisely, the right IFG and pre-SMA (but not DLPFC) were found to be associated with the effectiveness of tDCS stimulation in modulating response inhibition. Other contributing factors were the return electrode placement and the assessed measures / implemented tasks.

Overall, evidence (Dippel and Beste, 2015; Stock et al., 2016e) suggests that the IFG plays a key role in the automatic (bottom-up) implementation and reprogramming of response strategies, further stressing its important role in automatic response selection and modulating the interaction with inhibitory control. Furthermore, different components of inhibitory control, such as response cancellation, response retention, and interference control might partially share overlapping circuits involving the IFG and the pre-SMA (Aron et al., 2007b, 2007a; Cai et al., 2012; Neubert et al., 2010; Yang et al., 2018). Against this background, the disruption of activity in the pre-SMA with short trains of rTMS has been shown to reduce response inhibition (Chen et al., 2009), thus providing evidence for its role in controlling prepotent responses. Furthermore, rTMS selectively delivered to the pre-SMA at stimulus onset has demonstrated its role in implementing the stopping process (Cai et al., 2012). Interestingly, Neubert et al. (2010) disentangled the specific contributions of the IFG and pre-SMA on response inhibition and their role in modulating the motor response processed in the primary motor cortex via the neuromodulatory effects of TMS.

Individuals with AUD are usually characterized by a low level of cognitive control and relatively preserved (if not increased) automaticity. The neurostimulation of cortical circuits responsible for balancing cognitive control functions and automatic response tendencies along with habit consolidation may be helpful for determining the mechanisms of action underlying pathological behaviour in AUD patients. For example, we may hypothesize that the inhibition/normalization of activity in automaticity-related brain areas, such as the right IFG and pre-SMA, might lead to a reduction of automatic response tendencies in AUD patients. Importantly, such a reduction in impulsivity could help to exploit the remaining/spared cognitive control resources, thereby helping to re-establish the balance between control and automatic processes. Ideally, this should ultimately result in behaviour that is more similar to that of healthy controls. Excitatory rTMS, tDCS, and iTBS seem to have limited effects in increasing cognitive control abilities in healthy participants (Lowe and Hall, 2018; Schroeder et al., 2020), but this might be different in AUD patients. The limited results obtained in healthy participant populations may have resulted from a ceiling effect in the up-regulating excitatory stimulation. Although the altered glutamatergic signalling or hyper-excitability state in abstinent patients should be taken into consideration in order to design safe stimulation protocols, excitatory stimulation via TMS or tDCS may still carry a great





**Fig. 5.** Schematic illustration of the expected effects of NIBS-based interventions on the balance between goal-directed and habitual behaviour in AUD. We speculate that excitatory interventions (hf-TMS/iTBS/atDCS) directed over control-related areas may improve cognitive control functions, thus favouring goal directed behaviour. On the contrary, we expect that inhibitory interventions (lf-rTMS/cTBS/cTDCS) over automatic-related areas may decrease prepotent response tendencies and related habitual behaviour. By reducing the probability of habitual system to access cognitive and neural resources, a better use of the spared cognitive control functions can be made, hopefully increasing the changes of correct response inhibition.

potential for therapeutic effects in clinical populations (Fig. 5). When considering the possibility of restoring the imbalance between controlled and automatic actions in AUD, one could also consider the *zero-sum framework* of cognitive enhancement (Brem et al., 2014). The *zero-sum framework* suggests that cognitive enhancement is limited by a brain-bound operational capacity and, therefore, enhancement or improvement of a given function may result in a corresponding loss in another cognitive function (Colzato et al., 2020). Supporting this hypothesis, neural changes induced by non-invasive brain stimulation in different brain areas resulted in a double dissociation (i.e., an this increase-decrease pattern) between learning skills and automatic processes. In other words, the enhancement of a cognitive function was achieved at the expenses of the respective other cognitive function (Iuculano and Cohen Kadosh, 2013). We could speculate that a similar principle applies to the imbalance between automatic and cognitive control functions in AUD. Consequentially, enhancement of cognitive control functions via excitatory TMS/iTBS or atDCS might result in a concurrent reduction of automatic response tendencies, whereas a perturbation of automatic behaviour via inhibitory rTMS/cTBS or ctDCS may induce a beneficial effect on pathological cognitive control in AUD.

## 5. Conclusions

AUD is a relapsing disorder characterized by rigid drinking habits and insufficient control over impulsive responses. This pathological behaviour has been associated with multiple alterations in neurotransmitters and metabolic activity in cortical and subcortical structures. Even though the combination of cognitive and pharmacological therapy is currently the primary form of treatment in AUD, especially the latter has several limitations, including its efficacy, side effects, and poor therapy adherence. In addition, pharmacological interventions aimed at reducing the relapse rate are focused on alleviating symptoms of craving or, as in the case of disulfiram, inducing unpleasant effects if alcohol is ingested, but they do not directly target the underlying neurobiological mechanisms that contribute to the inability to remain abstinent. These issues, paired with a clinical practice that does not sufficiently account for recent findings, call for an investigation of different approaches. NIBS-based interventions mainly aim at directly reducing craving and the relapse rate, where they have yielded some modest results. Despite this, we think that the full potential of these stimulation techniques has not yet been fully explored. We propose that neuromodulatory interventions, such as rTMS or tDCS, could be used to directly modulate neural correlates of the imbalance between cognitive control functions and automatic response tendencies in AUD. Stimulation protocols

designed to induce a long-term form of neural plasticity in brain areas like the right IFG and pre-SMA, may be extremely useful for this purpose. The knowledge gained from experimental studies based on the modulatory effects of NIBS could help to design new therapeutic approaches aiming to restore damaged cognitive control abilities and altering automatic processes of habitual drinking, potentially also reducing the symptoms of craving and the risk of relapse.

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