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Inhibitory control, attentional bias and craving, and their underlying neural substrates, in the maintenance of alcohol consumption

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This thesis is submitted to the Department of Psychology, Edge Hill University, in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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I. Declaration

I declare that this thesis is my own work carried out under the normal terms of supervision. I confirm that this work has not been submitted for any comparable academic award.

Signed: 

Adam Michael McNeill

II. Acknowledgements

To my supervisory team, Rebecca, Derek and Adam, I can never thank you enough. Before the PhD commenced, you supported and fought for me, without that none of this would have been possible. You believed in me when many did not and for that I will be eternally grateful. If only you had known what you were getting yourself in for. The course of the PhD has not always been smooth, but you have always provided support, advice and guidance, often beyond the realm of the PhD. Thank you just does not seem adequate.

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III. Publications from Thesis

McNeill, A., Monk, R. L., Qureshi, A. W., Makris, S., & Heim, D. (2018). Continuous Theta Burst Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex Impairs Inhibitory Control and Increases Alcohol Consumption. *Cognitive, Affective and Behavioral Neuroscience*, *18*(6), 1198–1206. https://doi.org/10.3758/s13415-018-0631-3

Under review

McNeill, A. M., Monk, R. L., Qureshi, A. W., Litchfield. D., & Heim, D. The effects of placebo and moderate dose alcohol on attentional bias, inhibitory control and subjective craving

McNeill, A. M., Monk, R. L., Qureshi, A. W., & Heim, D. Intoxication without anticipation: Disentangling pharmacological from expected effects of alcohol

McNeill, A.M., Monk, R. L., Qureshi, A. W., Makris, S., Cazzato, V., & Heim, D. Elevated ad libitum alcohol consumption following continuous theta burst stimulation to the left-dorsolateral prefrontal cortex is partially mediated by changes in craving

IV. Abstract

Rationale: Theoretical accounts of substance use posit that changes in cognitive processes, particularly inhibitory control and attentional bias, are key determinants of consumption behaviour. However, existing research has lacked the nuance to examine (i) the relative contributions of alcohol's pharmacological and anticipated effects in causing said changes in cognition and (ii) the ability to isolate cognitions from one another and the wider neuropsychopharmacological effects of alcohol. **Aims:** The current body of research therefore aimed to engage novel methods to more closely examine the extent to which transient changes in inhibitory control, attentional bias and craving govern the maintenance of alcohol consumption. **Methods** ***Study 1****:* In a counterbalanced, within participants design, measures of inhibitory control, attentional bias, craving, alcohol expectancies and *ad libitum* consumption were taken following alcohol pre-load (.6g/kg), placebo and control. ***Study 2****:* In a vertex-controlled within participants design, continuous theta burst (cTBS) transcranial magnetic stimulation (TMS) was deployed to the right-dorsolateral prefrontal cortex (DLPFC) with measures of inhibitory control taken pre- and post-stimulation, followed by a bogus taste task. ***Study 3:*** cTBS was utilised to stimulate the right- and left-DLPFC, medial orbital frontal cortex (mOFC) and vertex (control), combined with measures of inhibitory control, attentional bias, attentional inhibition and craving, followed by *ad libitum* consumption. ***Study 4:*** A novel naïve alcohol administration (.4g/kg) method was developed in order to remove anticipatory effects. Naïve, alcohol pre-load, placebo and pure controls alcohol pre-loads were applied in a between participants design. Measures of inhibitory control, attentional bias, craving and *ad libitum* consumption were taken following beverage administration. **Results** ***Study 1:*** Alcohol pre-load and placebo impaired inhibitory control and elevated craving, but heightened alcohol-related attentional bias was only observed following placebo. Increased *ad libitum* consumption

was only evident following alcohol pre-load, with some tentative evidence to suggest that craving, but not inhibitory control, may play a mediatory role. ***Study 2:*** Stimulation to the rDLPFC impaired inhibitory control and was associated with increases in consumption *ad libitum.* There was, however, no apparent direct association between transient inhibitory control impairments and successive consumption. ***Study 3****:* cTBS to the right- and left-DLPFC impaired inhibitory control and cTBS to the mOFC reduced alcohol-related attentional bias. These changes, however, were not associated with one another. Craving increased following lDLPFC stimulation, but this was not associated with a heightening of attentional bias. Finally, elevated *ad libitum* consumption was observed following lDLPFC cTBS only and was mediated by changes in craving. ***Study 4****:* Both pharmacological (alcohol pre-load, naïve alcohol) and anticipation conditions (placebo alcohol) resulted in significant changes in inhibitory control and craving, however, heightened *ad libitum* consumption was observed only after pharmacological conditions. Furthermore, the association between initial beverage and subsequent consumption was partially mediated by craving, but not inhibitory control impairments. **Overall conclusions:** The current body of research is the first to explore and systematically unpick alcohol's pharmacology and anticipation on one hand and employ neuromodulation techniques to isolate cognitive changes and their respective roles in consumption behaviour on the other. It implicates craving as a potentially central motivational mechanism involved in driving and maintaining drinking episodes. Critically, transient fluctuations in craving appear to elevate consumption. It is also suggested that apparent losses of control are primarily driven by alcohol's pharmacological, not anticipated effects. It is therefore recommended that rather than focussing on improving inhibitory control, as has been hitherto more common, interventions targeting explicit cognitions such as craving may be beneficial in reducing alcohol-related harms. **Original contribution:** The current thesis offers two distinct

original contributions to knowledge, methodologically and theoretically. First, research within employed a novel alcohol naïve administration protocol to extricate alcohol pharmacology from anticipation. Second, TMS was utilised to isolate neural and cognitive changes from wider effects of alcohol pharmacology, to examine their respective contributions and interactions to drinking patterns. Theoretically moreover, the thesis findings implicate explicit (e.g., craving) rather than implicit (inhibitory control, attentional bias) cognitions as central mechanisms in the maintenance of consumption.

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Chapter 1: Introduction

1.1 The problem: What are the health and societal consequences of drinking behaviours?

Drinking has become so embedded in the culture of the UK, that we drink to celebrate and commiserate, it is associated with sporting events and to the point, most social occasions. While data suggests that overall alcohol consumption has been on the decline since 2007, it remains that 31% of men and 16% of women regularly consume over the recommended weekly guidelines[1] (*Health Survey for England 2016*, 2017). Therefore, issues associated with alcohol consumption still constitute a significant problem in the UK. Accordingly, in the UK, it is suggested that the approximate cost associated with the consumption of alcohol is £21 billion per annum (Health and Social Care Information Centre [HSCIC], 2013). However, it has been suggested that this figure may be too conservative and that calculating a representative figure may not entirely feasible (Bhattacharya, 2016). With this being said excessive drinking is associated with wider cultural and social problems, including alcohol-related crime, suggested to cost the UK £11 billion per annum, and loss of productivity costs amounting to £7.3 billion per annum (Institute of Alcohol Studies [IAS], 2013). It is therefore obvious that alcohol consumption behaviours constitute a significant problem not just for the UK, but globally.

Alcohol consumption is globally one of the top five risk factors for disease, disability and mortality (World Health Organization [WHO], 2014). The consumption of alcohol is associated with a vast number of health implications and, as such, it is listed as a causal factor for over 200 conditions in the International Classification of

[1] Recommended weekly guidelines for both men and women is 14 UK units (National Institute of Clinical Excellence [NICE], 2016).

Diseases and Related Health Problems (ICD-10; WHO, 2014). The health concerns associated with alcohol consumption vary with consumption behaviour and volumes. Alcohol dependence is associated with chronic health issues, including cirrhosis of liver, kidney failure, heart disease, cardiovascular disease and various forms of cancer (ICD-10; WHO, 2014). On the other hand, binge drinking[2] is associated with many acute health consequences including injury, sexually transmitted diseases due to risky sexual behaviour, and even death due to alcohol poisoning (Corte & Sommers, 2005; ICD-10; WHO, 2014). However, frequent binge drinking can also be associated with long-term health consequences similar to those of alcohol dependence. Moreover, although overall consumption may be falling, alcohol-related hospital admissions and frequent attenders have been on rise in the same period (Blackwood, Lynskey, & Drummond, 2017). This represents a considerable economic cost to the health service (~£3.5 billion), not to mention an added strain on wider resources such as staffing. It is therefore clear that alcohol consumption not only constitutes a significant social and economic dilemma, but a substantial risk to health and mortality.

Considering the significant health risks and economic consequences of alcohol consumption behaviour, it is therefore important to understand the processes driving and maintaining these patterns of behaviour in the face of this evidence. Specifically, it is the intention to of this thesis to enhance the understanding of the psychopharmacology of alcohol and the cognitive (e.g., inhibitory control and attentional bias) and explicit (e.g., subjective craving) processes underpinning drinking behaviours. The understanding of these mechanisms and how they specifically interact could have implications for the treatment of alcohol use and misuse, and inform future policy.

[2] Defined as the consumption of significant quantities of alcohol (≥6 units in a single session; National Institute of Clinical Excellence [NICE], 2016).

1.2 Neurocircuitry of 'Addiction'

The disease model of addiction suggests that drug and alcohol dependence should be treated as an acquired brain disease (see Volkow & Koob, 2015), though this is a very contentious position amongst scholars (see Heim et al., 2014). We must nevertheless recognise that the disease model of addiction has provided valuable insights into the neurocircuitry involved in alcohol use and dependence (see Volkow, Koob, & McLellan, 2016). It has shed light on how doses of alcohol can cause acute changes in activation of various neural structures and suggested that chronic use results in significant changes in neural physiology (see Koob, 2014). Specifically, the dorsal striatum (i.e., nucleus accumbent [NAc], ventral tegmental area [VTA]) and prefrontal regions, including the orbital frontal cortex (OFC), have been widely implicated in alcohol use and alcohol use disorder (AUD; ibid). While this body of work has illuminated which neural structures are associated with alcohol use, there is still some way to go in understanding how these structures exert influence over alcohol consumption behaviour.

The dorsal striatum, specifically the NAc and VTA, is considered the 'reward' centre of the brain, with activation associated with rewarding stimuli including sex (Voon et al., 2014), gambling (Brevers, Noël, He, Melrose, & Bechara, 2016), substances (see Koob & Volkow, 2010) and alcohol (Jessica Weafer et al., 2018). Research has implicated the rewarding nature of dopamine in the dorsal striatum as a response to substance (including alcohol) intoxication in the repetition of use and development of use disorders (Di Chiara, 2002; Wise, 2008). Specifically, it is suggested that patterns of use are the results of conditioned responses; the dopaminergic reward response pairs with contextual stimuli, reinforcing the association between substance and context (see Volkow et al., 2016). It is a central facet of the disease

model of addiction that recurring use of substance (i) strengthens the conditioned response and (ii) results in physiological changes at the receptor level, and these are processes are pivotal in substance and alcohol use disorder development (ibid). There is perhaps, however, a more logical explanation of these changes in the brain and that is the suggestion that addiction associated changes in the brain are the result of wider contextual and environmental (rather than internal) learning reinforcers (see Lewis, 2018). These changes, nonetheless, have been theorised as well as indicted to be associated with alcohol craving (Ray & Roche, 2018; Weiss, 2005) and with alcohol-related "cue" saliency (Robinson & Berridge, 1993, 2001).

The OFC has been suggested to mediate the saliency attribution, the value assigned to stimulus associated with striatal activity (see Koob & Volkow, 2010). Neuroimaging studies have demonstrated that in appetitive regulation, the OFC is active while a person is hungry, hence, food-related stimuli are salient (see Piech et al., 2009). However, when that hunger is satiated in healthy controls, OFC activation in response to food-related stimuli reduces (ibid). In alcohol use on the other hand, following alcohol intoxication OFC activation becomes elevated when presented with alcohol-related stimuli (e.g., Filbey et al., 2008). It is therefore suggested that the OFC plays an important role in behavioural self-regulation, with evidence from animal studies demonstrating that OFC lesions are associated with significant increases in substance self-administration (see Schoenbaum & Shaham, 2008). In humans, a recent study indicated that virtual lesions stemming from transcranial magnetic stimulation (TMS) to the OFC resulted poor salience attribution for devalued food-related stimuli (Howard et al., 2020). Hitherto, little is understood about the causal role the OFC may play in appetitive- and self-regulation. TMS however, represents a fruitful tool in this

exploration. The OFC is, nevertheless, suggested to be part of a wider array of prefrontal cortices implicated in behavioural regulation.

Wider prefrontal cortices have been implicated alongside the OFC in self-regulation, and specifically, impulse control (see Zilverstand, Huang, Alia-Klein, & Goldstein, 2018). Positron Emission Topography (PET) has indicated that on the whole, activity in prefrontal regions of the brain is reduced by 95% following alcohol intoxication (Volkow et al., 2008), suggesting that neural structures associated with behavioural regulation (including alcohol consumption) are significantly impeded by alcohol itself. Specifically, hypoactivation of the dorsolateral prefrontal cortex (DLPFC) has associated with impaired inhibitory control (see Luijten et al., 2014) and cognitive appraisal and self-regulation (see Zilverstand, Parvaz, & Goldstein, 2017). Recent neuromodulation studies have furthermore emphasised the importance of the DLPFC in impulse control (see Brevet-Aeby, Brunelin, Iceta, Padovan, & Poulet, 2016; Lowe, Manocchio, Safati, & Hall, 2018), and specifically, inhibitory stimulation protocols to DLPFCs have been shown to impair impulse control. Moreover, findings of another study indicated that TMS to the left-DLPFC not only impaired inhibitory control, but also elevated snack cravings and that increased snack consumption was mediated by inhibitory control impairments (Lowe, Hall, & Staines, 2014). This body of research converges to implicate prefrontal brain regions in self-regulation and impulse control. However, to date our understanding of how of these prefrontal regions wield control over drinking behaviours is limited and more causal explorations are required.

This body of literature has been important in highlighting the neural structures that are potentially crucial in regulating alcohol consumption behaviours. There remains limited evidence for the causal role prefrontal structures (i.e., DLPFC, OFC) have in

exercising control over drinking. While recent advances in neuromodulation have provided fertile insights into the relationship between prefrontal cortices and cognition, specifically, inhibitory control and attention (see Lowe et al., 2018),these methods, while representing a potentially effective approach for studying the causal links between brain functioning and consumption behaviour (similar to those of appetite; Lowe et al., 2014), have yet to be employed in alcohol use research. Such techniques also represent a means of isolating cognitive changes (i.e., inhibitory control, attentional bias, craving) from the wider neuropsychopharmacological effect of alcohol (discussed below) in an effort to (i) ascertain their respective contributions to driving and maintaining alcohol consumption, (ii) developing our understanding of how such processes interact with one another and (iii) how such interactions drive and maintain consumption.

1.3 Alcohol pharmacology versus anticipation

As evidenced, alcohol has widespread pharmacological effects on the human nervous system (see Koob & Volkow, 2010), as well as influencing various behaviours such as risk-taking (Lane, Cherek, Pietras, & Tcheremissine, 2004) and decision making (Bernhardt et al., 2019; George, Rogers, & Duka, 2005). It has been suggested however, that the mere anticipation of these effects can illicit similar psychological consequences (e.g., (Marlatt, Demming, & Reid, 1973). Unsurprisingly, this phenomenon is known as the anticipated effects of alcohol (Christiansen, Rose, Cole, & Field, 2013). The relative contributions of the pharmacological and anticipated effects in driving changes in cognition (i.e., inhibitory control, attentional bias, craving) and consummatory behaviour is hitherto poorly understood. This debate has been punctuated by the evolution of alcohol administration paradigms, with each iteration allowing for the unpicking of new components of the relationship between alcohol pharmacology and anticipation.

Alcohol's pharmacological effects are traditionally researched using alcohol pre-load designs, involving the administration of a dose of alcohol followed by cognitive and/or behavioural measures. Research employing alcohol pre-loads have highlighted the pharmacological effects of alcohol within the brain (see Bjork & Gilman, 2014) and their influence in various cognitive and behavioural changes. Studies have indicated the effects of alcohol on memory, and specifically that acute intoxication impairs working, episodic and semantic memory (see Mintzer, 2007). Furthermore, a number of lab-based studies have exhibited elevated risk-taking following acute alcohol exposure (e.g., Rose, Jones, Clarke, & Christiansen, 2014). Initial doses of alcohol have been suggested to have a 'priming' effect, reinforcing alcohol seeking behaviour (de Wit, 1996) and increasing motivations to drink (e.g., Rose, Hobbs, & Drummond, 2013). It is important

to recognise however, that early alcohol administration paradigms were placebo-controlled, in that placebo alcohol was administered alongside an alcohol pre-load. Placebo-controlled designs, however, are limited in their ability to expose alcohol's anticipated effects.

Theoretical accounts of anticipation suggest that experienced alcohol users become conditioned by the pharmacological effects of alcohol (e.g., Marlatt et al., 1973). Specifically, the dopaminergic 'rewarding' nature of alcohol (e.g., Robinson & Berridge, 1993; 2001) results in the 'priming' effect which initiates behavioural and cognitive changes. Neuroimaging research has highlighted the potentially comparable nature of alcohol's anticipation and pharmacology, with, for instance, placebo-alcohol (Di Chiara & Bassareo, 2007) and alcohol-related olfactory cues (Bragulat et al., 2008) both showing elevated activation of the NAc. Furthermore, recent research has recognised the importance of including a pure control condition; an alcohol-free beverage administered to cognizant participants. This paradigm allows for the comparison of the placebo-effect (anticipation) in changing behaviour and cognition. This research has provided indications that anticipation can alter alcohol-related cognitions, including increasing cognitive biases and heightening craving (Christiansen et al., 2013), impairing inhibitory control (Christiansen, Rose, Randall-Smith, & Hardman, 2016) and increasing motivations to drink (Christiansen, Townsend, Knibb, & Field, 2017). An alternative explanation is afforded by McAndrews and Egerton's (1969)Drunken Comportment theory, which posits that alcohol-related behavioural changes are learnt from the environment. Specifically, they suggest that alcohol-related behaviours are the result of contextual learning and social norms, contrary to the prevailing biological explanations (e.g., Robinson & Berridge, 1993, 2001; Goldstein & Volkow, 2002). Support for this position can be garnered from research signifying the

effect of alcohol-related context on alcohol expectancies (e.g., Monk & Heim, 2013b, 2013a; 2014) and motivations to drink (e.g., Field & Jones, 2017). Taken together both theories of anticipation and their associated evidence base implicate anticipation in fluctuations of alcohol-related cognitions (i.e., inhibitory control, attentional bias, craving) and alcohol seeking behaviours.

While pure controlled designs have illuminated the contributions of alcohol's anticipated effects in changing cognition and driving consumption, their limitation is the inability to ascertain if the effects of alcohol pre-loads are a consequence of combined pharmacology-anticipation or merely pharmacology. To date, our inability to extricate the pharmacological effects from the anticipated has been hindered by these methodological limitations, in that traditional alcohol pre-loads involve participants knowledge of beverage alcohol content and therefore, include both alcohol pharmacology and anticipation. One way this may be achieved is by utilising a naïve alcohol condition, where participants are unaware of the alcoholic nature of the beverage.

1.4 Alcohol-related cognition and patterns of consumption

1.4.1 Impulsivity

The relationship between impulsivity and drug use, including alcohol consumption, is fairly well established (de Wit & Richards, 2004; Harriet de Wit, 2009). In general research suggests that increased impulsivity is associated with increased alcohol consumption, however the current thesis will later suggest a cyclical relationship. Nonetheless, operationally defining impulsivity has come under recent scrutiny. Previously, impulsivity was considered to be a relatively stable trait, measured by questionnaires such as the Barratt Impulsivity Scale (BIS-11; Patton, Stanford, & Barratt, 1995). As such, there is some evidence for the relationship between elevated trait impulsivity and increased alcohol consumption or problem drinking (Diemen, Bassani, Fuchs, Szobot, & Pechansky, 2008; Gunnarsson, Gustavsson, Tengström, Franck, & Fahlke, 2008; McAdams & Donnellan, 2009). However, more recent research has utilised behavioural measures and suggested that impulsivity fluctuates within the individual and is susceptible to the influences of external factors (e.g. context) and changes in mood (see Jones, Christiansen, Nederkoorn, Houben, & Field, 2013). Furthermore, de Wit and Richards (2004) suggest that there are two distinct components of impulsivity, impulsive decision-making and inhibitory control. Impulsive decision-making is defined as a hypersensitivity to immediate reward and/or a hyposensitivity to greater future reward and/or negative consequences. The delay-discounting task (Madden, Petry, Badger, & Bickel, 1997), for example, is a task designed to measure such impulsive decision-making. Here, participants are asked to choose between two hypothetical sums of money, a smaller quantity (which is available immediately) or a larger amount (which is available following a delay). In a meta-analysis, MacKillop et al. (2011) found that the relationship between steeper discounting on the delay discounting task and alcohol consumption only approached

significance, but that steeper discounting was significantly associated with alcohol use disorders (AUD) and subjective craving.

On the other hand, inhibitory control is defined as the ability to control or suppress pre-potent responses (de Wit, 2009; de Wit & Richards, 2004; Olmstead, 2006). The relationship between inhibitory control and overall levels of alcohol consumption is well established. Here, dependent samples demonstrate poorer inhibitory control, as measured by the stop-signal task, compared to healthy controls (Goudriaan, Oosterlaan, Beurs, & Brink, 2006; Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009). This suggests that inhibitory control may play a role in the aetiology of such alcohol-related problems. Nonetheless, in non-dependent samples, high quantity drinking has also been found to be associated with poor inhibitory control (Paul Christiansen, Cole, Goudie, & Field, 2012a; Murphy & Garavan, 2011; Nederkoorn, Baltus, Guerrieri, & Wiers, 2009). Colder and O'Connor (2002) also found that commission errors (responding when it should be inhibited) on the Go/No-Go task was related to alcohol use. This task measures participants' ability to inhibit a dominant response, by presentation of go stimuli (to which participants are required to respond) and no-go stimuli (to which they are required to inhibit their response). The proportion of no-go stimuli is usually less than 20%, so the most common, and hence dominant, response is to respond. As such, findings suggest that difficulties in inhibiting dominant responses may be associated with heavier consumption. Oculomotor inhibitory control has also been shown to predict heavy drinking in participants with Attention Deficit and Hyperactivity Disorder (ADHD), but not in healthy controls (Weafer, Milich, & Fillmore, 2011). Oculomotor inhibitory control is a consequence of unconscious movements resulting from stimulation of the oculomotor nerve, with some researchers suggesting this is a more innate process and therefore a better measure of inhibitory

control compared to training paradigms (e.g. Go/No-Go and Stop-signal task requiring participants to learn the prepotent [go] response). Jones and Field (2015) also found that alcohol-related cues reduced oculomotor inhibitory control in a non-dependent sample. Weafer and Fillmore (2015) also found that inhibitory control was impaired in the present of alcohol-related cues, though they suggest that impaired inhibitory control was related to self-reported alcohol consumption. Taken in combination, such research therefore suggests that impaired inhibitory control is associated with alcohol consumption behaviour in both non-dependent and dependent populations.

The question of whether poor inhibitory control is a consequence or a determinant of alcohol use and misuse has, nevertheless, been a topic of debate. Two possible explanations are offered: First the neurotoxic effects of chronic heavy alcohol are suggested to cause decreases in inhibitory control through alterations in the prefrontal cortex. Evidence of this comes from the brain damage and structural reordering found in chronic heavy drinkers (Crews & Boettiger, 2009; Crews et al., 2004) - with adolescence suggested to be a particularly sensitive period due to the continuing development of the frontal lobe (Hanson, Medina, Padula, Tapert, & Brown, 2011). These prefrontal brain regions are involved in various executive functions, including inhibitory control (Goldstein & Volkow, 2002; Koob & Volkow, 2010) which may therefore explain the apparent deficits in inhibition. Second, those who display poorer inhibitory control, particularly children and adolescents, are suggested to be at greater risk of initiating alcohol use and problems (see Peeters, Vollebergh, Wiers, & Field, 2014). Here, research suggests that the underdevelopment of these prefrontal regions in adolescents is associated with an increase in risky behaviour, such as the initiation of alcohol and drug use (Casey, Jones, & Hare, 2008; Steinberg, 2007). Individual differences in inhibitory control have been shown to predict adolescent

alcohol involvement and problems (Nigg et al., 2006; Wong et al., 2006). Furthermore, inhibitory control has been shown to predict the severity of alcohol dependence in adults at four-year follow-up (Rubio et al., 2008). Therefore, what seem like opposing findings could rather be interpreted as alcohol use/misuse as both a consequence and determinant of impaired inhibitory control. Specifically, in early adolescence poor inhibitory control development serves as a risk factor for alcohol use onset and then later problematic use (see Peeters et al., 2014). The initiation of heavy or problematic use presents the potential for neural changes and impairments in inhibitory control, in turn leading to heightened alcohol use (ibid). Therefore, the relationship between inhibitory control and alcohol use behaviours can be seen to have an overarching cyclical theme in that poor inhibitory control leads to the initiation of alcohol consumption, this consumption in turn impairs inhibitory control, which then results in further increases of consumption. Importantly, while this evidence illuminates the role inhibitory control plays in the initiation of drinking episodes and overall drinking, it highlights little regarding the function of inhibitory control within a drinking episode and loss of control, a central tenet of the current research.

Research examining the nature of inhibitory control processes suggests that it is not a stable trait, and that, rather, its state fluctuates. De Wit (2009) states that, 'abrupt environmental, physiological or emotional event may cause transient 'state' changes in self-control or inhibition" (p.28). As such, exposure to alcohol-related environmental cues has been shown to reduce inhibitory control in alcohol dependent samples (Gauggel et al., 2010; Muraven & Shmueli, 2006). Muraven and Schmueli (2006) also found that when social drinkers were exposed to alcohol-related cues they also experienced reduced inhibitory control relative to their exposure to neutral cues. Research in this area has, however, been somewhat inconsistent. Weafer and Fillmore

(2012; 2014) found that non-dependent consumers experience reductions in inhibitory control in the presence of alcohol cues. Conversely, others have found no effect on inhibitory control when alcohol-related cues are presented (Jones, Rose, Cole, & Field, 2013; Nederkoorn et al., 2009). Similarly, Christiansen, Cole, Goudie and Field (2012) found that emotional arousal caused ego-depletion[3] and that this was associated with decreased inhibitory control and higher *ad libitum* alcohol consumption. Furthermore, a recent study found that the mere 'smell' of alcohol can also impair inhibitory control, and that this could link back to the anticipation of alcohol (Monk, Sunley, Qureshi, & Heim, 2016). Importantly, it has been demonstrated that daily fluctuations in inhibitory control were not found to predict consumption, but rather plans to consume and reported craving were able to establish a pattern of the days drinking (Jones, Tiplady, Houben, Nederkoorn, & Field, 2018). This is important as it may suggest that there is an overarching relationship between inhibitory and consumption, but that fluctuations are not necessarily involved in predicting nuances in drinking patterns. In summary, research suggests that inhibitory control fluctuates as a consequence of contextual factors and alcohol cues, further reinforcing the idea that the relationship between inhibitory control and alcohol consumption behaviour is reciprocal. Therefore, poor inhibitory control can lead to alcohol involvement, subsequently alcohol-related contextual factors (e.g., olfactory primes) cause fluctuation in inhibitory control and we suggest these fluctuations mediate the alcohol consumption relationship.

Research has indicated that acute doses of alcohol impair inhibitory control and are associated with elevated subsequent consumption, and that furthermore these changes are observed at doses below thresholds that exert global effects on the nervous system (see Weafer & Fillmore, 2016). Specifically, transient impairments in inhibitory

[3] Self-control is suggested to be a limited resource, ego-depletion relates to depletion of said self-control resources (Baumeister, Bratslavsky, Muraven & Tice, 1998).

control as result of acute alcohol intoxication have been suggested to mediate the association between initial intoxication and subsequent drinking (e.g., Field, Wiers, Christiansen, Fillmore, & Verster, 2010; Jones, Christiansen, Nederkoorn, Houben, & Field, 2013). To date however, few studies have directly examined this mediatory relationship, an exploration that will form a core hypothesis for the current thesis.

Acute alcohol intoxication has been shown to impair inhibitory control at low (.4g/kg) to high (.8g/kg) doses, with dose dependent effects observed and greater impairments observed at higher doses (e.g., Caswell, Morgan, & Duka, 2013; Jessica Weafer & Fillmore, 2012). Importantly, research has indicated that alcohol differentially effects sub-types of impulsivity. For example, alcohol has been shown to impair inhibitory control, but not reflective or temporal impulsivity (Caswell et al., 2013). Furthermore, while inhibitory control impairments have been observed at low doses (.4g/kg), impulsive decision making or 'delay discounting' has been shown to only be evident at higher doses (.8g/kg; Reynolds, Richards, & de Wit, 2006). Taken together these findings suggests that inhibitory control is sensitive to initial intoxication, which could prove vital in the transition from the early stages of a drinking episode to the loss of control over drinking, particularly in light of research implicating inhibitory control in other aspects of behavioural control.

Acute alcohol intoxication has been shown to deferentially effect more experienced or heavy drinkers, for example, heavy compared with light drinkers show less pronounced motor deficits following initial intoxication (e.g., Fillmore & Vogel-Sprott, 1996). However, this does not appear to be the case for inhibitory control. For instance, in heavy drinkers a moderate dose (.65g/kg) resulted in increases in inhibition failures, but no impairments in motor function, suggesting that tolerance can be

developed for alcohol's motor effects, but not its disinhibiting effects (Miller, Hays, & Fillmore, 2012). Furthermore, alcohol tolerance has been shown to have an effect of behavioural activation, in that heavier drinking participants show no effect in response reaction times on a cued Go/No-Go task, however, there was no tolerance related effects on inhibitory control (Ostling & Fillmore, 2010). Importantly, a study investigating the inhibitory control across the course of intoxication (ascending and descending limbs – see chapter 2) in heavy and light drinkers demonstrated that compared with light drinkers, heavy drinkers recovered their motor function on the descending limb of intoxication (Fillmore & Weafer, 2012). On the other hand, neither group recovered their inhibitory control processes, with this difference in recovery between inhibition and behavioural activation processes potentially explaining why heavy or 'at risk' drinker engage in heavier, episodic drinking (ibid). These findings present an important insight into the cyclical relationship between inhibitory control and drinking, as it may suggest that heavy drinking impairs inhibitory control, leading to increased drinking occasions and in turn the inability to regulate consumption within the drinking episodes.

A number of neural correlates have been established for inhibitory control, predominantly focused on prefrontal regions (e.g., Davis, Bruce, Snyder, & Nelson, 2003), moreover, reduced metabolism in cortical brain regions has been demonstrated following acute alcohol exposure (Volkow et al., 2008). Performance on a Go/No-Go task has been shown to induce activations in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC) and the insula cortex (Stevens, Kiehl, Pearlson, & Calhoun, 2007) and studies have shown a dampening of these activations following alcohol intoxication (e.g., Anderson et al., 2011). It remains however, that little is known about how the rewarding aspects of alcohol in the dorsal striatum are associated with these prefrontal regions associated with inhibitory control. A recent study has

provided some evidence to suggest the brains dopaminergic response to alcohol does not have global effects on inhibitory control processes, but rather differentially effects subcomponents of inhibitory control processes (Stock, Schulz, Lenhardt, Blaszkewicz, & Beste, 2016). Specifically, while pre-motor components of inhibitory control indicated in nigrostriatal dopaminergic pathways remain unaffected following alcohol consumption, inhibitory control may be affected by the downregulation of mesocorticolimbic pathways, implicated in process evaluation (ibid). Importantly, a recent study demonstrated that inhibitory failures following alcohol intoxication were associated with lower activation in the right frontotemporal regions (inferior frontal gyrus [IFG], anterior insula and DLPFC) and these inhibitory failures were associated with *ad libitum* consumption (Gan et al., 2014). It is suggested these changes in activation may be associated with the ability to assert control over drinking (ibid), however, no such study has directly examined this causal relationship. Transcranial Magnetic Stimulation (TMS) administered to prefrontal regions, including bi lateral PFC and rIFG, has been shown to impair inhibitory control as measured by a number task (see Lowe et al., 2018). No study has hitherto used TMS to examine the causal link between those brain regions and changes in alcohol seeking and consumption behaviours.

While alcohol's pharmacological effects on inhibitory control are well documented, there remains a dearth of research examining the influence of the anticipated effects of alcohol on inhibitory control. The majority of research previously presented utilised a placebo-controlled design, which merely highlights the pharmacological effects of alcohol on inhibitory control. Pure (alcohol-free) controlled designs are required to elucidate the influence of alcohol's anticipated effects in impairing inhibitory control. As previously mentioned, the expectation of alcohol's

effects (known as anticipated effects) has been suggested to alter cognitive processes similar to those changes observed following acute alcohol intoxication (Marlatt et al., 1973). A recent study has supported this notion for inhibitory control, with findings indicating impaired inhibitory control measured using the Go/No-Go task following placebo alcohol compared with a pure control (Christiansen et al., 2016). Therefore, future research investigating the effects of alcohol on cognition and behaviour should employ a pure controlled design to not only ascertain pharmacological effects, but also the anticipated effects.

It has been suggested that fluctuations of inhibitory control could mediate the alcohol priming (pharmacological and anticipated) effect, constituting a mechanism for the loss of control over drinking (Field et al., 2010; Jones et al., 2013). An important study in the formation of this assumption is that of Weafer and Fillmore (2008), who found that an alcohol pre-load of 0.65g/Kg resulted in impaired inhibitory control in one session, and predicted *ad libitum* consumption in a later session. While this study highlights the potentially important link between alcohol induced inhibitory control impairments and consumption, the correlational nature of the study limits the direct inferences that can be drawn. However, to our knowledge, this work by Christiansen and colleagues (2013) is the only study to investigate this directly. Their findings demonstrated that alcohol priming was associated with increased *ad libitum* consumption, but not decreased inhibitory control and there was no relationship between inhibitory control and consumption (ibid). This therefore suggests that the priming effect is not mediated by fluctuations in inhibitory control. On the other hand, a recent study indicated that alcohol-related context induced inhibitory control impairments partially mediated the association between context and *ad libitum* consumption (Field & Jones, 2017). This demonstrates the importance of inhibitory

control in alcohol seeking behaviour, and, given the preponderance of evidence demonstrating the ability of acute intoxication to impair inhibitory control and increase consumption, further research is required to examine this mediatory relationship. As previously discussed, alcohol effects a wide range of neurological and cognitive functions. Examining the role of inhibitory control impairments in the maintenance of consumption behaviour with methodological advancements such as TMS can isolate these specific impairments from the wider impairments to test the mediatory effect more directly. There is therefore growing evidence to suggest that impaired inhibitory control is predictive of alcohol consumption, but also that alcohol can both acutely and with chronic use impair inhibitory control. Therefore, it is the suggestion of the current thesis that this relationship is cyclical; inhibitory control is predictive of alcohol consumption, but in turn it is the fluctuations in inhibitory control, as a result of alcohol and/or contextual priming, that mediates the relationship with further alcohol consumption.

Poor inhibitory control has been suggested as both a determinant and consequence of alcohol consumption (de Wit, 2009) and its development implicated as a risk-factor for problematic future use in adolescents (see Peeters et al., 2014). These arguments have been supported furthermore by neurodevelopment (see Spear, 2013) and neuroimaging evidence in both chronic (see Dupuy & Chanraud, 2016) and acute use (Volkow et al., 2008). However, the role fluctuations of inhibitory control play in maintaining drinking behaviours are yet to fully illuminated. Specifically, research needs to examine how alcohol's pharmacology and anticipation induce transient impairments and in turn if these changes are a central mechanism driving consumption. Indeed, it may be more pertinent to isolate such impairments from the wider neurological effects of alcohol, as in doing so a greater understanding of the neural substrates underpinning inhibitory control and drinking behaviour can be acquired. Such

insights may also enhance our knowledge of how inhibitory control interacts with other processes, such as attentional bias and craving, and elucidate the role these interactions play in consumption regulation.

1.4.2 Attentional Biases

It is suggested that alcohol-related cues in the environment 'grab' the attention of practiced alcohol users, due to conditioned responses arising as the result of stimuli-reward (NAc dopamine response) occurring over repetitive use (Robinson & Berridge, 1993; 2001). Thus, alcohol-related cues become associated with alcohol use and motivations to drink, meaning that increased priority is given to alcohol-related stimuli leading to 'attentional bias' [AB] (Field & Cox, 2008). Theoretical descriptions of addiction put attentional biases at the centre of their explanations of substance seeking, use and dependence (e.g., Franken, 2003; Tiffany, 1990; Robinson & Berridge, 1993; 2001; Goldstein & Volkow, 2002). It appears however, that the relationship between attentional biases and alcohol use may not be simple as previously suggested, with evidence to suggest that attentional bias is a better predictor of alcohol involvement in heavier drinkers (see Field & Cox, 2008) and dose dependent reductions in attentional bias being observed following alcohol pre-loads (e.g., Weafer & Fillmore, 2013; Duka & Townshend, 2004).

Theories suggest that these attentional biases are the result of automatic, unintentional processes that are difficult to impede (e.g., Tiffany, 1990). They suggest that alcohol-related stimuli in an environment are detected automatically and once detected elicit alcohol seeking behaviour. Specifically, cravings for and urges to consume alcohol are initiated in parallel with automatic alcohol-related schemas resulting in attentional allocation towards related stimuli (ibid). Contemporary theories on the other hand, suggest that attentional biases are the result of subjective experiences

that interact with processes such as craving and urges to consume (e.g., Franken, 2003). Furthermore, Franken (2003) suggests that once attentional bias has been established, a hyperattentive state is activated which induces increased craving and motivations to drink in turn. A recent review however disputes many of the claims on which previous theories have been founded. Specifically, it was concluded that attentional bias was consistently associated with individual patterns of consumption, prediction of future drinking behaviour and is effected by both positive and aversive (or both) motivational processes (Field et al., 2016). Rather, Field and colleagues (ibid) offer an alternative theory for the role of attentional bias in obesity and drug addiction (including alcohol), positing that transient changes in stimuli evaluation give rise to attentional biases. Specifically, they suggest that attentional biases are associated with behavioural motivation; in that positive attributions elicit substance-seeking behaviour, while negative attributions activate aversive motivational states (ibid). Despite the apparently conflicting theoretical accounts of their mechanisms and nature, there is nevertheless an apparent consensus that AB plays at least some role in consumption.

The relationship between attentional biases and alcohol consumption can be seen as bidirectional, with heavier alcohol use associated with heightened alcohol-related attentional bias and elevated attentional bias predictive of higher future consumption (see Field & Cox, 2008). Research suggests that heavy social drinkers (relative to light drinkers) display greater attentional bias for alcohol-related cues (Cox, Brown, & Rowlands, 2003; M Field, Mogg, Zetteler, & Bradley, 2004; Sharma, Albery, & Cook, 2001; Townshend & Duka, 2001). Furthermore, Field and Eastwood (2005) manipulated attentional bias, training participants to bias towards alcohol cues, with subsequent findings indicating increased motivations to drink, as well as *ad libitum* alcohol consumption. These findings were replicated by meta analyses, although this

relationship could be moderated by various factors, including inhibitory control and contextual factors (Field, Munafò, & Franken, 2009). Attentional bias has also been shown to predict relapse in treatment seeking dependent samples (Cox, Hogan, Kristian, & Race, 2002; Garland, Franken, & Howard, 2012), though these findings are not consistent, as some studies have also found no association between attentional bias and relapse (Field, Mogg, Mann, Bennett, & Bradley, 2013). As such, attentional bias has been suggested to have clinical relevance. Specifically, it is suggested that attentional bias training could be utilised to address factors associated with consumption and dependence including craving, motivation and consumption itself (see Christiansen, Schoenmakers, & Field, 2015).

As well as alcohol-related stimuli creating a bias in attention, there is evidence that intoxication further exacerbates such biases. For instance, Duka and Townshend (2004) found that doses as low as 0.3g/Kg elicited increased attentional bias for alcohol-related cues in comparison to placebo, however they also found that attentional bias was reduced for higher doses (0.8g/Kg) compared with the 0.3g/Kg. Weafer and Fillmore (2013) furthermore indicated that heavy (compared with moderate) drinkers displayed elevated bias for alcohol-related stimuli, however, as pre-load doses increased attentional bias decreased in the same group. While baseline attentional bias was associated with self-reported retrospective and *ad libitum* consumption, alcohol pre-load induced fluctuations on the other hand were not predictive of lab-based consumption (ibid). These findings have been validated in a pub-based field study indicating that attentional bias was negatively predicted by the number of drinks consumed (Schoenmakers & Wiers, 2010). Fernie and colleagues (2012) on the other hand, found attentional bias in heavy drinkers that was unaffected by acute intoxication, while .4g/kg alcohol elevated attentional bias in moderate drinkers. Although, changes in

attentional bias were unrelated to *ad libitum* consumption in the lab (ibid). Taken together these findings suggest that while attentional biases may be predictive of prospective alcohol consumption, it appears that fluctuations resulting from acute intoxication may not be involved in maintaining a drinking episode, or possibly the loss-of-control. To date however, no such research has directly examined the influence of alcohol's anticipated effects (in pure controlled design) on attentional biases, and such research could illuminate how fluctuations under these conditions may play a role in the initiation of consumption.

While the existing body of research has indicated implications for alcohol-related attentional biases in motivations to drink and patterns of consumption (see Field & Cox, 2008; Field et al., 2016), how attentional bias is related to wider cognitive processes (i.e., inhibitory control, craving) and its causal role in drinking are relatively poorly understood. First, it is important to disentangle how the pharmacological and anticipated effect alcohol contribute to the fluctuating nature of attentional biases, and how respective fluctuations are associated with patterns of consumption. Second, neuromodulation techniques (e.g., TMS) may provide valuable insights into attentional biases potentially causal influence over the initiation and maintenance of drinking. Finally, TMS holds the potential to examine how attentional biases interact with other cognitive processes (inhibitory control, craving), isolated from the wider neuropsychopharmacological effects of alcohol.

1.4.3 Craving

Craving is often defined as a strong and/or persistent desire to consume alcohol and is commonly considered to be an important component in the aetiology of AUD (see Coates et al., 2019). The nature and measurement of craving have however, been a topic of debate within the research literature (e.g., Drummond, 2001; Kavanagh et al.,

2013; Tiffany & Conklin, 2000). Biological explanations suggest that craving is the anticipation of alcohol effects, triggering a dopaminergic response in the striatum (see Volkow et al., 2016), while cognitive models on the other hand, suggest that craving is a non-automatic regulatory process (e.g., Tiffany & Conklin, 2000). What is evident nonetheless, is that craving has a role to play in the initiation and regulation of alcohol consumption, however, the causal nature by which craving exerts its influence is poorly understood and lacking in theoretical justifications.

While theoretical accounts may not agree on the precise nature of craving, they widely implicate it in the regulation of drinking behaviours. Neurobiological accounts suggest that craving and alcohol-seeking behaviours are the result of associated learning, specifically, alcohol-related stimuli – striatal dopamine reward response pairings (see Weiss, 2005). There is, however, an important distinction arising from biological explanations in the suggestion that craving and associated neural networks are fundamental driving forces in consumption behaviour (see Koob, 2014). On the contrary, cognitive models of addiction suggest that alcohol-seeking behaviour is governed by automatic processes, positing craving (or urges) as a non-automatic process involved in either the up- or down-regulation of alcohol seeking (Tiffany, 1990; Tiffany & Conklin, 2000). These models, moreover, suggest that craving is elicited by stimulus exposure (Tiffany & Wray, 2009), a position common in the craving literature. In fact, theories often struggle to extricate craving from attentional bias, postulating a mediatory role for attentional bias between craving and alcohol-seeking behaviour (Franken, 2003). The reality is, however, that evidence would suggest the association between craving and attentional bias is a weak, albeit significant one (see Field, Munafö & Franken, 2009). Overall, craving has been broadly implicated in alcohol use and use disorders. For example, findings from a recent Ecological Momentary Assessment

(EMA) study indicated that daily alcohol-related cravings were predictive of same day drinking (Jones et al., 2018). Evidence from treatment seeking alcoholics moreover has suggested that variations in craving may signal subtypes of AUD that are treatment resistant (Oslin, Cary, Slaymaker, Colleran, & Blow, 2009). Craving has, furthermore, been suggested to hold significant clinical relevance, including predicting relapse in recovering AUD patients (e.g., Stohs, Schneekloth, Geske, Biernacka, & Karpyak, 2019). When taking this evidence into consideration, craving appears important in the aetiology and treatment of AUD, as well as potentially alcohol related-harms in subclinical samples.

Research has indicated that craving is sensitive to contextual signals, as well as both the pharmacological and anticipated effects of alcohol. For instance, craving has been shown to be elevated in alcohol-related compared with neutral contexts (e.g., Field & Jones, 2017) and following both alcohol pre-loads (e.g., Christiansen et al., 2013) and placebo (e.g., Christiansen et al., 2017). These fluctuations in craving, moreover, have been associated with maintaining patterns of alcohol consumption. Alcohol induced escalations in craving are suggested to be better predictors of binge drinking (Rose & Grunsell, 2008), while context heightened *ad libitum* alcohol consumption has been shown to be mediated by craving changes. Furthermore, studies have demonstrated the changes in craving across a drinking episode, specifying craving decreases across successive alcoholic drinks (Rose et al., 2010). Although a more complex pattern of craving has been observed between the pharmacological and anticipated effects of alcohol, specifically, that craving spiked initially following the first alcohol beverage and then decreased over consecutive drinks, the reverse was, however, evident for placebo beverages (Rose et al., 2013). This pool of evidence provides insight into the potentially important role of craving in maintaining consumption, however, further

explorations are required to examine if craving isolated from the effects of alcohol is associated with subsequent drinking.

The literature intimates that craving is both an important factor in predicting the occurrence of a drinking episode (Jones et al., 2018) and that fluctuations may hold a decisive role in the maintenance of consumption (e.g., Field & Jones, 2017; Rose & Grunsell, 2008). Research is yet to fully elucidate the relative contributions of alcohol's pharmacology and anticipation in compelling craving changes, and specifically whether variability in craving associated successive drinking is primarily driven by alcohol pharmacology. While theoretical accounts suggest craving is interwoven with wider cognitive processes (e.g., attentional biases), the causal nature of such interactions is scantly understood. Such examinations may employ neuromodulation techniques to further understanding the neural substrates, isolating changes in one process (e.g., craving) to ascertain how they bring about change in another (e.g., attentional bias).

1.4.4 Dual process models

Dual-process models of addiction, although they can differ from one theory to the next, generally suggest that consumption is the result of an interaction between two processes; implicit (automatic) and explicit cognitive processes (see Stacy & Wiers, 2010). Theoretically, it is suggested that these automatic approach tendencies arise due alcohol-related stimuli gaining motivational-incentivisation due to associative learning experienced during sustained heavy alcohol use (see Robinson & Berridge, 2001). These tendencies according to Briener, Stritzke and Lang (1999) one half of the conflict motivational system with avoidance tendencies, with both approach and avoid systems being independent. Models have suggested that these approach-avoid systems operate at varying levels of consciousness, put simply they are behavioural inclination to either approach or avoid alcohol or alcohol related stimuli (see Cox et al., 2012). Proposals

suggest that the influence these conditioned (automatic) appetitive processes exert over consumption is moderated by conscious reflection (Deutsch & Strack, 2006), alcohol expectancies (Moss & Albery, 2009) and inhibitory control (Houben & Wiers, 2009).

Dual-process models suggest that appetitive behaviours do not act independently, but rather are mediated or moderated by other cognitive or self-control processes. Following a review of neuroimaging data, Goldstein and Volkow (2002) suggested addiction was not only a matter of reward and pleasure processing, but also impaired executive functions (e.g., inhibitory control and salience attribution) and that these mechanisms must interact to contribute to addictive behaviours. Wiers and Colleagues (2007) suggested automatic appetitive behaviours elicited by alcohol-related stimuli elicit increased alcohol consumption, but this process would be moderated by individual differences in dimensions of impulsivity (e.g. impulsive decision-making, inhibitory control). Conditioned reward responses (e.g. motivations to drink and consumption) therefore will be moderated or controlled/reduced dependent on individual differences in impulse control. Houben and Wiers (2009) found that implicit associations with alcohol cues were moderated by inhibitory control. However, Christiansen et al. (2012) found that both automatic approach tendencies and two dimensions of impulsivity (decision-making and inhibitory control) were predictive of alcohol consumption behaviour, though their findings did not render support of either dimension of impulsivity moderating the automatic approach tendencies. These perspectives give rise to the suggestion that impaired inhibitory control would act a mediator to subsequent drinking, however, these theories largely neglect contextual effects of drinking behaviour.

Moss and Albery (2009) proposed an alternative dual-process model, suggesting that attentional allocation as the result of alcohol is moderated by alcohol expectancies. Specifically, they propose two phases to drinking, the preconsumption and consumption phases; positing that alcohol expectancies in the preconsumption phase can begin to moderate drinking in the consumption phase. Explicitly, Moss and Albery (2009), contrary to the aforementioned dual-process models, theorise that its alcohol's loosening of explicit cognitions (not implicit) that contribute to the loss-of-control over drinking. This position is rejected by Wiers and Stacy (2010) citing research suggesting that impaired inhibitory control is predictive of alcohol consumption behaviour, in excess of expectancies. More recent research by Monk and Heim (2013a) however, suggests that alcohol expectancies and related cognitions can be contextually altered, and that these increased alcohol expectancies are associated with a heightened desire to drink (Monk & Heim, 2013b). The argument is certainly strengthened by the Monk and Heim findings, as their studies investigated the influence in natural settings (e.g. the pub), while the experiments of Wiers and Stacy (2010) are laboratory based and lack actual alcohol-related contextual factors. Further support for Moss and Albery (2009) comes from findings indicating that alcohol pre-load and alcohol-related cues moderated the association between expectancies and urge to drink (Wardell & Read, 2014). When considered together there is plausible consideration for the pivotal role of explicit cognitions (e.g., expectancies, craving) in the regulation of drinking behaviours. Research is therefore required to unpick the specific contributions explicit processes play in driving and maintaining alcohol consumption.

It is not only plausible but highly likely that our consumption behaviour is not merely driven by primal reward-seeking, but is moderated by wider self-regulatory processes, a central premise of these dual-process theories. Which processes and the extent to which they exert control over consumption however, are scantly understood.

Research is required to unpick how alcohol pharmacology and anticipation drive subsequent consumption and, in doing so, which process alterations are pivotal in the maintenance of such behaviours. In order to truly unpick the associations between these implicit and explicit cognitions, and how such proposed interactions wield control over drinking behaviour, we need to isolate them from the rather 'messy' pharmacological effects of alcohol with use of neuromodulation.

1.5 Thesis overview

To date, the role of transient impairments of implicit cognitions (e.g., inhibitory control, attentional bias) and changes in explicit cognitions (e.g., craving) in the maintenance and loss-of-control over drinking have been inconsistent. Specifically, the suggestion that transient impairments in inhibitory control would mediate the relationship between acute alcohol intoxication and successive drinking (Field et al., 2010; Jones et al., 2013) has seen inconsistent support. Some studies find no mediational relationship (e.g., Christiansen et al., 2013), while others demonstrate context driven changes in inhibitory control are partially mediated (Field & Jones, 2017). Furthermore, a recent EMA study demonstrated that overall inhibitory control was not predictive of heavy episodes of drinking, rather indicating the role of implementation intentions (Jones et al., 2018). Furthermore, the relationship between attentional bias and successive drinking is marred by number of complexities, none more so than the apparent dose dependent effects. For instance, studies have indicated that alcohol-related attentional bias show dose dependent decreases (Weafer & Fillmore, 2013; Duka & Townshend, 2004). Hitherto, little is known about the role anticipated effects of alcohol play in changing alcohol-related attentional bias or the specific effects of alcohols pharmacology on changes in cognition (inhibitory control, attentional bias, craving). Furthermore, due to current methodological approaches little is known about the unique contributions of such cognitions to drinking behaviour or how neural substrates exercise causal influence of said cognitions and consumption in turn.

This thesis therefore, makes an original contribution to knowledge in two distinct routes, methodologically and theoretically. There are two methodological contributions made within this thesis; first, the development of a novel naïve alcohol administration

procedure, in the first attempt to insulate alcohol's pharmacological from its anticipated effects. Second, the first attempt to employ TMS protocols to examine neural substrates of alcohol-related cognitions (inhibitory control, attentional bias, craving) and if these substrates (DLPFC, OFC) exert influence over drinking. These protocols, moreover, allow cognitive changes to be isolated from the wider neuropharmacological effects of alcohol, to investigate their relative contributions to consumption maintenance. The findings contribute theoretically to our understanding of the processes governing drinking. Specifically, the more prevalent role of explicit process such as craving, rather than (current conceptualisations of) implicit processes in guiding consumption behaviours.

The laboratory studies presented in chapters 2 and 3 involved alcohol administration procedures aiming to disentangle the pharmacological and anticipated effects of alcohol in order to examine their respective contributions in inducing changes in cognition (i.e., inhibitory control, attentional bias, craving) and alcohol-seeking behaviour. Chapter 2 employs a pure controlled alcohol administration design to further unpick the contributions of alcohol anticipation, while chapter 3 introduces a novel, naïve alcohol administration method.

In chapters 4 and 5 TMS was utilised to isolate cognitive changes (e.g., impaired inhibitory control) from wider neuropsychopharmacological effects of alcohol. Specifically, chapter 4 applied TMS to the right-DLPFC to impair inhibitory control to directly test the hypothesis that transient impairments drive subsequent consumption (e.g., Field et al., 2010). Chapter 5 sought to extend on chapter 4, specifically, to examine how respective brain regions (right- and left-DLPFC, mOFC) and associated

cognitions (inhibitory control, attentional bias, craving) exert control over drinking behaviour and furthermore, how such cognitions interact with one another.

Chapter 5 presents the overall discussion of the thesis. The chapter begins with an overview of each study in the thesis, before discussing the limitations, future directions and implications of the PhD research. Finally, the overall conclusions derived from the cumulative findings from the body of literature presented in the thesis are described.

1.6 Statistical Analysis Overview

All studies contained within the thesis are empirical, lab-based studies and quantitative in nature and as such were subject to preliminary analysis, inclusive of initial inspection for missing data and outliers, as well as assumptions testing for all proposed inferential analyses. To determine if any missing data was missing at random and not dependent on any other data, Missing Completely at Random (MCAR; Little, 1988) tests were utilised. It was initially the intention that participants with significant missing data would be eliminated from subsequent analyses, however, this situation never arose. In instances where data was demonstrated to be MCAR, multiple imputation by regression was adopted to replace missing data with representative values based on the sample data (Wayman, 2003). All studies in the current these utilised Analysis of Variance (ANOVA) to test their respective hypotheses. Prior to analysis therefore, assumptions of ANOVA were tested for all data. Specifically, normality (Kolmogorov–Smirnov test), homogeneity of variance (Levene's test for equality of variances) and sphericity (Mauchly's test of sphericity). For instances when there were significant effects and interactions revealed by the ANOVA, Bonferroni corrected pairwise comparisons were employed to minimise the chances of type 1 errors. Finally, mediation analyses were undertaken using SPSS MACROS: PROCESS for between participants designs/variables (studies 2 & 4) and MEMORE for within participants designs/variables (studies 1 & 3).

Chapter 2: Methods

The following chapter supplies a methodological overview of all the key protocols and procedures that are used in the subsequent thesis chapters

2.1 Self-report measures

2.1.1 Time Line Followback (TLFB: Sobell & Sobell, 1990). Participants retrospectively self-report their alcohol consumption (in units) for the previous 14 days. Requiring participants to provide the number of units of alcohol consumed each day.

2.1.2 The Alcohol Use Disorders Identification Test (AUDIT: Saunders, Aasland, Babor, & de, 1993). The AUDIT consists of 10 items regarding alcohol consumption and its consequences. Scores range from 0-40, with scores ≥ 8 representative alcohol consumption of a hazardous level. The AUDIT has previously been validated in university student populations (e.g., Kokotailo et al., 2004) and is shown to be reliable in the current samples (study 1 $\alpha = .71$; study 2 $\alpha = .77$; study 3 $\alpha = .73$; study 4 $\alpha = .82$).

2.1.3 Barrett Impulsivity Scale (BIS-11: Patton, Stanford, & Barratt, 1995). The BIS is a multidimensional scale, consisting of three subscales; attentional, motor and non-planning impulsiveness. BIS-11 includes thirty fixed response items (e.g., I plan tasks carefully), each on a 4 point scale (rarely/never – almost always/always); higher scores are indicative of increased impulsivity. The scale was found to be reliable in the current samples (study 1 $\alpha = .87$; study 2 $\alpha = .81$; study 3 $\alpha = .84$; study 4 $\alpha = .82$).

2.1.4 Desire for Alcohol Questionnaire – brief form (DAQ; Love, James, & Willner, 1998). The DAQ is a14-item four-dimensional alcohol craving questionnaire. The

factors include; positive and negative reinforcement, strong desires and intentions, and mild desires and intentions. The scale is scored on 1-7 Likert scale, with higher scores indicative of higher craving. Reliability analysis revealed the DAQ to be reliable in study 2 both pre (α = .78) and post (α = .80) beverage administration, study 4 pre (α = .81) and post (α = .79), all showing acceptable internal reliability.

2.1.5 Mood and Subjective Intoxication Scales. The scales consisted of 10 statements to which participants responded on a 100mm Visual Analogue Scale ranging from 'Not at all' to 'Extremely'. Six mood statements (e.g., I feel happy, I feel sad) and 4 intoxication statements (e.g., I feel drunk, I feel dizzy). Negative statements were reversed.

2.2 Computerised cognitive tasks

2.2.1 Stop-signal task (SST: Verbruggen, Logan, & Stevens, 2008). The Stop Signal task consists of two concurrent tasks: A Go task (75% of trials), which is a choice reaction task where participants categorise arrows on the screen based on their orientation (left or right) and a stop task (25% of trials) where an auditory tone (the stop signal) indicates that participants should inhibit their response to the go signal. Participants are required to respond as quickly and accurately as possible to the stimuli with a predetermined corresponding key. Upon hearing the auditory tone (the stop signal) participants are required to inhibit their response. After 2000ms the trial times out.

On the stop trials, tones are delivered at fixed delays (known as Stop-signal delays or SSD) of between 50ms and 500ms following the presentation of the go stimulus. The stop signal task uses these SSDs dynamically, based on participant performance. The *one-up one-down tracking procedure* (Logan, Schachar, & Tannock, 1997) was implemented, which adjusts the SSDs after each trial. After successful inhibition trials, the SSD increases by 50ms, handicapping the stop signal process on the next stop signal trial. Unsuccessful inhibition trials result in the SSD decreasing by 50ms. In accordance with the 'horse race' model, the degree of difficulty in inhibiting responding increases as the delay between the go stimulus and the stop signal increases (Logan, Cowan, & Davis, 1984). The task provides an outcome variable of stop-signal reaction time (SSRT). SSRT is calculated by extracting the percentage errors (failure to inhibit response on stop trials) at each of the SSDs (50 – 500ms, at 50ms intervals), then calculating a SSRT value for each SSD based on the reaction time (RT) distribution. Overall SSRT score was calculated by averaging the SSRT values for each of the SSD's. Impaired response inhibition is demonstrated through longer SSRT values;

SSRT represents an estimate of the time required to stop initiated Go response (see Band, van der Molen, & Logan, 2003). Participants received 3 experimental blocks of 64 trials, allowing for a short break between each block. Internal reliability was assessed between each of the 3 experimental blocks for both pre- and post-manipulation (study 1 pre α = .83 and post α = .79; study 2 pre α = .77 and post α = .71; study 3 pre α = .76 and post α = .77; study 4 pre α = .80 and post α = .78) all indicating acceptable reliability.

2.2.2 Pictorial stimuli

The images used in all AB tasks (chapters 3, 4 and 6) and the gaze contingency task (chapter 6) consisted of ten alcohol-related pictures (as used by Christiansen et al., 2013) were matched with ten control pictures, based on brightness, complexity and valance. The alcohol-related pictures portrayed alcohol (e.g., bottle of beer, wine or spirits) or alcohol being consumed. The neutral pictures portrayed stationary (e.g., pens) or close-up action shots of stationary in use (e.g., a person licking an envelope). Pictures were presented in landscape (125mm wide x 100mm high).

2.2.3 Visual Probe task (Schoenmakers, Wiers & Field, 2008). The visual probe task was programmed in Experiment Builder and deployed in concurrence with the Eye-link 1000 eye-tracker (SR Research, Mississauga, ON, Canada) to assess attentional-bias. The task begins with the presentation of a fixation cross, signalling the beginning of each trial. Following this, manual submission of any key triggers the exhibition of images which are presented side-by-side 60mm apart, in alcohol/neutral pairs. Each trail had a duration of 2000ms and the task consisted of 40 trials in total. The reliability of the Visual Probe task was shown to fairly poor both pre (α = .58) and post (α = .56) and

in study 2 both pre (α = .53) and post (α = .36), however, this is consistent with previous findings (e.g., Field & Christiansen, 2012).

2.3 Alcohol administration

2.3.1 Alcohol Pharmacology

Alcohol has a complex pharmacological profile, characterised by a biphasic response or curve. During the early staged of intoxication (BAC >.055) alcohol acts as a central nervous system (CNS) stimulant, followed by sedation effects (King, Roche, & Rueger, 2011). During the initial stages of intoxication alcohol exerts its influence via the dopaminergic pathways in the dorsal striatum (NAc, VTA) associated with reward or pleasure processing (see Koob, 2010). It is this euphoric stimulant effect or "buzz" that typifies the first phase, otherwise known as the ascending limb of the biphasic curve (ibid). As alcohol intoxication increases, alcohol instigates sedative effects via the GABAergic system, the CNS primary inhibitory system (Koob, 2010). Specifically, alcohol mimicks gamma-aminobutyric acid (GABA) binding to the theta site of GABA receptors and resulting in decreased neuronal excitability (Davies, 2003) and an overall reduction in brain activity (Volkow et al., 2008). These processes explain the sedative effects or descending limb of curve. This phenomenon has been demonstrated in studies examining the subjective effects of alcohol priming (e.g., Holdstock & de Wit, 1998), with heavy drinkers more sensitive to the stimulant effects and less sedation compared to light social drinkers (King, Houle, Wit, Holdstock, & Schuster, 2002). This biphasic response or curve an important consideration and underpinning principle of experimental alcohol priming paradigms.

The biphasic response/curve is an important consideration in determining the appropriate dose and point at which the variables of interest are measured in alcohol

priming studies. For instance, low doses (.2-.3g/kg) appear to result in stimulant effects and may be associated with increased motivations to drink and elevated alcohol-related attentional bias (more pronounced in heavy social drinkers; see Rose, 2013). On the other hand, moderate (.5/.6g/kg) to high (.8g/kg) dose demonstrate both stimulant and sedation effects (e.g., King et al., 2002; Holdstock & de Wit, 1998), with the peak of the curve occurring at ~45 minutes. Studies therefore interested in investigating the effects of alcohol sedative or inhibiting effects (e.g., inhibitory control) initiate measures near the peak of curve and the start of the descending limb (see Rose, 2013). These considerations were borne in mind when designing the current studies, with a focus on using moderate doses for alcohol pre-loads and administering measures (e.g., inhibitory control, AB) 30 minutes post initial intoxication in a counterbalanced order to ensure measures took place across the upper ascending limb, peak and initiation of the ascending limb.

2.3.2 Alcohol pre-load/placebo

The administration of an alcohol pre-load is used to assess the acute pharmacological effects of alcohol. As per Rose and Grunsell (2008), participants were administered a volume of alcohol based on their weight (and gender in study 1, .5g/kg for females and .6g/kg for males; study 2 .4g/kg). Alcohol in the form of vodka was mixed with fresh orange juice and tonic water in equal parts and divided into three glasses. The placebo consists of equal parts fresh orange juice and tonic water, the mixture and the rim of the glass is lightly sprayed with vodka (>2ml). The control drink will consist of equal parts orange juice and tonic water, and the participants are informed the drink contains no alcohol. The participants were required to consume a strong mint to mask the taste of the alcohol (see Hopthrow, Abrams, Frings, & Hulbert, 2007) and then given 10 minutes to consume the total volume of the presented mixtures, followed by 20 minutes

rest period prior to completing any other experimental tasks.

2.3.3 Ad libitum consumption

Ad libitum consumption is a method of measuring immediate alcohol consumption, indicative of motivation to drink, following an experimental manipulation (e.g., the administration of an alcohol pre-load). The bogus taste test is a means of assessing *ad libitum* alcohol consumption while reducing participant demand characteristics, using deception (Christiansen, Mansfield, Duckworth, Field, & Jones, 2015). Participants were presented with three different beers (330ml of each) and asked to rate the taste of each beer on ten dimensions (e.g., pleasant and light; see Jones et al., 2011). For rating purposes, participants were informed that they may drink as little or as much as they need. The remaining volume was then measured and subtracted from the initial volume to indicate how much the participant consumed.

2.4 Transcranial Magnetic Stimulation (TMS)

2.4.1 Mechanistic principles of TMS

Transcranial Magnetic Stimulation (TMS) is a non-invasive method used to indirectly alter the excitatory threshold of neurons in the targeted brain region (Klomjai, Katz, & Lackmy-Vallée, 2015). It is important to recognise that at present we are not fully aware of TMS's mechanisms of function. Broadly speaking an electromagnetic coil produces magnetic fields that pass through the scalp inducing changes in activity in the neurons located below the coil (ibid); these magnetic fields oscillate producing electromagnetic pulses, the frequency of which determines if the effect is excitatory or inhibitory, with the pulse repetition determining duration of effect. These magnetic fields cause changes (or modulates) in the electric currents within these neurons and it is suggested that the 'pattern' of these changes results various different effects that can be exerted by TMS (Goldsworthy, Pitcher, & Ridding, 2012). The various functions and forms stimulation are beyond the remit of this thesis, rather focus will be given to repetitive-TMS (rTMS), specifically continuous Theta Burst Stimulation (cTBS).

Continuous TBS (cTBS) is a high frequency rTMS protocol capable of producing prolonged stimulatory effects, ideal for 'offline' manipulation of variables (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Vallence et al., 2015). A sequence (or train) of pulses are delivered at 50Hz (i.e., the theta frequency), at an oscillatory rate of 200ms for a continuous period of time (40 seconds in the enclosed protocol (Goldsworthy et al., 2012). This produces a long-lasting (~60 minutes) inhibitory effect on the targeted cortical region (ibid), meaning the excitatory threshold of target neurons is increased. However, while reviews have supported the time course efficacy of cTBS protocols, our understanding of its specific mechanisms of action are still rather limited

and currently an area of intense research (Chung, Hill, Rogasch, Hoy, & Fitzgerald, 2016).

TMS and specifically cTBS are non-invasive tools commonly utilised to research the links between neurophysiology and behaviour, however, methodological strengths and weakness must be bore in mind. The primary limitation of TMS is our current understanding its mechanisms of action, which as previously mentioned is rather limited (e.g., Chung et al., 2016; Goldsworthy et al., 2012; Wischnewski & Schutter, 2015). Conversely, TMS has significant advantages in studying the causal links between brain and behaviour. Historically, such links have been explored with use of lesion studies, often only making the link between damage in a specific brain region and patterns of behaviour following an autopsy (Vaidya, Pujara, Petrides, Murray, & Fellows, 2019). And while developments in neuroimaging has aided our understanding around behaviour and associated regions of activation, these inferences are not causal in nature. By employing different protocols TMS one the other hand, can answer a number of questions regarding location, timing, lateralization, functional relevance or plasticity of the neural substrates of cognitive processing (Sack & Linden, 2003). A final limitation specific to the current body of work should also be given consideration, that of region or location specificity. The current research employed 10/20 EEG mapping to locate target brain regions, a method common within the literature (see Sparing, Buelte, Meister, Pauš, & Fink, 2008). Advances in neuronavigation can significantly improve location specificity and thus reliability of findings (see Holmes et al., 2019), however, such techniques require expensive neuronavigation hardware and software (and ideally MRI) making them currently beyond the scope of many research teams. On the whole however, TMS is unique and promising tool to examine the link between brain and

behaviour, specifically between regions (DLPFC, mOFC) associated with alcohol related cognitions (inhibitory control, AB, craving) and alcohol consumption behaviour.

2.4.2 Continuous Theta Burst Stimulation (cTBS) protocol

cTBS was performed using a 70mm figure-of-eight stimulation coil (Magstim D70² Coil), connected to a Magstim SuperRapid 2 Stimulator (The Magstim Company, Carmarthenshire, Wales). This produces a magnetic field of up to 0.8 T at the coil surface. To appropriately select the TMS stimulation intensity for each participant, the resting motor threshold (rMT) for the first dorsal interosseous muscle (FDI) of the participant's dominant hand was visually determined (Pridmore, Fernandes, Nahas, Liberatos, & George, 1998). Here, the coil was positioned over the left or right motor cortex (for right or left-hand dominance respectively) in correspondence with the optimal scalp position (OSP). It was detected by moving the intersection of the coil in 1-cm steps around the motor hand area of the left motor cortex, while delivering TMS pulses at constant intensity. The rMT was defined as the lowest stimulus intensity able to evoke a visible finger twitch on at least five of ten trials.

cTBS was delivered over the rDLPFC. The vertex was chosen as a control site to account for non-specific effects of TMS. The approximate locations of the stimulating areas were identified on each participant's scalp by means of the 10-20 EEG System Positioning. In keeping with past research, for rDLPFC stimulation, the coil was positioned on the F4 location. Three-pulse bursts at 50 Hz repeated every 200ms for 40s were delivered at 80% of the subject's resting MT (equivalent to "continuous theta burst stimulation" cTBS), resulting in 600 pulses in total (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). The coil was positioned tangentially to the scalp, at 90^0 from the midsagittal line, to modulate contralateral M1 excitability and interfere with cognitive

functions. The coil was held by hand throughout stimulation and the exact coil position was marked by ink to ensure an accurate and consistent positioning of the coil throughout the experiment. The inhibitory effect of cTBS with this protocol lasts up to 30 minutes (see Cho et al., 2010; Huang et al., 2005).

Chapter 3: The effects of placebo and moderate dose alcohol on attentional bias, inhibitory control and subjective craving

McNeill, A. M., Monk, R. L., Qureshi, A. W., Litchfield. D., & Heim, D. The effects of placebo and moderate dose alcohol on attentional bias, inhibitory control and subjective craving (Under Review).

Having overviewed the important methodological considerations and procedures which are typical of this area of research, this chapter explores the relative contribution of alcohol's pharmacological and anticipated effects, with the inclusion of a pure control condition. Specifically, it examines the role of alcohol induced transient changes in cognition (e.g., inhibitory control, AB, craving) in the maintenance of alcohol consumption.

3.1 Abstract

Rationale: Previous research indicates that acute alcohol intoxication and placebo can inhibit people's control over consumption behaviour and heighten attentional bias towards alcohol-related stimuli, and craving. However, the extent to which the pharmacological and anticipated effects of alcohol contribute to these changes are not yet fully understood. *Objectives:* To disentangle anticipated from pharmacological effects of alcohol in order to gain a clearer view of their relative contributions to alcohol consumption. *Methods:* In a within-participants design (moderate alcohol dose, placebo and control), and over a minimum 2-week period, participants completed a battery of questionnaires and cognitive tasks, followed by a bogus taste task to measure *ad libitum* consumption. *Results:* Findings indicated that both alcohol pre-load and placebo resulted in cognitive and psychological changes, including impaired inhibitory control, heightened attentional bias and craving. However, *ad libitum* consumption only increased following alcohol and not placebo. Furthermore, inhibitory control impairments did not mediate the relationship between initial intoxication and *ad libitum* consumption, and findings indicate that increases in craving may mediate this association. *Conclusions:* Results suggest that psychological processes such as craving may be more important in driving consummatory behaviour, relative to transient changes in cognitive processes such as inhibitory control.

3.2 Introduction

By now it has become apparent that drinking alcohol is both a driver and a consequence of a range of cognitive processes that are implicated in the consumption of alcohol. These include people's ability to exert control over their behaviours (see de Ridder, Lensvelt-Mulders, Finkenauer, Stok, & Baumeister, 2012), to attend to stimuli (see Field et al., 2016), as well as their desire to consume the substance in question (e.g., Ostafin & Palfai, 2006). Sometimes, however, the mere anticipated effects of alcohol are sufficient to impact people's cognitions in a manner akin to that observed when alcohol is consumed (e.g., Christiansen et al., 2016). This presents a challenge to researchers seeking to disentangle the relative contribution of pharmacological and anticipated effects of alcohol since the belief that alcohol has been consumed alone can be sufficient to induce expectation effects. The implementation of placebo-controlled research has helped address this, however, a limitation of this body of work has been that most studies do not include a pure control condition, which diminishes the extent to which anticipatory effects can be ascertained.

The relationship between alcohol consumption, executive control and cognitive mediators is likely to be far from straightforward because alcohol affects a wide array of cognitive and psychological processes in distinct ways at different stages of (anticipated) consumption. This complexity is reflected in the literature. With regards to attentional bias), for example, some studies find heightened attentional bias following initial intoxication and that these effects are dose dependent (e.g., Duka & Townshend, 2004), while other research indicates that these changes are dependent primarily upon individuals' drinking experiences (e.g., Fernie, Christiansen, Cole, Rose, & Field, 2012). The picture for inhibitory control is similar. Some research suggests that impairments in inhibitory control are predictive of continued alcohol consumption

following initial intoxication (e.g., Weafer & Fillmore, 2008), while others have failed to demonstrate this (e.g., Christiansen et al., 2013), or suggest that subjective craving is a stronger predictor of alcohol involvement (Rose & Grunsell, 2008).

These discrepancies in this literature may, to a greater or lesser degree, be related to methodological differences between studies. For example, Leeman and colleagues (2009) found that craving following placebo, but not alcohol, correlated with *ad libitum* consumption. However, the absence of a pure control, in this instance, makes it difficult to ascertain whether placebo has induced any change in craving or whether those changes, in turn, predict consumption. Accordingly, research has begun to include a non-alcohol control condition to explore the relative contributions of the anticipated and pharmacological effects of alcohol, and the resultant changes to alcohol consumption behaviours.

However, to date relatively few studies have utilised this more stringently controlled design. Doing so, Christiansen, and colleagues (2016) found both impaired inhibitory control and increases in subjective craving following placebo, relative to non-alcohol control. This study utilised a moderate dose consumption condition (.65g/kg), alongside placebo and control, revealing that alcohol impaired executive functioning compared to both placebo and control. Christiansen and colleagues (2013) also found increases in craving and automatic approach tendencies following placebo, however, these did not translate into increases in *ad libitum* consumption, which was only evident following an alcohol dose. Their work is important in advancing understanding regarding the influence of anticipation on alcohol-related cognitions and consumption behaviours in the absence of pharmacological driven effects.

Indeed, a pure control condition avoids any suggestion that alcohol has been ingested and, in contrast to traditional placebo conditions, alcohol-related cues (both visual and olfactory) are consequently removed - which is potentially important in light of early suggestions that alcohol-related smells (Monk et al., 2016) or visual stimuli (Qureshi, Monk, Pennington, Li, & Leatherbarrow, 2017) may reduce inhibitory control impairments. Early research in this field therefore appears to suggests that the anticipated effects of alcohol may result in changes in cognition but not necessarily alcohol consumption (Christiansen et al., 2013), although more research is needed to establish the validity of these early findings. Specifically, although attentional bias is implicated as an important contributory factor shaping drinking motivations and consumption behaviour (see Fadardi & Cox, 2008; Field & Cox, 2008; Field et al., 2016), it is necessary for research to tease apart pharmacological from anticipatory effects of alcohol on such cognitive biases.

Theoretically, alcohol-related attentional processing can be explained using two theories: Alcohol myopia theory (AMM) posits that there is a narrowing of attention following intoxication, with attention being directed towards alcohol-related cues (Steele & Josephs, 1990). On the other hand, incentive sensitization theory suggests that experienced users are particularly susceptible to alcohol-related cues, which 'grab' their attention (Robinson & Berridge, 1993; 2001). In other words, though myopia theory emphasises the importance of pharmacology, incentive sensitization theory stresses the importance previous alcohol experience. The introduction of placebo and control conditions alongside alcohol pre-loads may therefore represent a means of testing the utility of these contrasting theoretical predictions regarding alcohol's effects on cognitive processes and subsequent consumption behaviours. As such, myopia theory would predict increased attentional allocation for alcohol related cues as a consequence

of intoxication, while incentive sensitization theory would foresee that attentional bias would be predicted by participants' past alcohol involvement independent of intoxication (see Albery, Sharma, Noyce, Frings, & Moss, 2015; Fernie et al., 2012). Similarly, heightened attentional bias has been shown to be associated with increased motivations to consume alcohol (see Field & Cox, 2008).

The present study aims to examine the effects of alcohol on inhibitory control, attentional bias, subjective craving, and how these processes impact further consumption. Specifically, by introducing a control beverage condition alongside more commonly used alcohol and placebo pre-loads, the present study uses a within-participant design to disentangle anticipated from the pharmacological effects of alcohol in order to gain a clearer view of their relative contributions. It was hypothesised that both alcohol pre-load and placebo consumption would impair inhibitory control relative to the control beverages, and that alcohol pre-load would result in greater impairments compared to placebo. Alcohol pre-load was expected to lead to increased craving and *ad libitum* alcohol consumption to a greater extent than placebo, and these increases were hypothesised to mediate the relationship between initial intoxication and *ad libitum* consumption. Finally, both alcohol pre-load and placebo were expected to result in heightened attentional bias and, in turn, *ad libitum* consumption.

3.3 Method

3.3.1 Participants

Participants (n = 30**,** 17 female) aged between 18 and 27 years (M = 20.23, SD = 1.96) were recruited from a UK university. Participants were invited to take part if they self-reported regular consumption of alcohol and consumed over the recommended guidelines of 14 units per week, spoke fluent English and were aged between 18 and 49 years. Exclusion was restricted to those whom had suffered from an alcohol dependence disorder or had sought help regarding their consumption previously. Participants were either awarded course credit or £20 as reimbursement for their time. This study was sanctioned ethically by the Faculty Research Ethics Committee.

2.3.2 Design

A counterbalanced within-participants design was implemented, with all participants completing measures of inhibitory control (Stop-Signal task), attentional bias (Alcohol Dot Probe task) and *ad libitum* alcohol consumption (bogus taste test) were taken during each study session in three different alcohol administration condition (alcohol pre-load, a placebo and a control session). Sessions were a minimum of 48 hours apart.

3.3.3 Materials

Questionnaires

See Chapter 2: Methods for Timeline Followback (TLFB; 2.1.1), the Alcohol Use Disorders Identification Test (AUDIT; 2.1.2) and the Barrett Impulsivity Scale (BIS-11; 2.1.3).

Alcohol Urge Questionnaire (AUQ: Bohn, Krahn, & Staehler, 1995). The AUQ is a three dimensional measure of subjective alcohol craving; desire for alcohol, positive expectations of alcohol consumption and ones' inability to avoid consuming alcohol that is available. Eight items (e.g., It would be difficult to turn down a drink at this minute) on scored on a seven-point scale ranging from 'strongly disagree' to 'strongly

agree'. The AUQ produces a single factor for alcohol urges and shows high internal consistency (MacKillop, 2006), and high reliability within the present sample (α = .83).

Alcohol Outcome Expectancies Scale (AOES: Leigh & Stacy, 1993). The AOES assess both positive and negative outcome expectancies on a 6-point Likert scale (1= no chance of happening and 6 = certain to happen), consisting of 34 items (e.g. WHEN I DRINK ALCOHOL 'I feel guilty'). The questionnaire consists of four positive subscales (social facilitation, fun, sex and tension reduction) and four negative subscales (social, emotional, physical and cognitive/performance); both the positive and negative subscales are shown to be reliable measures with Cronbach's of .90 and .86 respectively, comparable previous analyses indicating alpha values of .94 and .88 in turn (see Leigh & Stacy, 1993).

Behavioural measures

Alcohol visual dot probe task (Schoenmakers, Wiers, & Field, 2008). The alcohol visual dot probe task was used concurrently with the Eye-link 1000 eye-tracker to measure attentional-bias. Each trial was initiated by the presentation of a black fixation cross in the centre of the computer screen for 1000ms. Two pictures were then presented side-by-side 60mm apart, in alcohol-neutral pairs for 2000ms. The probe (a black 'X') is then presented on either the right or left side of the screen until the participant responds with the corresponding key; 'V' if the probe appears on the left or 'N' if the probe appears on the right, or until the trial times out at 6000ms. The alcohol and neutral pictures are presented an equal number of times on the right and left side of the screen in a random order. Probes replace alcohol pictures on 50% of the trails and neutral pictures on 50%. The task consisted of 40 trials, each image appeared on the both sides of the screen twice, once replaced with the probe and once not. Reliability analysis of

the current sample revealed that both the probe reaction time (α = .59) and dwell time (α = .61) indices to be unreliable, comparable with other such findings (e.g., Field & Christainsen, 2012). For pictorial stimuli see 2.2.2 Chapter 2: Methods, along with details of the stop-signal task.

3.3.4 Alcohol Administration

See Chapter 2: Methods for general alcohol pre-load and *ad libitum* administration. In the current study dosing was administered as per Rose and Grunsell (2008), based on their weight and gender; 0.5g/kg for females and 0.6g/kg for males.

3.3.5 Procedure

All study sessions took place in the in laboratories between 12 and 6pm. Participant were told they should refrain from consuming alcohol for a minimum of 12 hours and eating for 3 hours prior to participation; all participants provided a breath alcohol level of 0.0mg/l (Lion Alcolmeter 400, Lion Laboratories, Vale of Glamorgan, United Kingdom) before commencing each study session. During the first session, participants completed a battery of questionnaires including demographic information, the TLFB and AUDIT. The within-participant order of conditions was allocated at random and counterbalanced; dependent on condition participants were either presented with an alcohol pre-load, placebo or control drink. Participants had 10 minutes to consume the drink, followed by a 20 minute absorption period. Two further questionnaires were completed, the AUQ and AOES. Participants then completed a battery of cognitive tasks (alcohol dot probe task and pro-, anti- and mixed- saccade), the order the alcohol dot probe task and saccade tasks were presented was counterbalanced. Finally, participants completed the bogus taste task to measure their *ad libitum* consumption. Each study session lasted approximately 1 hour and participants were fully debriefed following completion of the final study session.

3.4 Results

Sample characteristics

Table 1 shows the means and standard deviations for the sample characteristics. A one-way ANOVA was used to assess gender differences in the sample characteristics, including previous drinking involvement. No significant gender differences were observed (*p's* > .05).

Table 1: *Descriptive statistics of participant characteristics*

	M	*SD*
Age	20.23	1.96
TLFB	24.07	15.82
AUDIT	11.10	3.58
BIS	63.53	11.86

TLFB = Timeline Follow back; 14-day alcohol consumption in UK units. AUDIT = Alcohol Use Disorder Identification Test, scores >8 indicative of hazardous drinking. BIS = Barratt Impulsivity Scale.

Cognitive tasks

Inhibitory control

The effects of beverage condition on inhibitory control, indicated by SSRT, were analysed using a repeated measures ANOVA, $F(2, 58) = 44.04$, $p < .001$, $\eta_p^2 = .60$. Bonferroni corrected pairwise comparisons demonstrated that greater impairments in inhibitory control following acute alcohol, compared with placebo ($p < .001$), which, in turn, showed greater levels of impairment in comparison with control ($p < .001$). See Table 2 for means and standard deviations.

Table 2: *Means and standard deviations for stop-signal reaction time, subjective craving and ad libitum beer consumption for each condition; alcohol, placebo and control*

	Alcohol		Placebo		Control	
	Mean	SD	Mean	SD	Mean	SD
SSRT	275.95	47.34	241.88	37.11	220.42	28.34
Craving (AUQ)	29.14	9.42	19.82	7.71	15.00	4.93
Ad libitum consumption (ml)	427.70	316.41	241.03	239.89	205.23	232.82

SSRT = Stop-Signal Reaction Time (ms) AUQ = Alcohol Urge Questionnaire

Attentional bias

A 3x2 repeated measures ANOVA was performed with beverage condition (acute alcohol pre-load, placebo and control) and cue type (alcohol versus neutral) as within participant variable to assess dwell time. There was a significant beverage by cue type interaction $F(2, 58) = 13.71$, $p < .001$, $\eta_p^2 = .32$. Bonferroni adjusted simple main effects analysis revealed that for alcohol cues dwell time was significantly greater following placebo compared with alcohol preload ($p = .002$) and control ($p < .001$). However, there was no difference between alcohol pre-load and control ($p > .999$). As for neutral cues there was no significant differences in dwell time between any of the beverage conditions (all p's > .45). Furthermore, there was significant differences between alcohol and neutral cues following acute alcohol pre-load ($p < .001$), placebo ($p < .001$) and control ($p = .001$). This suggests there was attentional bias for alcohol cues following each of the conditions, however, it would appear attentional bias was heightened following placebo compared with alcohol pre-load and control. See Table 3 for means and standard deviations.

A second 3x2 repeated measures ANOVA was performed with beverage condition (acute alcohol pre-load, placebo and control) and cue type (alcohol versus neutral) as within participant variable to assess probe response RT. The was no significant beverage by cue type interaction $F(2, 58) = 2.09$, $p = .13$, $\eta_p^2 = .07$. There was also no significant effect of cue type on probe response RT $F(1, 29) = .01$, $p = .92$, $\eta_p^2 = .00$. On the other hand, there was a significant main effect of beverage condition $F(2, 58) = 9.33$, $p < .001$, $\eta_p^2 = .24$, indicating that probe response RTs were significantly slower following the acute alcohol pre-load compared both placebo ($p < .02$) and control ($p = .001$). There was no significant difference between placebo and control ($p = .76$). These finding fail to validate the dwell time attentional bias from the previous analysis. See table 3 for means and standard deviations.

Table 3: *Means and standard deviations for Alcohol Dot Probe task dwell time and probe reaction time for each condition; alcohol, placebo and control*

	Alcohol		Placebo		Control	
	Mean	SD	Mean	SD	Mean	SD
Alcohol Dwell (ms)	420.93	88.52	508.97	96.06	409.48	73.48
Neutral Dwell (ms)	333.62	63.62	333.71	71.85	347.34	62.75
Alcohol RT (ms)	472.03	74.12	445.24	74.13	435.12	71.38
Neutral RT (ms)	480.32	71.30	441.46	73.48	432.20	67.19

Alcohol and neutral dwell refer to the dwell time in milliseconds for alcohol-related and neutral images. Alcohol and neutral RT refers to the response reaction time (RT) in milliseconds when the probe replaced an alcohol-related or neutral image respectively

An additional attentional bias variable was computed by subtracting dwell times for neutral images from dwell times for alcohol images (Weafer & Fillmore, 2013). Bivariate correlations were used to assess the relationship between attentional bias, subjective craving and *ad libitum* consumption, all were insignificant (*p's* > .05).

Self-report measures

Subjective craving

A repeated measures ANOVA was used to analyse subjective craving, as measured by the AUQ, in acute alcohol, placebo and control conditions. Overall, there was significant of beverage condition on AUQ $F(2, 58) = 21.98$, $p < .001$, $\eta_p^2 = ..43$, with Bonferroni pairwise comparisons revealing higher ratings of subjective craving following acute alcohol compared with placebo ($p = .004$) and control ($p < .001$). Subjective craving was also higher following placebo compared with control ($p = .029$). See Table 2 for means and standard deviations.

Outcome-expectancies

Two further repeated measures ANOVAs were used to investigate effects of acute alcohol and placebo on positive and negative outcome expectancies. Neither positive $F(2, 58) = .34$, $p = .71$, $\eta_p^2 = .01$ or negative $F(2, 58) = .45$, $p = .96$, $\eta_p^2 = .002$ outcome expectancies were found to be affected by alcohol or placebo. Post hoc analyses were performed on each of the AOES subscales, revealing no significant outcomes ($p > .05$).

Ad libitum alcohol consumption

A final repeated measures ANOVA was undertaken to analyse the volume of beer (ml) consumed *ad libitum* following acute alcohol, placebo and control $F(2, 58) = 22.18$, $p < .001$, $\eta_p^2 = .43$. Bonferroni corrected pairwise comparisons revealed that significantly

more beer was consumed following acute alcohol compared with placebo ($p < .001$) and control ($p < .001$). However, there was no significant difference in the volume of beer consumed following placebo in comparison with control ($p < .86$). See Table 2 for means and standard deviations.

Mediation analysis

Repeated measures mediation analyses were undertaken using the MEMORE macro with SPSS (Montoya & Hayes, 2017) to assess the mechanisms that may mediate the relationship between acute alcohol intoxication and subsequent *ad libitum* consumption. The first path-analytic model assessed the relationship between acute alcohol intoxication, inhibitory control (SSRT) and *ad libitum* consumption. There was an effect of alcohol intoxication on *ad libitum* consumption (c_1) $t(26) = 4.42$, $p < .001$ 95% CI [101.14, 276.93]. There was also a significant relationship between alcohol intoxication and inhibitory control (a_1) $t(26) = 7.70$, $p < .001$, 95% CI [39.72, 71.36], but the relationship between inhibitory control and *ad libitum* consumption (b_1) was not significant $t(26) = .74$, $p = .47$, 95% CI [-4.12, 1.94]. The relationship between acute alcohol intoxication and *ad libitum* consumption remained significant (c'_1) $t(26) = 2.69$, $p = .01$, 95% CI [58.36, 440.62], suggesting that impairments in inhibitory control do not mediate subsequent alcohol consumption. See pathway 1 in Figure 1.

A further repeated measures mediation analysis was undertaken using subjective craving a mediator. Results showed a significant relationship between acute alcohol intoxication and *ad libitum* consumption (c_2) $t(28) = 4.97$, $p < .001$, 95% CI [133.52, 320.62]. A significant relationship between alcohol intoxication and subjective craving was also found, (a_2) $t(28) = 6.83$, $p < .001$, 95% CI [9.46, 17.57], however the path between subjective craving and *ad libitum* consumption (b_2) was non-significant $t(26) = 1.89$, $p = .07$, 95% CI [-11.84, 7.98]. Furthermore, the relationship between alcohol

intoxication and *ad libitum* consumption (c'_2) remained significant $t(26) = 3.26$, $p < .01$, 95% CI [93.36, 412.99]. See pathway 2 in Figure 1.

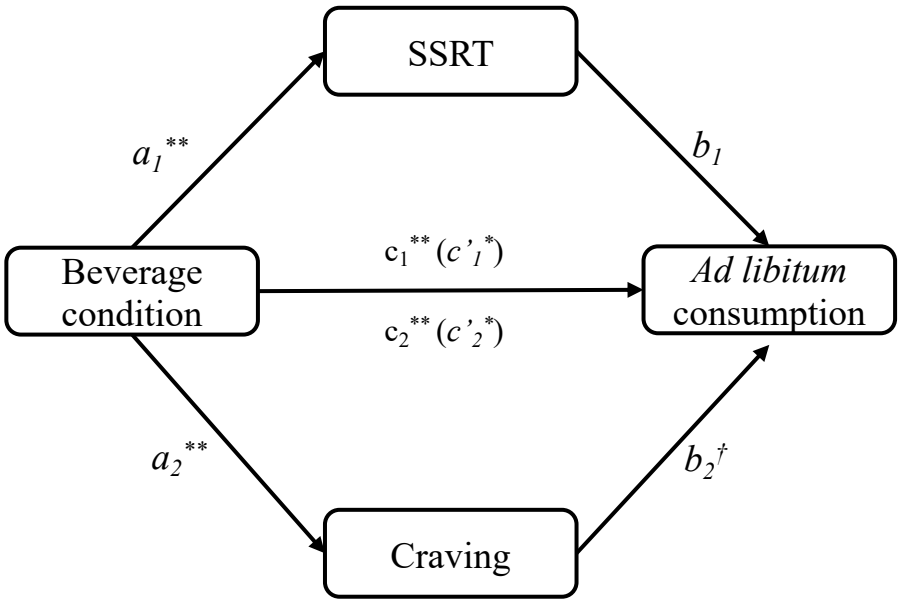

Figure 1: Path-analytic mediation model; Path 1 assesses whether inhibitory control impairments mediate the relationship between beverage condition and ad libitum consumption. Path 2 assesses whether changes in craving mediate the relationship. *$p <$ .01, **$p <$ .001. † approached significance, $p = .07$

3.5 Discussion

The aim of the present study was to examine the effects of alcohol on inhibitory control, attentional bias and subjective craving to elucidate how these processes impact further consumption. By introducing a control beverage condition alongside more commonly used alcohol and placebo pre-loads, the present study used a within-participant design to disentangle anticipated from the pharmacological effects of alcohol to ascertain the way in which intoxication contributes to both alcohol-related cognitions and further alcohol consumption. As predicted, and in line with previous research, results suggest that, in comparison to control, both acute alcohol (e.g., Caswell, Morgan, & Duka, 2013; Weafer & Fillmore, 2008) and placebo (Christiansen, Rose & Jennings, 2016) impaired inhibitory control, with the greatest impairments being observed in the alcohol pre-load condition. With regard to subjective craving, the current study also found increases in craving following both alcohol and placebo, and these were once again higher following alcohol compared to placebo, consistent with previous research (e.g., Christiansen et al., 2013; Rose & Grunnsell, 2008). However, impairments in inhibitory control did not mediate subsequent consumption, and findings suggest that subjective craving partially mediated this relationship.

While no heightened attentional bias was found following control, attentional bias was found to increase in both alcohol and placebo admin conditions and the strength of this effect was observed to be higher after placebo relative to alcohol consumption. Whilst not in line with predictions, this is interesting as it may suggest that anticipated effects play a greater role in driving attentional bias than pharmacological effects. Specifically, it has been postulated that alcohol ingestion is associated with heightened attentional bias (De Wit, 1996). However, it has also been suggested that increased satiety is associated with diminished attentional sensitivity

towards substance-related cues (Duka & Townshend, 2004). In other words, the acute alcohol intoxication of the participants in the current study may have induced satiation effects such that they became less drawn to the cues presented, dampening attentional bias. On the other hand, the placebo condition would be expected to elicit anticipatory effects (see Marlatt et al., 1973) without the associated dampening effects of satiation on attentional bias, as might be expected as a result of intoxication. This may potentially explain why attentional bias appeared to be stronger for those in the placebo relative to the alcohol condition as, from this perspective, the pharmacological effects of alcohol may have impacted attentional bias adversely. This does not appear consistent with theoretical explanations offered by the AMM (Steele & Josephs, 1990), as current findings suggest that anticipated effects had a greater influence on attentional allocation for alcohol-related (as opposed to control) cues. On the other hand, given the relatively high consumption rates reported by our sample, it is possible that the incentive sensitisation hypothesis (Robinson & Berridge, 1993; 2001) may help explain our findings concerning heightened attentional bias following placebo. From this perspective, as our participants may be considered to be 'practised' alcohol users, it is possible to hypothesise that this may, to an extent, account for the alcohol-related cues 'grabbing' attention in the current study. While speculative and requiring further exploration, such suggestions appear consistent with findings from Weafer and Fillmore (2013), who identified dose dependent decreases in attentional bias in heavy drinkers, and also in line with research from the field of subjective craving (Rose et al., 2013).

It has previously been proposed that transient inhibitory control impairments may mediate the association between initial intoxication and continued consumption (see Field, Wiers, Christiansen, Fillmore, & Verster, 2010; Jones, Christiansen, Nederkoorn, Houben, & Field, 2013). However, while current findings evidence

increased *ad libitum* consumption following alcohol pre-load, there were no apparent differences between placebo and control conditions. This may suggest that pharmacological, but not anticipatory effects, may drive *ad libitum* consumption (Christiansen et al., 2013). Furthermore, impairments in inhibitory control did not appear to mediate the association between initial intoxication and *ad libitum* consumption, although increased craving appeared to be implicated in heightened *ad libitum* consumption. It may therefore be postulated that people's desires rather than transient changes in cognitive processes (e.g., inhibitory control) may be more important in driving consummatory behaviour. Such an assertion would seem to be in line with research from Rose and Grunsell (2008), which indicates that alcohol-induced increases in craving may be a better predictor of binge drinking, compared with inhibitory control. As such, while inhibitory control is potentially implicated in the maintenance of consumption, our findings suggest that these impairments may not be the central mechanism driving alcohol consumption. Rather, it may be the role of inhibitory control to moderate the influence of craving on alcohol consumption. In other words, people's ability to exert control over their desires may be a particularity important explanatory factor for diverse consumption patterns.

By separating the pharmacological from anticipated effects using pure control, placebo and acute alcohol, the current study contributes to the emerging literature which seeks to study the effects of cognitive and psychological changes in the maintenance of alcohol consumption. Nevertheless, a number of limitations need to be taken into consideration when interpreting the findings of the current study. First, while the within-participants design allowed us to control for conceivable individual differences effects, this design limited our ability to undertake a post-hoc moderation analysis. Further research is therefore required in order to assess the potential moderating

influence of inhibitory control on cravings and how they drive consumption. For example, the use of neurostimulation techniques (e.g., transcranial magnetic stimulation) to impede inhibitory control may provide valuable insights into the relationship between craving, inhibition and the maintenance of alcohol consumption. Second, the alcohol-dot probe task is only one of the established measures for assessing attentional bias and others include the Stroop task (see Cox, Fadardi, & Pothos, 2006) and attentional bias (Stoet & Hommel, 1999). The current assertions should therefore be tempered with a need for caution before further examinations have been carried out using a broader spectrum of attentional bias tasks. Finally, the current research used a student sample. University students are immersed in a heavy drinking culture (Borsari & Carey, 2001; Karam, Kypri, & Salamoun, 2007; Knight et al., 2002) and it is therefore possible that findings may not generalize to populations with different drinking experiences (see Albery et al., 2015).

In conclusion, the current study sought to examine the effects of alcohol-related cognitive and psychological changes in the maintenance of alcohol consumption, separating the pharmacological from anticipated effect using pure control, placebo and acute alcohol. Findings suggest that attentional bias may be more susceptible to anticipated relative to pharmacological effects, as higher levels of attentional bias were found following placebo relative to alcohol and control. This could potentially be explained by the devaluation of alcohol-related stimuli as a consequence of satiation following alcohol pre-load. Furthermore, both alcohol and placebo conditions resulted in impaired inhibitory control and heightened craving, with the greatest changes being observed following alcohol intoxication. However, only the pharmacological effects (evidenced in the alcohol condition) appeared to be associated with increased consumption. Here, impaired inhibitory control was not found to mediate the

association between initial alcohol intoxication and continued consumption, while, on the other hand, results may suggest that craving could partially mediate this relationship. In sum, results suggest that psychological processes such as craving may be more important in driving consummatory behaviour, relative to potentially more transient changes in cognitive processes.

Chapter 4: Intoxication without anticipation: Disentangling pharmacological from expected effects of alcohol

McNeill, A. M., Monk, R. L., Qureshi, A. W., & Heim, D. Intoxication without anticipation: Disentangling pharmacological from expected effects of alcohol (Under Review).

The findings from the preceding chapter 3 suggest that transient changes in cognition and subsequent alcohol consumption are primarily driven by alcohol's pharmacological effects. However, the nature of existing alcohol administration paradigms utilised means that it was not possible to fully disentangle the pharmacological from the anticipated effects of alcohol. This chapter therefore employs a novel methodological approach, whereby alcohol is administered under deception in an alcohol naïve condition. In so doing, it is better able to isolate the pharmacological effects of alcohol from anticipatory.

4.1 Abstract

Alcohol's effects can impact executive function and attentional processes, in turn exacerbating alcohol-seeking behaviour. To date, however, the relative contributions of the pharmacological and anticipatory effects of alcohol on associated cognitive processes remains unclear due to the widespread use of methods with insufficient controls. Utilising a newly developed naïve alcohol administration method, the current study addresses this gap by disentangling the relationship between anticipated and actual effects of alcohol consumption on these processes. One hundred participants took part in a study where pure grain alcohol was masked in a sweetened orange juice solution under deceptive conditions. Changes in Inhibitory Control, attentional bias, craving and *ad libitum* consumption were compared across alcohol pre-load, placebo, naïve and control conditions. Findings indicate that the pharmacological conditions (alcohol pre-load and naïve) showed greater impairments on inhibitory control compared with anticipatory effects (placebo). Anticipation, but not the pharmacological effect of alcohol, were found to increase attentional bias. Both the pharmacology and anticipation resulted in increases of craving, though higher levels of craving were observed in the alcohol pre-load compared with the placebo condition. Furthermore, the alcohol administration conditions resulted in heightened *ad libitum* consumption compared with anticipatory (placebo) conditions. Importantly, changes in subjective craving mediated the relationship between initial intoxication and successive drinking, however, impairments in inhibitory control did not. These findings suggest that while the pharmacological effects of alcohol may play a greater role in driving subsequent consumption, subjective anticipatory effects may also play a role in navigating the relationship between intoxication and further drinking.

4.2 Introduction

Research has established that both the pharmacological impact of intoxication and the psychologically anticipated effects of alcohol consumption impact alcohol behaviours in important ways. For example, low doses of alcohol have been found to increase subsequent consumption (Fernie, Christiansen, Rose, Cole & Field, 2012), possibly by impairing inhibitory control mechanisms (Weafer & Fillmore, 2016) or by activating attentional biases and craving (Tiffany, 1990). It is also established that the psychosocially negotiated expectations about one's own and other's alcohol behaviour (McAndrew & Edgerton, 1969), and related cognitions (Marlatt et al., 1973) and can exert significant influences on alcohol behaviours (Christiansen et al., 2017). To date, however, it has not been possible to disentangle fully the effect of the pharmacological from the anticipated effects of alcohol. This is because existing placebo-controlled paradigms necessitate that participants either experience anticipation (in placebo conditions where non-alcoholic drinks are made to appear alcoholic) or pharmacological effects of alcohol combined with anticipation (in alcohol pre-load conditions whereby participants are 'primed' by drinking alcohol). In other words, to date it has not been possible to assess the pharmacological effects of alcohol without also eliciting anticipatory effects. In order to achieve intoxication without anticipation, the current study addresses this limitation by introducing a novel methodology whereby beverages are administered to participants who are naïve to their alcoholic nature.

Existing research on the impact of alcohol pharmacology on cognitive processing and consumption behaviour has primarily used placebo-as-control alcohol administration methods. Here effects are assessed between participants who knowingly receive alcohol and those who falsely believe their drinks to be alcoholic. This approach has illuminated how alcohol affects various cognitive processes including impairing

inhibitory control (e.g., Caswell, Morgan, & Duka, 2013; Weafer & Fillmore, 2008), dose dependent effects on attentional bias (e.g., Duka & Townshend, 2004; Weafer & Fillmore, 2013), heightened craving (e.g., Rose & Grunsell, 2008) and increased risk taking (e.g., Rose, Jones, Clarke, & Christiansen, 2014).

The effects of alcohol pharmacology on cognitive processes have therefore been well documented, and the resulting transient changes have been found to be associated with subsequent alcohol consumption (see Field, Wiers, Christiansen, Fillmore, & Verster, 2010). Specifically, alcohol pre-loads or "priming" appear to be associated with increased alcohol seeking behaviours (including consumption; de Wit, 1996) and it has been suggested that these changes in behaviour are mediated by transient impairments in inhibitory control (Field et al., 2010). This theoretical view is informed by Weafer and Fillmore's (2008) work indicating that *ad libitum* consumption in a follow-up session correlated with alcohol induced inhibitory control impairments. While this work points to important relationship facets between inhibitory control changes and consumption, owing to its correlational nature this research was not designed to examine this relationship causally. Attempts to establish a causal link between inhibitory control and consumption by administering Transcranial Magnetic Stimulation to the right Dorsolateral Prefrontal Cortex (rDLPFC) have yielded mixed findings and highlight the possibility that other mechanisms may underpin this relationship (McNeill, Monk, Qureshi, Makris, & Heim, 2018).

Alcohol-related attentional bias has been identified as a further potential driver of consumption (see Field & Cox, 2008) which has generated inconsistent findings. For instance, a bidirectional association between heightened attentional bias and alcohol-seeking behaviours has garnered support (ibid), and recent studies indicated that

alcohol-related attentional bias is most pronounced immediately prior to a drinking (Spanakis, Jones, Field, & Christiansen, 2019). However, the acute effects of alcohol on attentional bias also appear to be affected by peoples' previous alcohol involvement and the pre-load doses. For instance, one study found that dose increases were associated with attentional bias decreases in heavy social drinkers but not among moderate social drinkers (Weafer & Fillmore, 2013). On the other hand, Fernie and colleagues (2012) found no effect of low dose alcohol pre-loads on attentional bias in heavy social drinkers, but an increase in light social drinkers. In both of these studies changes in attentional bias were unrelated to *ad libitum* consumption. The existing literature therefore points to an intricate relationship between initial alcohol consumption and attentional bias, and future research to unpick the relative contributions of alcohol pharmacology and anticipation on this relationship is required.

Theoretically it has been proposed that alcohol anticipation is driven by the associated reinforcing effects of its pharmacology (Marlatt et al., 1973) in that alcohol initiates a "priming" effect on alcohol seeking behaviour and triggers cognitive changes which, to a greater or lesser extent, are comparable with the effects of alcohol itself (Marlatt et al., 1973). Complimenting cognitive approaches, McAndrews and Edgerton (1969) suggest theoretically that alcohol-associated environments and drinking social norms can illicit similar changes in alcohol seeking behaviour. Both cognitive and social research therefore converge to that the mere suggestion of alcohol, whether that be smell of alcohol (e.g., Monk et al., 2016) or alcohol-related contexts (e.g, Field & Jones, 2017), can induce both cognitive and behavioural changes associated with alcohol consumption.

Overall, significant attempts have been made to understand the contributions of alcohol anticipation on inhibitory control and attentional bias on consumption, with the inclusion of pure control conditions (e.g., Christiansen et al., 2013). The findings have illuminated the effects of anticipation on inhibitory control and craving fairly consistently. Specifically, studies have shown that placebo-alcohol produces inhibitory control impairments, however, these impairments may not be comparable with alcohol pre-loads (e.g., Christiansen et al., 2016). Similarly, there is some evidence to suggest that placebo alcohol also heightens craving (Christiansen et al., 2013; Christiansen et al., 2016), but that patterns of craving may differ between alcohol and placebo-alcohol (Rose et al., 2013). However, the literature evidencing the relationship between anticipation and attentional bias is scant, with one study demonstrating a heightening of attentional bias following placebo in heavy drinkers (Weafer & Fillmore, 2013). Furthermore, findings supporting anticipation provoked increases in seeking behaviour are inconsistent, specifically, consumption (e.g., Christensen et al., 2017; Christiansen et al., 2013). Therefore, a major limitation of pure-controlled designs is our inability to ascertain if the effects of alcohol pre-loads are a consequence of the combined pharmacological-anticipation or merely pharmacology.

The current study developed a novel naïve alcohol administration method in order to contribute further to our understanding of the pharmacological and anticipated effects of alcohol. Specifically, by administering naïve alcohol alongside traditional alcohol pre-loads and placebo, in a pure-controlled design, it aims to tease apart the relative contributions of pharmacology and anticipation on alcohol-related cognitions. Examining how these cognitions may drive or interact to shape subsequent consumption. A mixed design was implemented to test the hypotheses that both the pharmacological (alcohol pre-load and naïve) and anticipatory (placebo) conditions

result in cognitive changes compared with pure-control. Explicitly, it was hypothesised that the pharmacological effects of alcohol will result in greater impairments in inhibitory control and increases in craving compared with placebo. Furthermore, it is predicted that pharmacological and anticipatory conditions will result in heightened *ad libitum* consumption compared with control, but more pronounced following alcohol intoxication. Finally, these patterns of *ad libitum* consumption will be mediated by inhibitory control impairments and heightened craving.

4.3 Method

4.3.1 Participants

One hundred (57 female) participants aged 18 to 49 (M = 21.18, SD = 4.73) who spoke fluent English speakers and whose weekly consumption regularly exceeded the recommended limit of 14 UK units were recruited. Participants were from the student and staff populations of a University in Northwest England. They completed a medical screen questionnaire and participants indicating that they had medical conditions or were taking certain medications were excluded from the study. Those with a personal or family history of Alcohol Use Disorder were also excluded. Participants were reimbursed for their time by way of course credit or £10. The study was given ethical scrutiny and approval by the Faculty of Arts and Sciences Research Ethics Committee, Edge Hill University.

3.3.2 Design

A randomised mixed design was implemented, with a between participants independent variable consisting of 4 beverage conditions; alcohol pre-load, placebo, naïve alcohol and control. Measures of inhibitory control, attentional bias and craving were taken, both pre and post beverage administration, followed by a measure of *ad libitum* alcohol consumption.

4.3.3 Materials

See Chapter 2: Methods for all materials including self-report measures TLFB (2.1.2), AUDIT (2.1.2), BIS-11 (2.1.3), DAQ (2.1.4) and mood and intoxication scales (2.1.5), plus cognitive tasks SST (2.2.1) and Visual Probe Task (2.2.3).

4.3.4 Alcohol Administration

Alcohol pre-load/placebo

See Chapter 2: for traditional alcohol pre-load (.4g/kg) and placebo administration

protocols (2.3.1). For the alcohol naïve condition, grain ethanol (.4g/kg) was mixed with orange juice, calculated to match the dilution of the alcohol pre-load condition mixture. Ten millilitres of liquid sweetener (Canderel®) were added to the mixture to mask the bitterness of the ethanol and participants were asked to consume a strong mint prior to drinking. In the naïve alcohol condition, participants were informed they were in a control condition, where the beverage was matched for calories with the alcohol condition. The control drink consisted of equal parts orange juice and tonic water, and the participants are informed the drink contains no alcohol.

See Chapter 2: Methods for *ad libitum*/bogus taste task procedures.

4.3.5 Procedure

Each experimental session took place between 12-6pm in a laboratory. Participants were informed that they were required to refrain from drinking alcohol a minimum 12 hours prior and upon arriving at the laboratory a breathalyser reading was taken in order to ensure a reading of .00mg/l (Lion Alcolmeter 400, Lion Laboratories, Vale of Glamorgan, United Kingdom). Participants were also asked to avoid eating 3 hours before the session. After providing informed consent, participants completed an initial questionnaire battery (TLFB, AUDIT, BIS, DAQ, mood and intoxication scales), followed by baseline measures of inhibitory control and attentional bias, in a counterbalanced ordered. Participants were then provided with a beverage, dependent on their randomly allocated beverage condition. They were informed they had 10 minutes to drink the whole drink and they were then given a 20-minute rest period. Participants were then breathalysed for a second time, before repeating the DAQ, mood and subjective intoxication scales, measures of inhibitory control and attentional bias, all in a counterbalanced order. Finally, participants completed the bogus taste task to measure their *ad libitum* consumption. Experimental sessions took approximately 1

hour 40 minutes and all participants were fully debriefed following completion of the study.

4.4 Results

Sample Characteristics

A MANOVA was performed to assess any differences between conditions or genders in terms of baseline sample characteristics (e.g., AUDIT, BIS). No significant differences were revealed between conditions (all *p's* > .16) or between genders (all *p's* > .09). A further ANOVA was performed to ensure that there were no difference between genders for breath alcohol level post beverage (only alcohol containing conditions assessed), $F(1, 48) = .20$, $p = .66$, $\eta_p^2 = .004$. As such, none of these variables were included into the main analysis as covariates. Table 4 contains means and standard deviations for all baseline measures.

Table 4: *Means and standard deviations for sample characteristics*

	Mean	SD
AUDIT	11.25	4.64
TLFB	31.15	25.12
BIS Attentional	16.51	3.45
BIS Motor	23.80	4.72
BIS Non-planning	24.54	4.74
BIS Total	64.29	9.72

AUDIT = Alcohol Use Disorder Identification Test, TLFB = Timeline Followback, BIS = Barrett Impulsivity Scale and Attentional, Motor and Non-planning are subscales of the BIS

Mood and Subjective Intoxication

Two 2 (time; pre- and post-beverage) x 4 (beverage condition; alcohol pre-load, placebo, naïve alcohol and control) mixed ANOVAs were employed to assess changes in mood, one for positive and one for negative aspects of mood. For positive mood rating there was significant pre-/post-beverage effect $F(1, 96) = 5.08$, $p < .03$, $\eta_p^2 = .05$,

with overall higher positive mood ratings post-beverage. However, there was no interaction with beverage condition $F(3, 96) = .21$, $p = .89$, $\eta_p^2 = .01$. On the other hand, there was a significant time x beverage condition interaction $F(3, 96) = 7.40$, $p < .001$, $\eta_p^2 = .19$. Bonferroni corrected pairwise comparisons revealed that negative mood rating significantly increased post beverage ($p < .001$), there was no other significant differences evident (all *p's* > .38).

A further 2 (time; pre- and post-beverage) x 4 (beverage condition; alcohol pre-load, placebo, naïve alcohol and control) mixed ANOVA was used to scrutinise the effects of beverage on ratings of subjective intoxication. A significant time x beverage interaction was apparent $F(3, 96) = 33.20$, $p < .001$, , $\eta_p^2 = .51$, Bonferroni corrected comparisons indicating that for alcohol pre-load ($p < .001$), placebo ($p < .001$) and naïve ($p < .001$) subjective intoxication ratings increased post-beverage. Additionally, subjective intoxication post-beverage was significantly higher for alcohol pre-load compared with placebo ($p < .001$) and naïve alcohol ($p < .02$), however, there was no significant difference evident between placebo and naïve alcohol ($p = .70$). This may suggest that the anticipated effects of alcohol change our perceptions of the experiences of intoxication.

Inhibitory Control

A 2 (time; pre- vs post-beverage) x 4 (beverage condition; alcohol pre-load, placebo, naïve alcohol and control) mixed ANOVA was undertaken to assess the effects of beverage condition on inhibitory control. The was a significant time x beverage interaction $F(3, 96) = 14.93$, $p < .001$, $\eta_p^2 = .32$, with Bonferroni corrected pairwise comparisons revealing that following alcohol pre-load ($p < .001$), placebo ($p < .001$)

and naïve alcohol ($p < .001$) SSRTs significantly increased, indicating impaired inhibitory control . Moreover, Bonferroni corrected pairwise comparisons indicated alcohol pre-load increased SSRT significantly more than placebo ($p < .05$) and naïve alcohol approached significance ($p < .08$) compared to placebo. Alcohol pre-load ($p < .001$), placebo ($p < .004$) and naïve alcohol ($p < .001$) all showed significantly longer SSRTs compared with control. These findings suggest that both the pharmacological and anticipated effects of alcohol can significantly impair inhibitory control, however, the pharmacological effects show the greatest potential to impair. See figure 2 for means and standard errors.

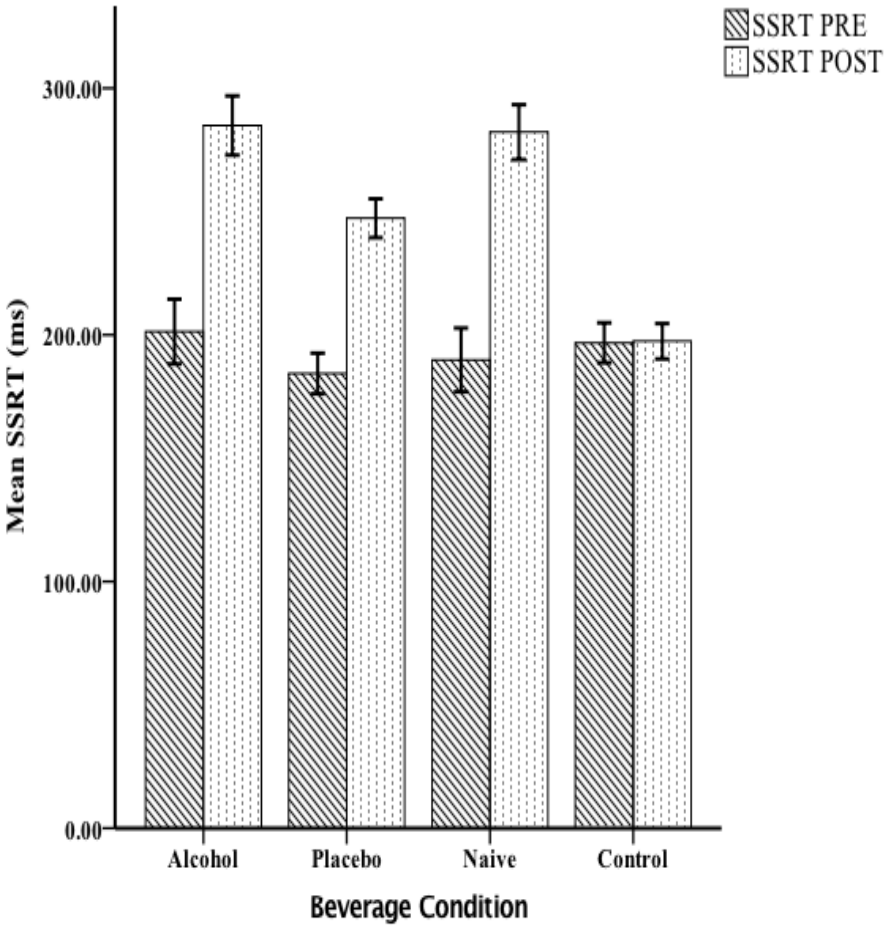

Figure 2: Bar graph showing the mean and standard error Stop-Signal Reaction Times (SSRT) for pre- and post-beverage administration

Attentional Bias

A 2 (cue type; alcohol vs neutral) x 2 (time; pre vs post) x 4 (beverage condition; alcohol pre-load, placebo, naïve alcohol and control) mixed ANOVA was performed to assess attentional bias for alcohol related cues. There was significant main effect of cue type $F(1, 96) = 195.17$, $p < .001$, $\eta_p^2 = .67$, no effect of time $F(1, 96) = 2.79$, $p = .10$, $\eta_p^2 = .03$, but a significant cue type x time x beverage condition interaction $F(3, 96) = 3.78$, $p < .02$, $\eta_p^2 = .11$. See Table 5 for mean and standard deviation alcohol and neutral cue type dwell times (ms) for each condition.

Table 5: *Mean and standard deviation cue type dwell times (ms) for each beverage condition*

	Pre-beverage				Post-beverage			
	Alcohol Cues		Neutral Cue		Alcohol Cue		Neutral Cue	
	M	SD	M	SD	M	SD	M	SD
Alcohol	789.34	167.96	623.09	130.35	806.75	126.64	661.20	159.96
Placebo	798.90	123.47	673.80	129.34	894.52	103.36	600.47	127.17
Naïve	793.68	111.08	668.71	134.12	805.14	111.06	662.16	111.96
Control	777.38	135.24	657.31	137.16	813.09	137.53	667.22	118.56
Overall	789.83	135.24	655.73	132.25	829.87	124.38	647.76	131.40

For clarity and ease of presentation, a single attentional bias score for both pre- and post-beverage was calculated by subtracting the neutral cue dwell time from the alcohol cue dwell time, with greater values indicative of heighten attentional bias for alcohol-related cues (see Weafer and Fillmore, 2013). Mean attentional bias scores and standard errors are presented in Figure 3. A 2 (time; pre- vs post-attentional bias) x 4 (beverage condition; alcohol pre-load, placebo, naïve alcohol and control) mixed

ANOVA to assess the effects of beverage condition on attentional bias. Revealing a significant time x beverage condition interaction $F(3, 96) = 3.78$, $p < .02$, $\eta_p^2 = .11$, with Bonferroni corrected pairwise comparisons highlighting that only following placebo did attentional bias significantly increase ($p < .001$). Furthermore, post-beverage placebo showed significantly higher levels of attentional bias compared with alcohol pre-load ($p < .01$), naïve alcohol ($p < .01$) and control ($p < .01$). This suggests that while all participants prior to beverage administration displayed significant attentional bias for alcohol-related cues, only the anticipated effects of alcohol associated with placebo amplifies that attentional bias.

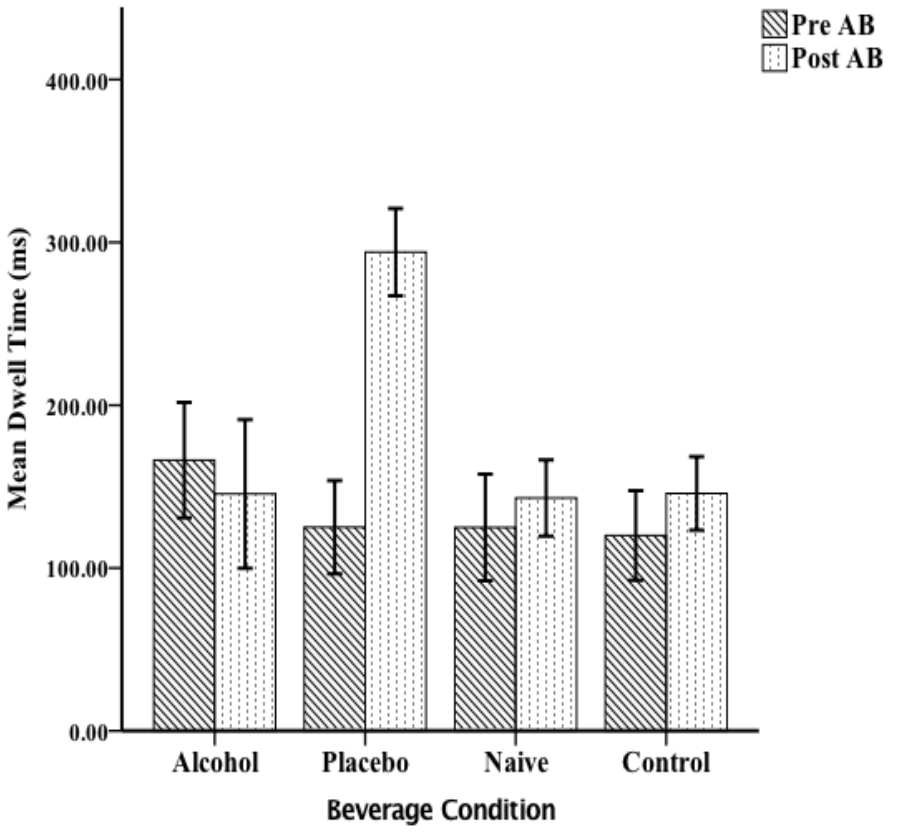

Figure 3: Bar graph showing mean and standard error attentional bias dwell times (ms) for pre- and post-beverage administration for each condition

Craving

A 2 (time: pre- vs post-beverage) x 4 (beverage condition; alcohol pre-load, placebo, naïve alcohol and control) mixed ANOVA was performed to assess the effects of beverage condition on craving (DAQ), with pre and post as within participant variables and beverage condition as between participant variables. A significant time x beverage condition interaction was found $F(3, 96) = 12.62$, $p < .001$, $\eta_p^2 = .28$, Bonferroni corrected pairwise comparisons revealed that craving in the alcohol ($p < .001$), placebo ($p < .001$) and naïve alcohol ($p < .001$) conditions had significantly increased following beverage consumption, but control ($p = .72$) did not. Signifying that both the pharmacological and anticipated effects of alcohol increase craving for alcohol. Furthermore, while there were no differences between conditions for pre-beverage craving (all *p's* > .999), there were significant differences between conditions for post beverage craving. Alcohol ($p < .001$), placebo ($p = .02$) and naïve alcohol ($p < .01$) all displayed significantly higher levels of craving compared with control. Furthermore, there were significantly higher levels of craving following alcohol pre-load compared with placebo ($p = .01$), with the difference between alcohol pre-load and naïve approaching significance ($p = .085$). This suggests that the pharmacological and anticipated effects of alcohol have similar effects on craving. See Table 6 for means and standard deviations.

Table 6: *Means and standard deviations for DAQ scores pre- and post-beverage for each beverage condition*

	Pre-beverage		Post-beverage	
	Mean	SD	Mean	SD
Alcohol	39.92	6.70	54.68	8.84
Placebo	38.68	7.06	46.84	10.13
Naïve alcohol	40.28	7.10	49.52	11.34
Control	38.60	10.07	37.96	11.44

Ad libitum Consumption

A univariate ANOVA was undertaken to examine the effects of beverage condition (alcohol pre-load, placebo, naïve alcohol and control) on *ad libitum* consumption. Findings indicated a significant difference in *ad libitum* consumption levels between conditions $F(3, 96) = 8.79$, $p < .001$, $\eta_p^2 = .22$. Bonferroni corrected pairwise comparisons revealed that those in the alcohol pre-load condition consumed significantly more beer *ad libitum* compared with placebo ($p < .003$) and control ($p < .001$), but not the naïve alcohol condition ($p > .999$). The naïve alcohol condition also consumed more than the placebo ($p < .05$) and control ($p < .01$) conditions, but the placebo did not significantly differ from control ($p > .999$). This may suggest that it is the pharmacological, not the anticipated effects of alcohol that drive subsequent alcohol consumption. See Table 7 for means and standard deviations.

Table 7: *Means and standard deviations for ad libitum consumption (ml) following beverage administration*

	Mean	SD
Alcohol pre-load	475.40	183.94
Placebo	270.12	200.57
Naïve alcohol	422.68	185.60
Control	234.12	215.22

Mediation

A path analytic mediation analysis using the PROCESS 3.0 macro for SPSS was employed to examine if inhibitory control impairments mediate the relationship between initial intoxication and successive alcohol consumption. There was a significant direct effect of beverage condition on *ad libitum* consumption (*c* pathway) $F(1, 98) = 9.24$, $p = .003$, $R^2 = .09$. SSRT was also significantly predicted by beverage condition (*a* pathway) $F(1, 98) = 21.93$, $p < .001$, $R^2 = .18$. Overall, the model predicting *ad libitum* consumption was significant $F(2, 97) = 5.32$, $p < .01$, $R^2 = .10$, however, SSRT did not significantly predict *ad libitum* consumption (*b* pathway) $t(1) = 1.17$, $p = .24$, $SE = .39$. Additionally, the relationship between beverage condition and *ad libitum* consumption remained significant (*c'* pathway) $t(2) = 2.25$, $p < .03$, $SE = 20.75$. This suggests that inhibitory control impairments do not mediate the relationship between initial intoxication and resultant alcohol consumption. See Figure 3 for path analytic model.

A further path analytic mediation analysis was undertaken using the PROCESS 3.0 macro for SPSS to assess if subjective craving as measured by the DAQ mediates the relationship between initial intoxication and subsequent consumption. There was a significant direct effect of beverage condition on *ad libitum* consumption (*c* pathway) $F(1, 98) = 9.24$, $p = .003$, $R^2 = .09$. Beverage condition also significantly predicted

craving (*a* pathway) $F(1, 98) = 24.19$, $p < .001$, $R^2 = .20$. Overall, there was a significant indirect effect of beverage condition on *ad libitum* consumption via craving $F(2, 97) = 17.58$, $p < .001$, $R^2 = .27$, specifically, craving predicted *ad libitum* consumption (*b* pathway) $t(2) = 4.89$, $p < .001$, $SE = 1.77$. Importantly, beverage condition no longer predicts *ad libitum* consumption (*c'* pathway) $t(2) = .85$, $p = .40$, $SE = 18.90$, therefore indicating mediation. This suggests that following initial intoxication, craving increases which in turn results in heightened subsequent alcohol consumption. See Figure 4 for path analytic model.

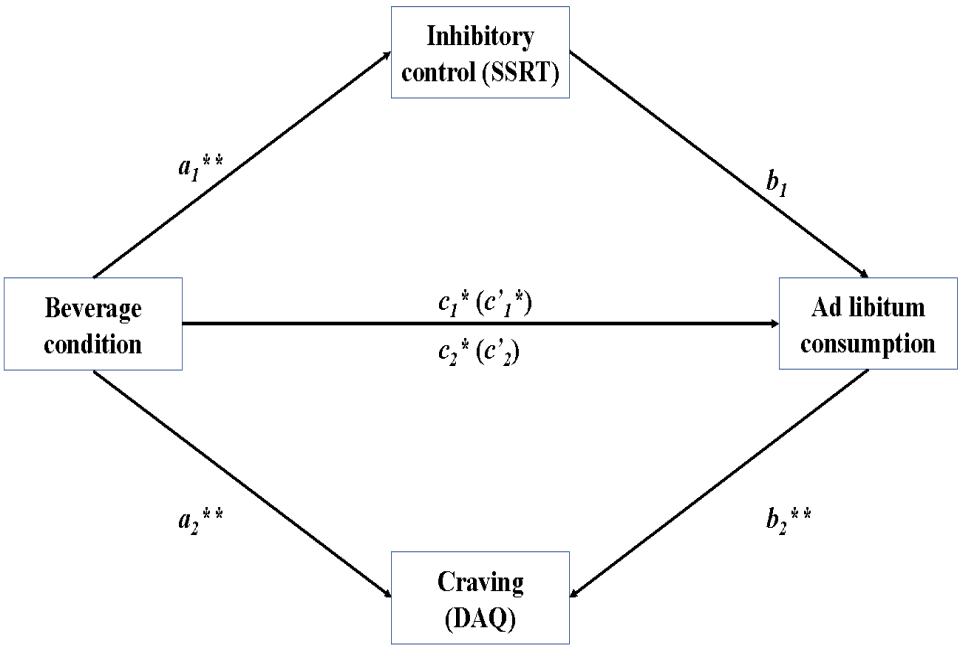

Figure 4: Path-analytic mediation model examining the relationship between beverage administration condition and *ad libitum* consumption. Pathway 1 tests inhibitory control as a mediator and pathway 2 subjective craving

4.5 Discussion

In the first of its kind, the current study introduced a naïve alcohol administration procedure whereby participants were administered a dose of alcohol under deceptive circumstances to isolate the pharmacological from the anticipated effects of alcohol on inhibitory control, attentional bias, craving and alcohol seeking behaviours. Findings can be summarised as follows. First, pharmacological (alcohol pre-load and naïve) effects of alcohol appeared to be associated with the greatest changes in cognition and heightened alcohol consumption. Second, both the pharmacological and anticipated effects seemed to heighten craving, but the greatest increases appeared to be the result of an interaction between the two evident in the traditional alcohol pre-load. Finally, increased *ad libitum* consumption associated with alcohol pharmacology was partially mediated by changes in craving, but not transient changes in inhibitory control.

The current findings implicate alcohol's pharmacological effects rather than anticipated in driving subsequent consumption. Specifically, elevated *ad libitum* consumption was only evident following alcohol conditions, suggesting anticipation has no role in increased consumption. This is consistent within the literature showing heightened consumption following alcohol, but not placebo (e.g., Christiansen et al, 2013). With only one comparable study to our knowledge demonstrating heighten consumption following placebo (Chirstiansen et al., 2017). Christiansen and colleagues (2013) suggested this may be due to the anticipation being comparably shorter lived that the pharmacological effects, meaning placebo may drive changes in cognition but not consumption due to the delay. While this is plausible methodological explanation, we suggest that alcohol consumption results in greater activation of reward circuitry eliciting the heightened alcohol seeking behaviour. The alcohol naïve findings further

emphasise this point, in the absence of anticipation *ad libitum* consumption was akin to that following the traditional alcohol pre-load. Furthermore, alcohol conditions displayed the greatest elevation in craving levels, with associations between the craving and activation in the dorsal striatum well documented in the literature (see Volkow et al., 2016). When taken together these findings downplay the role of alcohol's anticipatory effects on consecutive consumption, however, they may combine with the pharmacological effects to drive changes in alcohol-related cognitions and initiation of drinking episodes.

However, while the current study did not directly implicate the anticipated effects of alcohol in successive consumption, its influence was apparent across the alcohol-related cognitions. Specifically, anticipation was associated with significant increases alcohol-related attentional bias. It must be noted that these findings in relation to the Dopamine Sensitisation Hypothesis (DSH; Robinson & Berridge, 1993; 2001) are inconsistent with our previous explanation of alcohol-related striatal activation eliciting increased consumption. As the DSH would suggest that alcohol's effects on striatal activation would increase the salience of alcohol-related stimuli and biasing attention, this was not the case for current findings. Rather the placebo associated attentional bias elevation may be due to the absence 'reward' satiation in striatum, activating a hypervigilance for alcohol-related stimuli, in an attempt to attain satiety. However, the current findings could also be seen as discordant with theories suggesting attentional bias is associated with subjective processes such as craving (e.g., Franken, 2003; Tiffany, 1990), which would suggest that higher levels of craving to be associated with heightened attentional bias. While it is true that the current findings showed elevated craving following placebo, this was lower compared with alcohol conditions (although not significantly compared with naïve), neither of which demonstrated pronounced

attentional bias. Therefore, future research is required to disentangle the evidently nuanced relationship between craving and attentional bias, and the role anticipation may play.

The current findings suggest a very complex interplay between pharmacology and anticipation in terms of craving, potentially indicating an additive association. The most apparent elevations in craving were preceded by alcohol conditions, however, placebo did increase craving but was not significantly lower than naïve alcohol. These findings are consistent within the literature (Christiansen et al., 2012) and may suggest that anticipation may be involved in the initiation of consumption. Specifically, Christiansen and colleagues (2017) suggest that anticipation activates that alcohol-related cognitions such as expectancies and elicit motivational changes in alcohol seeking behaviour. Arguing the importance of pre-consumption phases of a drinking episode. We argue for anticipations involvement in merely the initiation and not the maintenance of consumption is evidenced in the absence of raised *ad libitum* consumption. A point further emphasised by decreasing patterns craving over subsequent placebo drinks compared initial increases over successive alcoholic drinks (Rose et al., 2014). While the relative contributions of alcohol anticipation and pharmacology to patterns of craving and drinking initiation require further exploration, the role of craving in both the initiation and maintenance of consumption is more evident in the current findings.

Findings indicated that although inhibitory control impairments were evident across all experimental manipulations, these did not mediate *ad libitum* consumption as previously suggested (Field et al., 2010; Jones et al., 2013). Rather craving emerged as a more central tenant in the initiation and maintenance of drinking, indicated by the

partial mediatory association between initial intoxication and *ad libitum* consumption. These two findings are not now uncommon in the literature. Findings in our lab suggested that transient impairments in inhibitory control are not directly associated with heighten consumption (McNeill et al., 2018) and implementation intentions and craving have been shown to supersede daily fluctuations in inhibitory control in predicting drinking episodes (Jones et al., 2018). We make the tentative suggest when taking all the results together that anticipation may induce elevation of craving and may then combine with alcohol pharmacology to initiate drinking, but it is the sustained effect of pharmacology on craving that drive the maintenance. As such future research should focus on evolution of craving throughout the drinking episode and how this is influenced by both anticipated and pharmacological effects.

A number of limitations must be taken into consideration for the current study. First, there were increases in subjective intoxication following naïve alcohol. While subjective intoxication did significantly increase from baseline, it did not vary from placebo and more importantly, it was significantly lower than alcohol pre-load. So, while the researchers are reasonably assured that participants in the naïve condition were deceived regarding the presence of alcohol, it should be noted that anticipated effects cannot be ruled out entirely. In future the inclusion of a simple question asking if the participant was deceived combined with ratings subjective intoxication would add additional layer of certainty. Indeed, procedural signalling (John B Davies & Best, 1996) may mean that probing participants about alcohol-related craving may have intimated the presence of alcohol. In short, while this research methodology constitutes a significant step forward in untangling the pharmacological from the anticipated effects of alcohol, it remains to be seen whether future research methods may be able to eradicate this entirely. It should also be noted that, as with much of the laboratory-based

alcohol research, the sample was student-centric. As such, future research is recommended in order to explore how the current findings may generalise to wider populations where heavier, atypical drinking behaviour is less common (Borsari & Carey, 2001; Karam, Kypri, & Salamoun, 2007; Knight et al., 2002).

In conclusion, by using a novel naïve alcohol administration method the current study represents the first attempt to disentangle the pharmacological from the anticipated effects of alcohol on related cognitions (inhibitory control, attentional bias, craving). The findings suggest that alcohol's pharmacology compared with anticipation, is the primary driver of subsequent alcohol consumption, holding clear implications for loss-of-control over drinking and the existing 'pre-drinking' culture. Specifically, the present findings indicated that pharmacology induced the greatest changes in cognition, but importantly the associated increases in consumption were mediated by changes in craving, not inhibitory control as previously suggested. It is important to recognise the apparent additive influence of anticipation to pharmacology where craving is concerned, as such future research needs to address the nuances in craving and how they contribute to the initiation and maintenance of consumption.

Chapter 5: Continuous Theta Burst Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex Impairs Inhibitory Control and Increases Alcohol Consumption

McNeill, A., Monk, R. L., Qureshi, A. W., Makris, S., & Heim, D. (2018). Continuous Theta Burst Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex Impairs Inhibitory Control and Increases Alcohol Consumption. *Cognitive, Affective and Behavioral Neuroscience*, *18*(6), 1198–1206. https://doi.org/10.3758/s13415-018-0631-3

As noted in chapter 1, alcohol administration techniques (such as those used in chapters 3 & 4) make it difficult to investigate the specific contributions of transient cognitive changes (e.g., inhibitory control) to consumption behaviour. This is due to the complex and biphasic response to alcohol in the CNS. TMS methodologies provide researchers with the ability to isolate transient changes in inhibitory control from the global sedative effects of alcohol. This is particularly important given that the role of inhibitory control in the maintenance of alcohol consumption is not yet fully clear. The current chapter therefore utilises TMS in order to examine the hypothesis that transient changes in inhibitory control (caused by TMS to the DLPFC) are a central mechanism by which consumption maintenance is regulated.

5.1 Abstract

Previous research indicates that alcohol intoxication impairs inhibitory control and that the right dorsolateral prefrontal cortex (rDLPFC) is a functional brain region important for exercising control over thoughts and behaviour. At the same time, the extent to which changes in inhibitory control following initial intoxication mediate subsequent drinking behaviours has not been elucidated fully. Ascertaining the extent to which inhibitory control impairments drive alcohol consumption, we applied continuous theta burst transcranial magnetic stimulation (rDLPFC cTBS v control) to isolate how inhibitory control impairments (measured using the Stop-Signal task) shape *ad libitum* alcohol consumption in a pseudo taste test. Twenty participants (13 male) took part in a within-participants design; their age ranged between 18 and 27 years (M = 20.95, SD = 2.74). Results indicate that following rDLPFC cTBS participants' inhibitory control was impaired and ad libitum consumption increased. The relationship between stimulation and consumption did not appear to be mediated by inhibitory control in the present study. Overall, findings suggest that applying TMS to the rDLPFC may inhibit neural activity and increase alcohol consumption. Future research with greater power is recommended to determine the extent to which inhibitory control is the primary mechanism by which the rDLPFC exerts influence over alcohol consumption, and the degree to which other cognitive processes may also play a role.

5.2 Introduction

When talking about alcohol-related behaviours, "just going for one!" is a commonly expressed sentiment that all too frequently appears to precede heavy (albeit unplanned) drinking. According to such anecdotal wisdom, the consumption of alcohol may lessen self-control and undermine good intentions of engaging in restrained drinking. The (in)ability to control or suppress pre-ponent responses, known as inhibitory control (de Wit & Richards, 2004; de Wit, 2009; Olmstead, 2006), is increasingly being recognized in the literature as both a determinant and a consequence of alcohol consumption (De Wit 2009), as well as being implicated in other behaviours which require exerting a degree of self-control (Houben, Nederkoorn, & Jansen, 2014; Lane et al., 2004). Inhibitory control impairments have been documented in samples of alcohol dependent individuals (Goudriaan et al., 2006; Lawrence et al., 2009) and longitudinal studies suggest that inhibitory control predicts both future alcohol consumption and alcohol-related problems (Nigg et al., 2006). Concurrently, lower levels of inhibitory control also appear to be associated with heavy, hazardous and problematic drinking in non-dependent samples (Christiansen et al., 2012; Murphy & Garavan, 2011; Nederkoorn et al., 2009). As such, current evidence converges to implicate inhibitory control in the regulation of alcohol consumption.

Alcohol pre-loads (acute intoxication) have been found to result in subsequent increases in consumption (Rose & Grunsell, 2008) and to be associated with transient impairments in inhibitory control (Caswell et al., 2013; Fillmore & Rush, 2001; Rose & Duka, 2006; Weafer & Fillmore, 2008). Fluctuations in inhibitory control have been proposed to mediate the relationship between the alcohol pre-load and subsequent alcohol consumption (Field et al., 2010; Jones et al., 2013). Empirical evidence of the extent to which inhibitory control mediates the association between initial intoxication

and continued alcohol consumption, however, is mixed. Some studies find that impairments in inhibitory control correlate with subsequent consumption (Weafer & Fillmore, 2008), while others investigating this directly find no mediation (Christiansen et al., 2013). A particular research challenge is to unpack the reasons why initial alcohol consumption may inadvertently lead to continued drinking (e.g., via impulsivity or craving; Rose & Grunsell 2008). Existing paradigms frequently administer alcohol to induce impaired inhibitory control and to examine how this impacts control over subsequent alcohol consumption. However, acute alcohol intoxication is also associated with a range of changes to other cognitive and psychological processes (e.g., attentional bias and motivations to drink; Fadardi & Cox (2008)), and it has therefore been difficult to disentangle the extent to which inhibitory control is implicated in the maintenance of alcohol consumption. Also, in view of wide-reaching costs associated with excessive alcohol consumption (World Health Organization, 2014) more research is therefore required to examine this relationship, and to ascertain underlying neuropharmacological processes (see Volkow et al., 2016).

Anticipation of reward has been associated with heightened activations in the dorsolateral prefrontal cortex (DLPFC), the medial orbital frontal cortex and activation in the ventral striatum (VS) in individuals with substance use disorders (see Luijten, Schellekens, Kuehn, Machielse, & Sescousse, 2017 for a recent review). In response to alcohol consumption, *f*MRI studies point to acute decreases in the activation of neural regions associated with inhibitory control, including the DLPFC (see Bjork & Gilman, 2014). Meanwhile, Positron Emission Tomography (PET) research on healthy participants suggests that moderate doses of alcohol are associated with reductions in overall brain metabolism, although metabolic increases are observed in mesolimbic regions involved in the incentive-motivational system, including the VS and nucleus

accumbens (NAc) (Volkow et al., 2008). Thus, by examining the acute responses of the brain to alcohol, researchers have begun to illuminate the effects and drivers of alcohol intoxication, behaviour and cognition (Bjork & Gilman 2014; Volkow et al., 2008). However, methods such as *f*MRI and PET do not allow us to investigate how alcohol-related neurological changes directly influence cognitive processes and how these may, in turn, drive fluctuations in alcohol consumption.

Addressing this by enabling researchers to assess the causal links between specific regions and their functions, Transcranial Magnetic Stimulation (TMS) is a useful means of impeding particular brain areas. Existing research implicates regions of the prefrontal cortex, including the rDLPFC, in inhibitory control processes, and a recent review documents that active TMS stimulation (compared with control) to prefrontal regions including the rDLPFC is an effective means of impairing inhibitory control (Lowe et al., 2018a). While this evidence implicates rDLPFC in the inhibitory control processing, the extent to which this impacts alcohol consumption has yet to be elucidated fully.

The present study uses TMS to impede rDLPFC functioning to ascertain the extent to which inhibition impairments contribute to alcohol consumption. Specifically, in view of the preponderance of research impairing inhibitory control by acute administration alcohol (Caswell et al., 2013; Fillmore & Rush 2001; Rose & Duka 2006; Weafer & Fillmore 2012), we use TMS to assess directly the relationship between impaired inhibitory control and alcohol consumption, independent from the wider pharmacological effects of alcohol. A within-participant design was utilized to the test the hypothesis that TMS-induced impaired inhibitory control would result in increased alcohol consumption *ad libitum* compared with control stimulation, and that impaired inhibitory control would mediate this relationship.

5.3 Method

5.3.1 Participants

Twenty participants (13 male, aged between 18 and 27**,** M **=** 20.95, SD = 2.74) were recruited in response to online advertisements which sought to recruit fluent English speakers aged between 18 and 49 years who regularly use alcohol, and exceed recommended weekly drinking guidelines (14 units). Due to the risks associated with TMS, participants were also required to complete a medical screening form. Participants whose medical history indicated any neurological risk factors, syncopy, drugs active in the central nervous system (e.g., antipsychotics, antidepressants or recreational stimulants) and poor levels of sleep were excluded from the study (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Wassermann, 1998). It is worth noting that the risks associated with cTBS are minimal, with only one known case of seizure as of Rossi and colleagues (2009). Participants who had sought help concerning their drinking or had a history of alcohol dependency were also excluded. As reimbursement for their time, participants were either awarded course credit or £12. The study received ethical review and clearance from the University's Department of Psychology Research Ethics Committee.

5.3.2 Design

A counterbalanced within-participants design was implemented. The independent variable of TMS stimulation consisted of 2 levels; cTBS TMS stimulation to the rDLPFC and control stimulation consisting of cTBS at the same intensity to the Vertex. Measures of inhibitory control and subsequent drinking were taken. Approximately 6 minutes passed between cTBS and the subsequent drinking task, this is the approximate time to complete the inhibitory control task.

5.3.3 Materials

See Chapter 2: Methods for all materials including self-report measures TLFB (2.1.2), AUDIT (2.1.2) and BIS-11 (2.1.3) plus the SST (2.2.1).

5.3.4 Theta Burst Stimulation procedure

See Chapter 2: Methods for Continuous Theta Burst Stimulation (cTBS) procedure (2.4).

5.3.5 Ad libitum alcohol consumption

See Chapter 2: Methods for *ad libitum* consumption protocol (2.3.2)

5.3.6 Procedure

Participants who expressed an interest in participation were first required to complete a medical screening questionnaire to ensure they could undergo TMS, additionally affording them the opportunity to ask the researcher questions. Upon entering the laboratory, participants were required to provide informed consent and supply a Breath Alcohol Concentration (BrAC) of 0.0mg (Lion Alcolmeter 400, Lion Laboratories, Vale of Glamorgan, United Kingdom). During the first session, participants completed a battery of questionnaires including demographic information, the TLFB, AUDIT and BIS-11. Participants completed the SST prior to TMS stimulation in the first session to provide a baseline measure of SSRT. The within-participant order of conditions was counterbalanced. Participants either received cTBS or control stimulation in the first session and in the second session, which took place at least one week later, participants completed the opposite TMS condition. In both cases, participants completed the SST post stimulation, followed immediately by the bogus taste task.

5.3.7 Data Reduction and Statistical Analysis

Prior to calculating SSRT, trails where the reaction times were less than 100ms and greater than 2000ms, and those greater than three standard deviations above the participants mean were removed. SSRT was then calculated by extracting the percentage errors (failure to inhibit response on stop trials) at each of the SSDs (50 – 500ms, at 50ms intervals), then calculating an SSRT value for each SSDs based on the reaction time (RT) distribution. Overall SSRT score was calculated by averaging the SSRT values for each of the SSDs. Impaired response inhibition is demonstrated through longer SSRT values; SSRT represents an estimate of the time required to stop initiated Go response (see Band, van der Molen, & Logan, 2003). Repeated measures ANOVAs were used to analyze differences between baseline and conditions for both SSRT and GoRT, and for *ad libitum* consumption following rDLPFC and control cTBS. Within-participants mediation analysis to assess the relationship between impairments in inhibitory control and *ad libitum* consumption was implements as per Montoya and Hayes (2017), using the MEMORE macro for SPSS developed by the same authors.

5.4 Results

With regard sample characteristics, participants age and alcohol involvement descriptive statistics are comparable with previous studies investigating the effects of acute alcohol on inhibitory control (e.g., Christiansen et al., 2013; Rose & Duka, 2008) (see Table 8). Table 1 also contains descriptive statistics for the TMS protocol including the output required to stimulate the motor cortex (rMT) and the cTBS TMS intensity output.

Table 8: *Descriptive statistics of participant characteristics*

	M	*SD*
Age	20.95	2.74
TLFB (UK Units)	39.60	35.83
AUDIT	11.75	4.40
BIS Total	64.20	10.83
Attentional BIS	16.70	4.23
Motor BIS	24.75	4.64
Non-planning BIS	23.50	4.92
rMT (%)	65.90	11.07
cTBS intensity (%)	52.80	8.79

TLFB = Timeline Follow back; 14-day alcohol consumption in UK units. AUDIT = Alcohol Use Disorder Identification Test, scores >8 indicative of hazardous drinking. BIS = Barratt Impulsivity Scale. Attentional, motor and non-planning BIS are subscales of BIS. RMT = resting motor threshold. cTBS = continuous Theta Burst Stimulation.

A repeated-measures Analysis of Variance (ANOVA) was conducted to investigate the effects of stimulation on inhibitory control as measured by stop-signal reaction time (SSRT). A main effect of stimulation was found ($F(2, 36) = 16.70$, $p < .001$, $\eta_p^2 = .47$). Planned comparisons revealed that while there was a significant

increase in SSRT found post active stimulation (M = 249.97, SD = 31.40; F(1, 18) = 18.58, p <.001, η_p^2 = .51), there was no significant difference between baseline SSRT (M = 217.83, SD = 19.41) and post control stimulation (M = 217.64, SD = 15.48; F(1, 18) = .003, p = .96, η_p^2 =.00). This suggests the active TBS to the rDLPFC resulted in significant impairments to inhibitory control (see Figure 5). A further repeated-measures ANOVA was undertaken to assess if stimulation resulted in changes in go reaction times (RT), revealing no significant differences (F(2, 34) = .41, p = .67, η_p^2 = .02; see Figure 6).

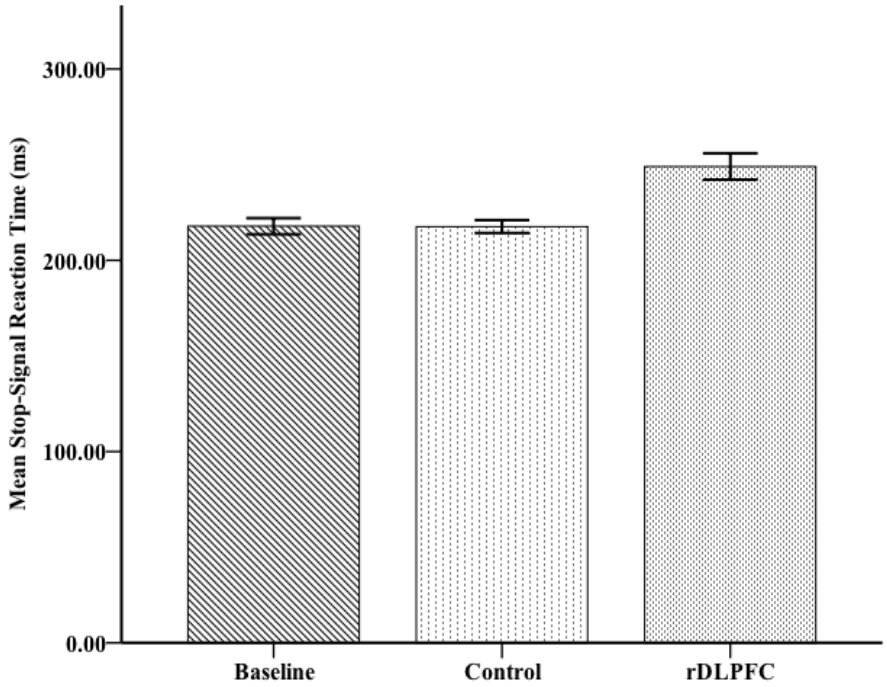

Figure 5: Mean Stop-Signal Reaction Times (SSRT) in milliseconds and standard error bars for baseline, and following continuous theta burst transcranial magnetic stimulation to the rDLFPC and control.

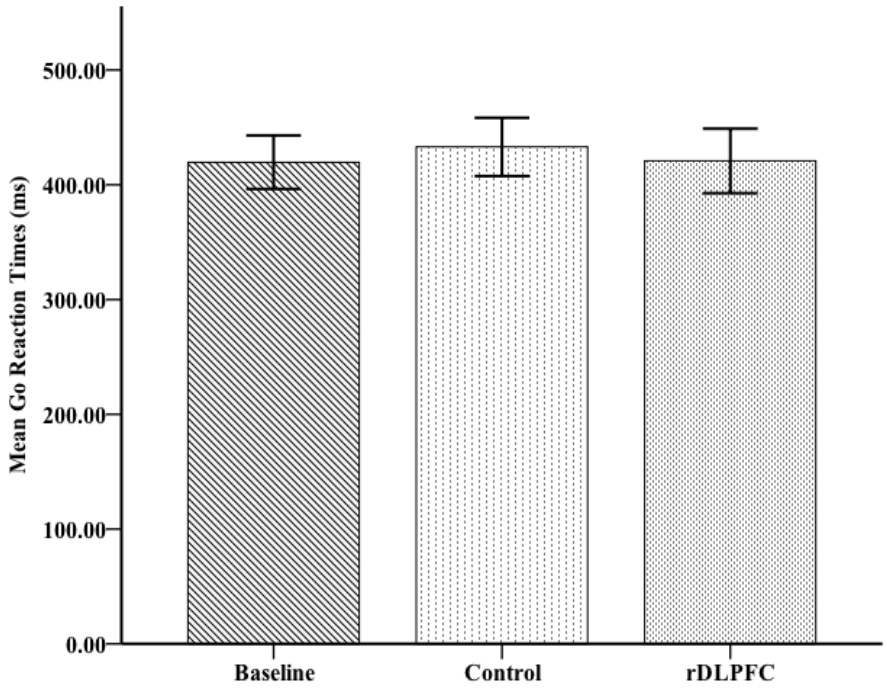

Figure 6: Mean go reaction times (GoRT) in milliseconds and standard error bars for baseline, and following continuous theta burst transcranial magnetic stimulation to the rDLFPC and control.

A final repeated-measures ANOVA was used to determine whether there was an effect of cTBS stimulation on *ad libitum* alcohol consumption. Results showed that participants consumed significantly more beer following active stimulation (M = 525.70, SD = 313.29) compared to post control stimulation (M = 293.40, SD = 289.56; $F(1, 19) = 19.22$, $p < .001$, $\eta_p^2 = .50$; see Figure 7).

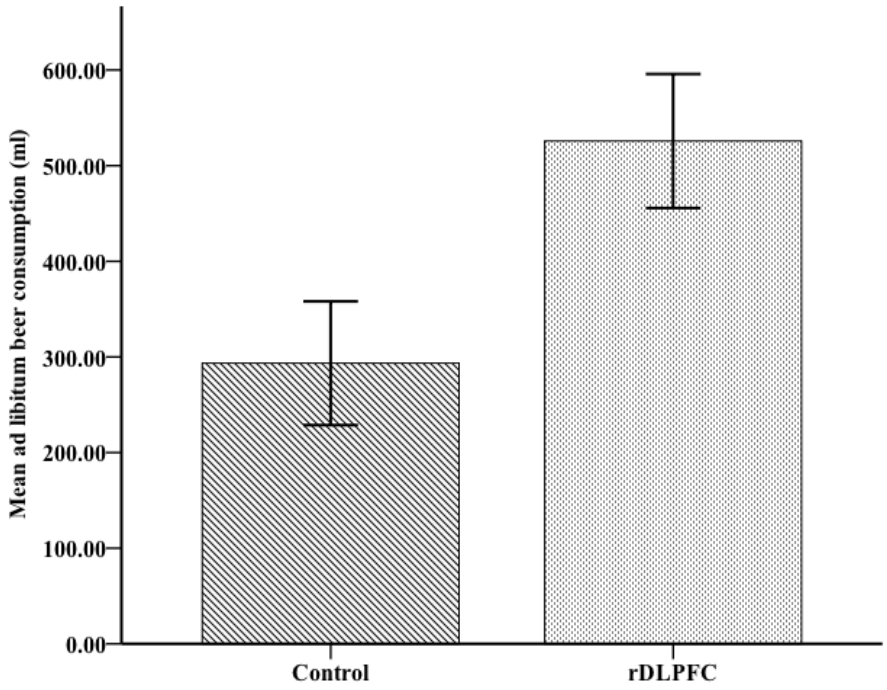

Figure 7: Mean and standard error ad libitum beer consumption following control and rDLPFC stimulation.

A within-participants mediation analysis was undertaken using the MEMORE macro for IBM SPSS (Montoya & Hayes, 2017) to test whether impairments in inhibitory control mediate changes in *ad libitum* alcohol consumption (see Figure 4). Overall, the analysis showed no significant mediated pathway. The analysis revealed a significant direct effect (*c*) of cTBS on *ad libitum* beer consumption (c_1 = 232.30, $t(19)$ = 4.38, $p < .001$, 95% CI [121.38, 343.22]). A significant pathway *a* was also found (a_1 = -31.43, $t(19)$ = -4.38, $p < .001$, 95% CI [-46.45, -16.42]), confirming the effect of stimulation on inhibitory control. However, the *b* pathway was insignificant (b_1 = 2.08, $t(19)$ = .95, p = .36, 95% CI[-2.57, 6.75]). Furthermore, a significant indirect pathway (*c'*) was found (*c'* = 297.96, $t(19)$ = 3.38, $p < .01$, 95% CI [112.13, 483.79]). However, as the *b* pathway in the current model was insignificant, the indication of the current findings is that impairments to inhibitory control do not mediate subsequent *ad libitum* consumption. Post-hoc Monte Carlo Simulation power analysis, running 1000 simulations, revealed that to achieve a power of .80 an *N* of 200 is required.

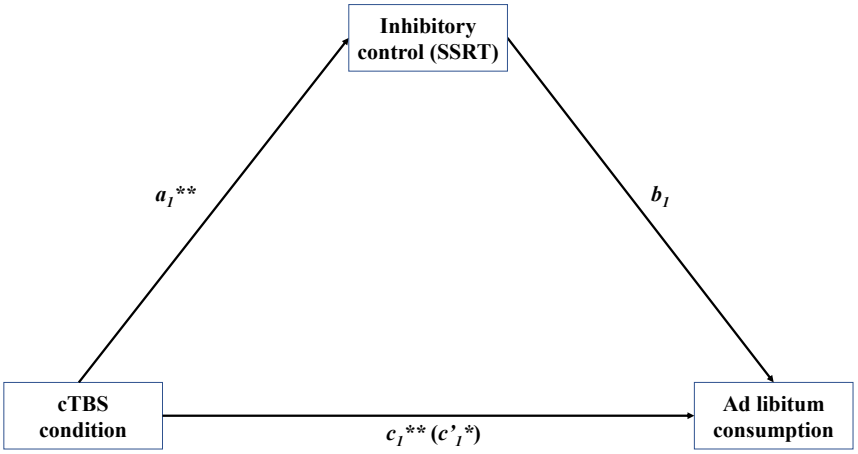

Figure 8: Path-analytic mediation model assessing whether impairments in inhibitory control mediate the relationship between continuous theta burst transcranial magnetic stimulation (cTBS) and *ad libitum* consumption. Significant pathways are denoted by *$p < .01$ **$p < .001$

5.5 Discussion

Using TMS to impede the functioning of the prefrontal cortex, the current study tested the hypothesis that inhibitory control impairments mediate the relationship between cTBS to the rDLPFC and alcohol consumption. Results indicate that active (relative to control) stimulation impaired inhibitory control and increased alcohol consumption. This suggests that the rDLPFC is important in the regulation and maintenance of alcohol consumption. However, contrary to previous suggestions (e.g., Field et al., 2010; Jones et al., 2013), the current study did not yield support for the notion that impairments in inhibitory control mediate the relationship between initial and continued alcohol consumption. Our findings therefore indicate that while the rDLPFC appears to be implicated in the maintenance of alcohol consumption and impaired inhibitory control, other executive functions and psychological processes may also play a role in elevated alcohol consumption following initial intoxication.

A strength of the current study was that we were able to instigate behavioural change in terms of actual alcohol consumption by transiently impairing the rDLPFC using TMS. Previous research investigating the extent to which alcohol undermines people's ability to exert control over behaviours has tended to rely on administering alcohol to individuals as the means of impeding behavioural control (e.g., Caswell et al., 2013; Fillmore & Rush 2001; Rose & Duka 2006; Weafer and Fillmore 2012). This work has been important in documenting the effects of acute intoxication on attentional bias (e.g., Jessica Weafer & Fillmore, 2013), executive functioning (e.g., Christiansen et al., 2013) and risk-taking (e.g., Lane et al., 2004). However, in view of findings indicating that acute alcohol exposure impacts wider executive and psychological functions (see Field et al., 2010), to date it has been difficult to disentangle the relative contribution of inhibitory control to the continuation of alcohol consumption following

initial intoxication. By using TMS to isolate inhibitory control impairments at the neurological level from pharmacological effects of alcohol, our study implicates temporally induced changes to the rDLPFC and inhibitory control in heightened alcohol consumption.

Our findings suggest that there was an association between stimulation of rDLPFC and impaired control and alcohol consumption, respectively. This provides support for research implicating the DLPFC in alcohol consumption (Volkow et al., 2008) as well as appetitive behaviours (see Jansen et al., 2013; Lowe, Vincent, & Hall, 2017) more generally. Using, PET, Volkow et al. (2008), for example, found reduced activity in prefrontal regions following alcohol consumption. Our findings add to this body of work by causally implicating activity in prefrontal regions with alcohol consumption behaviours. In conjunction with previous work, our findings suggest that applying TMS to the rDLPFC may inhibit neural activity and increase alcohol consumption. In light of research suggesting that left prefrontal regions are also associated with impairments in inhibitory control (Lowe et al., 2018) and appetitive craving (Lowe, Hall, & Staines, 2014), future research should also examine the role of the lDPFC in alcohol consumption.

However, the current study found no direct effect of inhibitory control on alcohol consumption, and findings indicate that the association between cTBS of the rDLPFC and consumption did not appear to be mediated by impairments in inhibitory control. One explanation of this null finding is that inhibitory control may not be the central route through which rDLPFC exerts influence over alcohol consumption, and that other mechanisms (e.g., craving; Rose & Grunsell, 2008 or motivation; Rose et al., 2010) might play a more determinant role. Whilst not acting as a direct mediator, our

findings may therefore indicate that inhibitory control acts via a different route, possibly as a 'brake' on other cognitive and psychological mechanisms. For example, inhibitory control may moderate processes such as automatic approach tendencies (e.g., Reinout W Wiers et al., 2007) and implicit associations (e.g., Houben & Wiers, 2008). Nevertheless, this interpretation is merely speculative and future research with greater power is recommended to determine the extent to which inhibitory control is the primary mechanism by which the rDLPFC exerts influence over alcohol consumption, and the degree to which other cognitive processes may play a role.

Several limitations need to be borne in mind when considering current findings. First, the within-participants design limited our ability to analyse moderation although the sample size was in line with similar work (e.g., Lowe et al., 2018). Second, to prevent procedural signalling (Davies & Best, 1996) during the bogus taste task, we did not take measures of subjective craving or motivations to drink. This precludes our ability to assess the extent to which inhibitory control may exert a moderating influence. Third, the current study delivered SST shortly after stimulation to ensure that both the SST and the bogus taste task were conducted within appropriate time frames for effects of cTBS to be observed (~35-40 minutes). However, it is worth noting the findings from Huang et al. (2005) which suggest that the peak effects of 600 pulse cTBS occur at around 14-40 minutes post stimulation. Considering these previous findings, the null findings with regards to mediation in the current study warrant future investigations with longer delays prior to the delivery of cognitive tasks if procedural/technological advances make this feasible. Fourth, the current research used a student sample. University students are immersed in a heavy drinking culture (Borsari & Carey, 2001; Karam, Kypri, & Salamoun, 2007; Knight et al., 2002) and it is possible that findings may not generalize to other populations. Finally, the small sample size of the current

study may be incompatible with detecting a small mediational effect, with post hoc power analysis suggesting that a sample of 200 may be required to detect an effect. However, it is worth noting that to our knowledge to date no such study testing the relationship between fluctuations in inhibitory control and subsequent alcohol consumption meet these power analysis requirements (e.g., Field & Jones, 2017 $N = 81$; Weafer & Fillmore, 2008 $N = 26$) and the current sample size is comparative with other TMS studies (Lowe et al., 2018: N's = 7-40). In view of the amount of time required to conduct this kind of research it may prudent for researchers to collaborate via multi-site studies to address power concerns (Button et al., 2013).

In conclusion, the current study represents the first attempt to apply TMS to the rDLPFC to examine the resulting effect on actual alcohol consumption. Results point to the important role of this brain structure in shaping drinking behaviour as well as driving inhibitory control. However, inhibitory control was not found to mediate the observed association between stimulation of the rDLPFC and alcohol consumption, although future investigations with more highly powered designs could fruitfully revisit this hypothesis. Overall, our findings highlight that further research appears warranted to unpick the nuanced ways in which the rDLPFC and inhibitory control shape behaviours which require the exertion of a degree of self-control.

Chapter 6: Elevated ad libitum alcohol consumption following continuous theta burst stimulation to the left-dorsolateral prefrontal cortex is partially mediated by changes in craving

McNeill, A.M., Monk, R. L., Qureshi, A. W., Makris, S., Cazzato, V., & Heim, D. Elevated ad libitum alcohol consumption following continuous theta burst stimulation to the left-dorsolateral prefrontal cortex is partially mediated by changes in craving (Under Review)

Chapter 5 did not yield support for the hypothesis that transient impairments of inhibitory acts as a central mechanism by which patterns of drinking are maintaned. However, while there was no evdence of a direct causal link between inhibitory control impairments and subsequent drinking, they did arise somewhat in parallel. This may suggest that inhibitory control exerts influence over drinking in a indirect manner or by interacting with other processes (e.g., AB, craving). Our current understanding of such processes interact to influence drinking behaviour is limited, therefore the current study utilised TMS to isolate changes in specific processes (inhibitory control, AB, craving) to examine how they influenced each other and consumption behaviour.

6.1 Abstract

Previous research indicates that following alcohol intoxication, activity in prefrontal cortices is reduced, linking to changes in associated cognitive processes, such as inhibitory control, attentional bias (AB) and craving. While these changes have been implicated in alcohol consumption behaviour, it has yet to be fully illuminated how these frontal regions and cognitive processes interact to govern alcohol consumption behaviour. The current pre-registered study applied continuous theta burst transcranial magnetic stimulation (cTBS) to directly examine these relationships while removing the wider pharmacological effects of alcohol. A mixed, vertex-controlled design was implemented, with real cTBS stimulation to right and left dorsolateral prefrontal cortex (DLPFC), and the medial orbital frontal cortex (mOFC), with measures of inhibitory control, AB and craving taken both pre- and post-stimulation. *Ad libitum* consumption was measured using a bogus taste task. Results suggest that rDLPFC stimulation impaired inhibitory control but did not significantly increase *ad libitum* consumption. However, lDLPFC stimulation heightened craving and increased consumption, with findings indicating that changes in craving partially mediated the relationship between cTBS stimulation of prefrontal regions and *ad libitum* consumption. Medial OFC stimulation and AB findings were inconclusive. Overall, results implicate the left DLPFC in the regulation of craving, which appears to be a prepotent cognitive mechanism by which alcohol consumption is driven and maintained.

6.2 Introduction

Numerous humorous memes circulating on the internet poke fun at the notion of 'just going for one drink' by documenting how planned moderate consumption of alcohol can, at times, escalate. Theoretically, alcohol-related cognitions such as inhibitory control (Weafer & Fillmore, 2008), attentional bias (AB; see Field & Cox, 2008) and craving (Rose & Grunsell, 2008) have been identified as influences on people's ability to curtail their alcohol consumption. These accounts have tended to place AB (e.g., Franken, 2003; Tiffany, 1990; Tiffany & Conklin, 2000) at the heart of explanations of addiction and empirical work has examined how AB affects inhibitory control (see Leung et al., 2017) and craving (see Field, Munafò, & Franken, 2009). However, empirical research and theoretical contributions to date have painted a mixed picture as to how these cognitive mechanisms interact. On the one hand, research indicates that impairments of inhibitory control heighten AB, while, on the other, studies also suggest that drug-related AB impairs inhibitory control (see Leung et al., 2017). These accounts further point to a link between AB and craving, with elevated craving driving increases in AB and vice versa (Franken, 2003; Tiffany, 1990). Research has, however, tended to rely on alcohol administration techniques which make it difficult to unpick the relative contributions of each of these processes, and this also limits our ability to understand how their potential interactions drive consumption. Specifically, alcohol has been shown to exert widespread neuropsychopharmacological effects, such that whilst low doses activate the dopaminergic 'reward' system in the dorsal striatum, higher doses appear to inhibit activity in prefrontal brain regions associated with executive functioning (see Volkow, Koob, & McLellan, 2016). Research is therefore required to isolate cognitive changes from those wider effects of alcohol in order to ascertain their respective contributions to consumptive behaviours.

The literature documents a close relationship between inhibitory control and AB with a recent meta-analysis finding a small but significant positive relationship between inhibitory control and attentional processes (Leung et al., 2017). However, the direction of causation is in need of further elucidation. Previous findings suggest that alcohol impairs the ability to exert control over responses to alcohol-related stimuli (Adams, Ataya, Attwood, & Munafò, 2013), while others find that the presence of alcohol-related stimuli can be associated with in higher levels of inhibitory control impairments (e.g., Monk, Qureshi, Pennington, & Hamlin, 2017) and that elevated levels of AB and inhibitory control impairments predict consumption (Roberts, Miller, Weafer, & Fillmore, 2014). In short, it appears that attentional and inhibitory processes are interwoven, however, the relationship appears to be complex and multifaceted. It is also possible that the association between inhibitory control and AB may hinge on salience, whereby relevant cues may 'grab' attention and, in turn, result in increased inhibitory control impairments which can also result in a diminished ability to exert control over responses to salient stimuli (Wilcockson & Pothos, 2015). It therefore seems plausible that there may be a cyclical relationship between inhibitory control and AB in how these processes govern appetitive behaviours.

Research has also examined the extent to which fluctuations in inhibitory control may mediate the association between the initial exposure to alcohol and successive alcohol consumption (Field, Wiers, Christiansen, Fillmore, & Verster, 2010; Jones, Christiansen, Nederkoorn, Houben, & Field, 2013). In partial support of this hypothesis, Weafer and Fillmore (2008) found a correlation between inhibitory control impairments and drinking in a subsequent session, although others have found no direct association between transient changes in inhibitory control and successive consumption in the laboratory (e.g., Christiansen, Rose, Cole, & Field, 2013). Moreover, in a recent

Ecological Momentary Assessment study, daily fluctuations in inhibitory control were associated of daily consumption (more so than prior planned consumption), while daily craving and implementation intentions appeared to be better predictors of drinking patterns throughout the period of study (Jones, Tiplady, Houben, Nederkoorn, & Field, 2018). Taken together, this body of work suggests that fluctuations in inhibitory control may not be as central in the maintenance of drinking behaviour as previously suggested. Instead, the effect of inhibitory control may be exerted through its interaction with AB and/or craving. In order to assess this assertion, research aided by methodological approaches that can isolate respective cognitive processes from alcohol's wider pharmacological effects is required.

The complex relationship between inhibitory control, AB and craving may be explained at the neural level, with research implicating adjacent prefrontal brain regions in both impulse control and salience attribution (see Volkow, Koob & McLellan, 2016). The Orbital Frontal Cortex (OFC), including the medial OFC (mOFC), has been shown to be related to salience attribution of potentially rewarding stimuli, including drugs and food (Volkow, Wang, Tomasi, & Baler, 2013). Furthermore, AB for alcohol-related stimuli is associated with increased motivations to drink (e.g., Fadardi & Cox, 2008), heightened craving for food (Wang et al., 2004) and other drugs (Blum, Liu, Shriner, & S. Gold, 2012; Volkow et al., 2013) and has also been linked with increases in OFC activation (Volkow et al., 2008). The DLPFCs have also been widely implicated in the maintenance and regulation of drug seeking behaviour and particularly in wider substance-related executive functioning (see Zilverstand, Huang, Alia-Klein, & Goldstein, 2018). Specifically, DLPFCs have been associated with various components of inhibitory control (e.g., Robbins, Gillan, Smith, de Wit, & Ersche, 2012) and a moderating role has been suggested with regards to the DLPFCs in substance-related

craving (see George & Koob, 2013). Nevertheless, as research has increasingly documented the neurological underpinnings of these processes, traditional imaging techniques have been hampered by their ability to elucidate causal links. Deploying neuromodulation techniques is therefore be required to examine the role of the DLPFCs in the cognitive mechanisms implicated in initiating and sustaining substance-use behaviours.

Transcranial Magnetic Stimulation (TMS) has therefore increasingly been utilised as a tool to examine associated links between focal brain regions and specific cognitive processes and behaviours. For instance, research has investigated the role of prefrontal cortices in inhibitory control processes (see Lowe, Manocchio, Safati, & Hall, 2018).TMS to the right Dorsolateral Prefrontal Cortex (rDLPFC) has, for example, been found to impair inhibitory control and to increase *ad libitum* alcohol consumption, although transient changes in inhibitory control do not appear to be directly associated with consumption (McNeill, Monk, Qureshi, Makris, & Heim, 2018). Similarly, TMS of the left-DLPFC was shown to induce inhibitory control impairment (as measured by the Stroop task), as well as increase food-related craving and consumption (Lowe, Hall, & Staines, 2014), suggesting that lDLPFC is potentially important in appetitive regulation. More recently, research using rTMS indicates that lDLPFC may play a moderating role in craving, by reducing activation in the nucleus accumbens and mOFC (Li et al., 2017). While not examined in alcohol behaviours to date, Li and colleagues found that activation stimulation (relative to sham) in smokers resulted in lower levels of cue-induced craving, supplying evidence of a complex interplay between prefrontal regions in the regulation of consumption behaviours.

This pre-registered study (osf.io/hjy4n) applied a randomised mixed design to transiently inhibit the neural structures associated with AB, inhibitory control and craving (DLPFCs, mOFC) to illuminate how these processes interact and drive consumption. In accordance with previous findings (McNeill et al., 2018), it was hypothesised that stimulation to the DLPFCs will impair inhibitory control, while stimulation of the mOFC would significantly reduce AB for alcohol-related cues in a manner akin to observations in smokers (Li et al., 2017). As previously indicated (e.g., Adams et al., 2013; Monk et al., 2017), it was expected that inhibitory control impairments will, in turn, increase alcohol-related AB. Furthermore, stimulation to the lDLPFC was expected to result in increased alcohol-related craving and to increase AB, in a manner akin to observations of wider appetitive behaviours (see Lowe et al., 2018). Finally, heightened *ad libitum* alcohol consumption was hypothesised to be observed post right- and left-DLPFC stimulation, but not following mOFC, in accordance with appetite research (Lowe et al., 2018).

6.3 Methods

6.3.1 Participants

Eighty participants aged 18 to 23 years (M_{age}= 20.38, *SD* = 2.79, 44 male) were recruited via digital advertising within a University in the United Kingdom. To be eligible, participants were required to be aged between 18 and 49 years, regularly exceed the 14 UK units weekly recommendation and speak fluent English. Prior to taking part participants underwent medical screening due to the risks associated with TMS, although these risks are considered to be very minimal if screened correctly (Rossi et al., 2009). Participants were prohibited from taking part in instances where medical screening indicated any neurological risk factors, syncopy, drugs active in the central nervous system (e.g., antipsychotics, antidepressants or recreational stimulants) and low levels of sleep of the previous night (Rossi et al., 2009; Wassermann, 1998). Furthermore, participants who specified a personal or family history of problematic alcohol use were also excluded. Participants either received course credit or £10 as a means of reimbursing them for their time. The study received ethical review and clearance from the University's Department of Psychology Research Ethics Committee

6.3.2 Design

A mixed design was employed, the between participants independent variable was the brain region stimulated. Participants were randomly allocated to 1 of 4 stimualtion region conditions; rDLPFC, lDLPFC, mOFC or Vertex. Measures of subjective craving, inhibitory control and attentional bias were taken both pre- and post-stimulation, followed by an *ad libitum* consumption task.

6.3.3 Materials

See Chapter 2: Methods for all materials including self-report measures TLFB (2.1.2), AUDIT (2.1.2), BIS-11 (2.1.3), DAQ (2.1.4) and mood scales (2.1.5), plus cognitive tasks SST (2.2.1) and Visual Probe Task (2.2.3).

Gaze Contingency Task (Wilcockson & Pothos, 2015). The gaze contingency task was programmed using Experimenter Builder software and delivered on an EyeLink Desktop 1000 eye-tracker, to measure inhibitory control for AB. Here, each trial presented a fixation target on the screen. Participants are instructed to focus their attention on the fixation target. Once participants have attended to the fixation target for a fixed interval of 1 second, a distractor stimulus will appear (only one per trial), either an alcohol-related or neutral image. If the participant looks at the distractor stimulus (i.e. if the participant's gaze was to leave the fixation target boundary), then the distractor stimulus will disappear instantly. Therefore, participants are unable to fixate upon the distractor stimuli. The distractor stimuli will only reappear once participants fixate on the fixation target again for 10 ms (i.e., less than one frame on a 60 Hz monitor). The fixation target will be displayed for 5s in total, so the maximum duration for which a distractor stimulus will be displayed on the screen is 4s. 'Break frequency' - the number of times that participants attended peripherally presented stimuli - will be measured, producing a DV that is a direct measure of the level of distraction created by peripheral stimuli of different types.

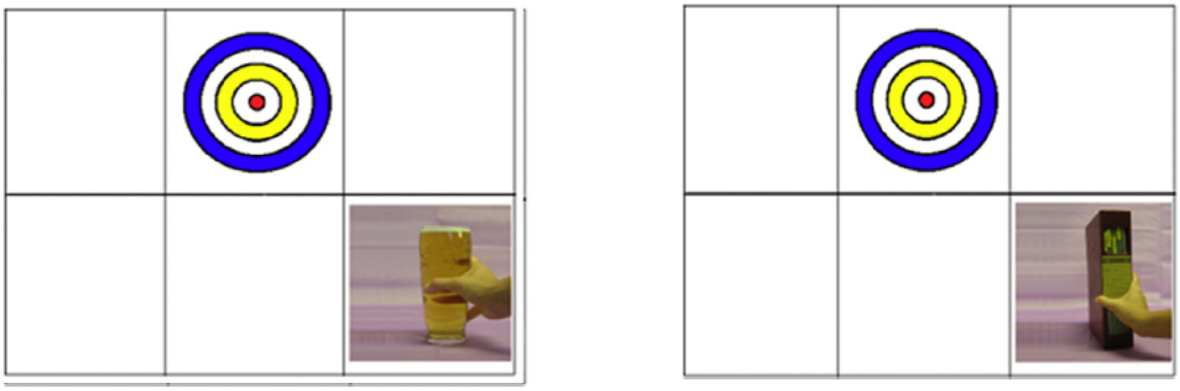

Figure 9: Taken from Wilcockson & Pothos (2015) Example of the presentation of alcohol-related (left) and neutral stimuli (right).

6.3.4 Theta Burst stimulation procedure

See Chapter 2: Methods for Continuous Theta Burst Stimulation (cTBS) procedure (2.4)

6.3.5 Ad libitum alcohol consumption

See Chapter 2: Methods for *ad libitum* protocol (2.3.2).

6.3.6 Procedure

As per ethical and risk assessment guidelines, participants interested in partaking in the study had to complete medical screening a minimum of 24 hour prior to any arranged session. This gave them opportunity to consult friends, family or a health professional, or ask any questions of the researcher. Experimental sessions took place in University laboratories between 12 and 6pm. Before the study session commenced, participants were required to provide a breathalyser reading of .00mg/l (Lion Alcolmeter 400, Lion Laboratories, Vale of Glamorgan, United Kingdom), confirm they had not consumed excessive caffeine and had adequate sleep the night previous. A battery of questionnaires was then completed (TLFB, AUDIT, BIS-11, DAQ, mood scale), followed by baseline SST and VPT. Participants were then randomly allocated to a stimulation condition and received cTBS to associated brain region according to the protocol. Once the cTBS was completed participants repeated the DAQ, mood scale, SST and VPT in a counterbalanced order, taking approximately 15 minutes. Finally, participants completed the bogus taste task and were fully debriefed on completion.

6.4 Results

Demographics and baseline measures

A MANOVA was performed to assess if any differences in baseline measures (TLFB, AUDIT, BIS and rMT) between conditions were present. Findings indicated that no significant differences between conditions *Wilks' Lambda* = .72, $F(12, 199.16) = 1.63$, $p = .07$, $\eta_p^2 = .10$, as such none of these measures were taken forward into the main analysis as covariates. See Table 9 for means and standard deviations.

Table 9: *Means and Standard Deviations for demographics and baseline measures*

	Mean	**SD**
Age	20.38	2.79
AUDIT	9.51	4.44
TLFB	29.41	28.90
BIS	58.19	11.48
rMT (%)	60.85	10.85

AUDIT = Alcohol Use Disorder Identification Test, TLFB = Timeline Follow Back, BIS = Barratt Impulsivity Scale and rMT = Resting Motor Threshold

Subjective mood ratings

The influence of stimulation on mood ratings was assessed using two (one for positive and one for negative mood ratings, 2 (time; pre- and post-stimulation) x 4 (condition; rDLPFC, lDLPFC, mOFC and Vertex) mixed ANOVAs. No effect of time $F(1, 76) = .50$, $p = .48$, $\eta_p^2 = .007$ or time x condition interaction $F(3, 76) = 1.92$, $p = .13$, $\eta_p^2 = .07$ was observed for positive mood ratings. Neither was there an effect of time $F(1, 76) = .13$, $p = .72$, $\eta_p^2 = .002$, or time x condition interaction $F(3, 76) = 1.05$, $p = .38$, $\eta_p^2 = .04$ for negative mood state ratings. This indicates that stimulation does not appear to alter

the mood of participants, eliminating mood as potential explanation for changes in cognitive performance and *ad libitum* consumption

Inhibitory Control

A 2 x 4 mixed ANOVA was undertaken to assess the effects of stimulation on SSRT, with time as the with participants variable (pre- and post-SSRT) and stimulation condition as the between variable (rDLPFC, lDLPFC, mOFC and Vertex). There was a significant difference between pre- and post-SSRT score $F(1, 76) = 24.36$, $p < .001$, $\eta_p^2 = .24$. The ANOVA also revealed a significant time x condition interaction $F(3, 76) = 18.11$, $p < .001$, $\eta_p^2 = .42$. Bonferroni corrected pairwise comparisons indicated that SSRT scores significantly increased following rDLPFC ($p < .001$) and lDLPFC ($p < .01$), demonstrating inhibitory control impairments. No significant differences were revealed between pre- and post-SSRT scores for any other condition (all p's > .11). For means and standard deviations see Table 10.

Table 10: *Means and standard deviations for Pre- and Post- SSRT scores by condition*

	Pre		**Post**	
	Mean	**SD**	**Mean**	**SD**
rDLPFC	223.05	20.42	291.57	30.16
lDLPFC	230.62	24.17	257.19	51.74
mOFC	239.27	41.63	225.75	29.25
Vertex	226.79	28.22	228.38	29.48
Total	229.93	29.76	250.72	43.32

Craving

A 2 (time; pre- vs post-stimulation) x 4 (condition; rDLPFC, lDLPFC, mOFC and Vertex) mixed ANOVA was used to examine the relationship be modulation of prefrontal regions and alcohol-related craving. There was a significant effect of time $F(1, 76) = 12.83$, $p < .01$, $\eta_p^2 = .14$, indicating an overall increase in craving following stimulation. More pertinently, a significant time x stimulation condition was detected $F(3, 76) = 9.57$, $p < .001$, $\eta_p^2 = .27$, with Bonferroni corrected pairwise comparisons indicating that craving significantly increased from baseline following stimulation to the lDLPFC ($p < .001$). Craving did not increase following stimulation to any other brain region (all *p's* > .23). For means and standard deviations see Table 11.

Table 11: *Means and standard deviations for Pre- and Post- Desires for Alcohol Questionnaire scores by condition*

	Pre		**Post**	
	Mean	**SD**	**Mean**	**SD**
rDLPFC	37.90	7.83	39.75	12.85
lDLPFC	37.95	8.51	47.90	10.45
mOFC	39.70	10.44	41.11	9.36
Vertex	36.58	8.92	34.77	9.94
Total	38.01	8.88	40.88	12.54

Attentional Bias

For greater clarity and ease of interpretation a single value was calculated for pre- and post-AB, subtracting the values for neutral dwell time from alcohol cue dwell time (see Weafer & Fillmore, 2013). A 2 (time; pre- vs post-stimulation) x 4 (condition; rDLPFC, lDLPFC, mOFC and Vertex) mixed ANOVA was used to examine the relationship

between modulation of prefrontal regions and AB. There was a significant time x condition interaction, $F(3, 76) = 3.98$, $p < .025$, $\eta_p^2 = .14$. While Bonferroni corrected pairwise comparisons revealed that there was a significant decrease in AB following stimulation to the mOFC ($p < .001$), there was no other significant changes in AB for other stimulation conditions (all *p's* > .41). This suggests that stimulation to the mOFC impairs the saliency processing of alcohol-related cues, resulting in the diminishment of AB. See figure 10 for means and standard errors.

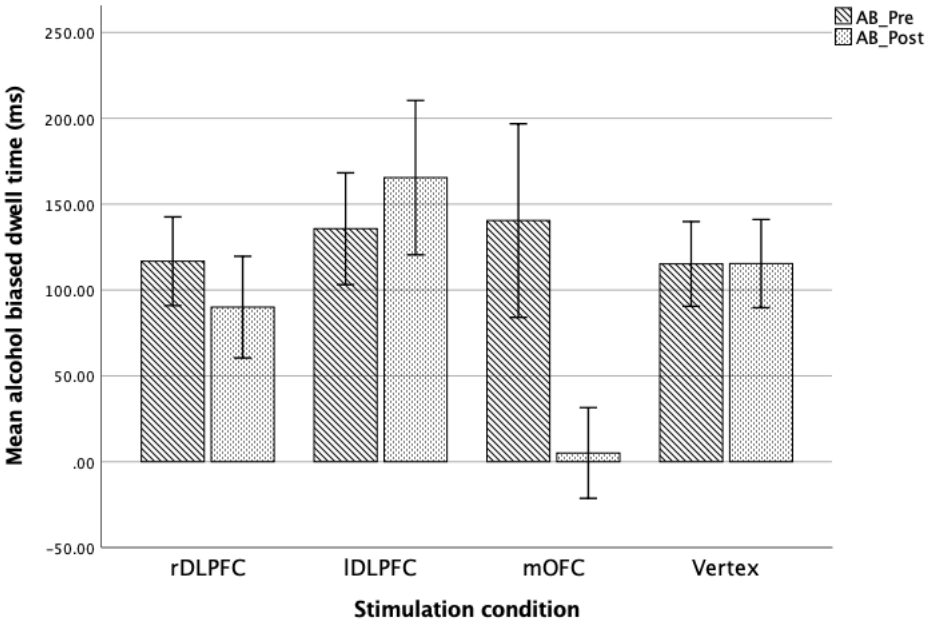

Figure 10: Means and standard errors for attentional bias dwell time, pre- and post-stimulation, following each stimulation condition

Gaze Contingency Task

A series of 2 (cue; alcohol vs neutral) x 2 (time; pre- vs post- stimulation) x 4 (condition; rDLPFC, lDLPFC, mOFC and Vertex) mixed ANOVAs were used to assess the effects of stimulation on inhibitory control for AB. Overall 'break frequency' for each cue type indicated no effect of cue type, time or condition interactions (all *p's* > .07). Previous research has found that distractor stimuli further away from the fixation target significantly increases 'break frequency' rate (Qureshi, Monk, Pennington, Wilcockson & Heim, 2019). Hence, further two further ANOVAs were used to assess

'near' and 'far' stimuli. Findings for 'near' were the same as overall, indicating no significant effects (all *p's* > .05). However, for 'far' there was significant effect of cue x time interaction $F(1, 76) = 6.13$, $p < .025$, $\eta_p^2 = .08$, however, this was significantly greater for neutral compared to alcohol-related stimuli. No other significant effects or interactions were observed (all $p > .21$).

Ad libitum consumption

A univariate ANOVA was used to evaluate the influence of stimulation condition on *ad libitum* consumption, demonstrating a significant effect $F(3, 76) = 9.35$, $p < .001$, $\eta_p^2 = .27$. Bonferroni corrected pairwise comparisons revealed that *ad libitum* consumption was considerably greater following stimulation to the lDLPFC compared with mOFC ($p < .001$) and vertex ($p < .001$), and consumption post rDLPFC compared with vertex was significantly higher ($p < .05$). No other comparisons were significant (all *p's* > .08). See figure 11 for means and standard errors.

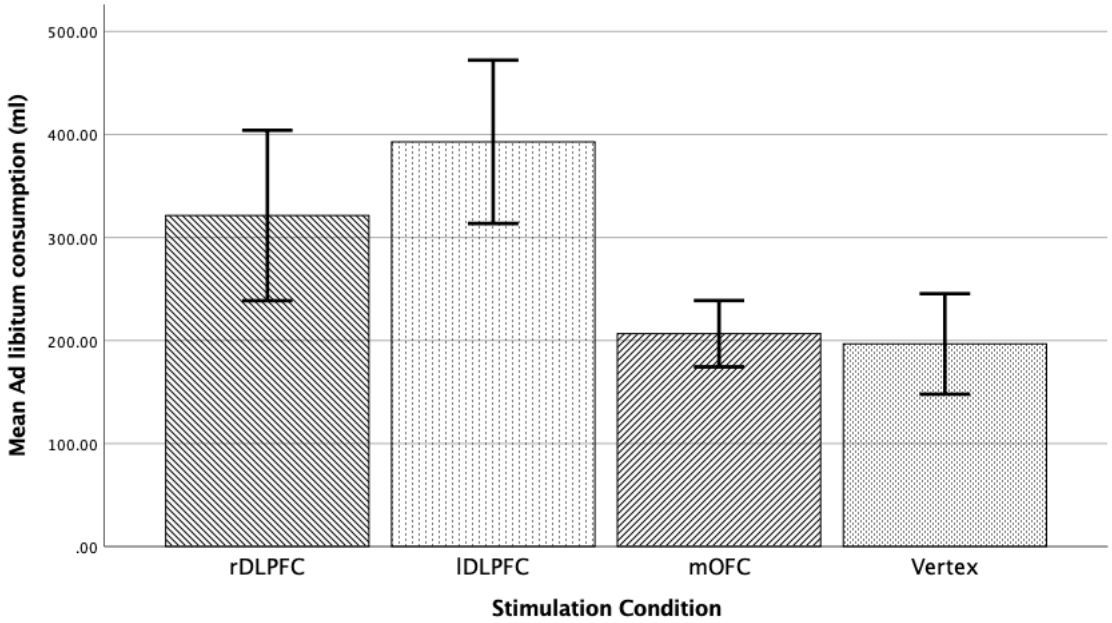

Figure 11: Means and standard errors for ad libitum alcohol consumption following each stimulation condition

Mediation Analyses

A path analytic mediation model was undertaken using the PROCESS 3.0 macro for SPSS to assess whether impairments in inhibitory control mediate the relationship between cTBS condition and *ad libitum* consumption. Firstly, a variable representing impairments of inhibitory control was computed by subtracting the pre-stimulation SSRT value from the post-stimulation SSRT values, with greater SSRT change values indicating greater impairments of inhibitory control. Firstly, there was a significant direct effect of stimulation condition on *ad libitum* consumption (c_1 pathway) $F(1, 78) = 13.65$, $p < .001$, $R^2 = .15$, and the model also indicated stimulation condition as a significant predictor of SSRT change (a_1 pathway) $F(1, 78) = 35.62$, $p < .001$, $R^2 = .31$. Conversely, SSRT change did not predict *ad libitum* consumption (b_1 pathway) $t(2) = .52$, $p = .60$, $SE = .43$. However, the overall model predicting *ad libitum* consumption was significant $F(2, 77) = 6.90$, $p < .01$, $R^2 = .15$, due stimulation condition continuing to predict *ad libitum* consumption (c'_1 pathway) $t(2) = 3.40$, $p < .01$, $SE = 18.38$. This, therefore, suggests that inhibitory control impairments do not mediate subsequent alcohol consumption. See Figure 12 for path analytic model.

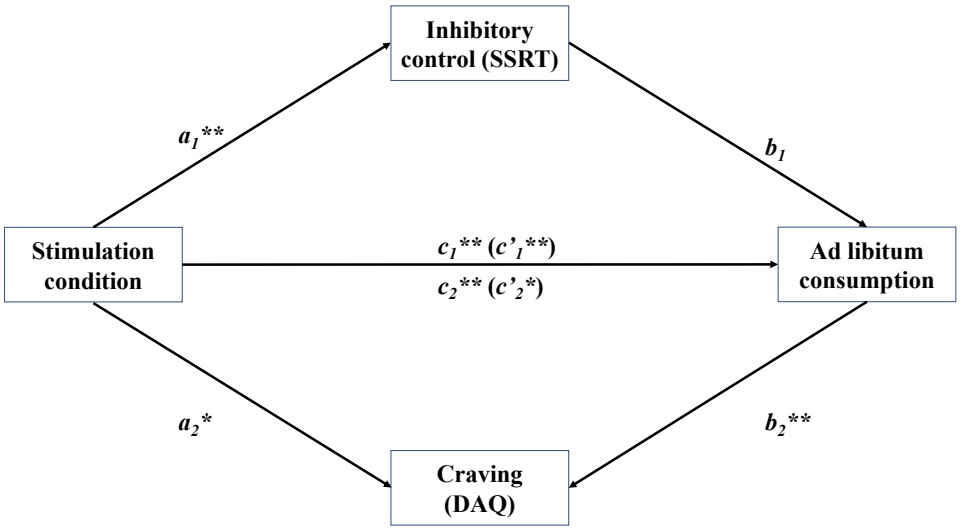

Figure 12: Path analytic model assessing impairments in inhibitory control and alcohol-related craving as mediators between stimulation condition and ad libitum consumption. *$p < .05$ **$p < .01$

The path analytic mediation model investigating craving as a mediator between stimulation and *ad libitum* consumption, and as above the direct effect (c_2 pathway) was significant $F(1, 78) = 13.65$, $p < .001$, $R^2 = .15$. Furthermore, stimulation condition significantly predicted craving (a_2 pathway) $F(1, 78) = 5.69$, $p < .025$, $R^2 = .07$. The overall indirect effects model was significant $F(2, 77) = 15.67$, $p < .001$, $R^2 = .29$, with craving significantly predicting *ad libitum* consumption (b_2 pathway) $t(2) = 3.90$, $p < .001$, $SE = 1.96$, however, stimulation condition continued to predict *ad libitum* consumption (c' pathway) $t(2) = 2.86$, $p < .01$, $SE = 14.44$. These findings imply that craving only partially mediates the relationship between stimulation and continued *ad libitum* consumption.

6.5 Discussion

The current study applied cTBS to inhibit the neural structures associated with attentional bias, inhibitory control and craving (DLPFCs, mOFC), in order to illuminate how these processes interact and drive consumption. Findings can be summarised as follows: First, in accordance with our hypothesis, stimulation to the DLPFCs resulted in impaired inhibitory control, while mOFC stimulation decreased alcohol-related AB. Second, impairments in inhibitory control resulting from DLPFC stimulation did not appear to be related to increases of alcohol-related AB. Although craving following lDLPFC was heightened, as anticipated, the predicted associated changes in the AB were not evident. However, while stimulation to the rDLPFC did not result in increases *ad libitum* consumption, as expected, drinking was heightened following lDLPFC stimulation and this increase appeared to be partially mediated by changes in self-reported craving.

Beginning with a discussion of null findings, we failed to identify a relationship between transient inhibitory control impairments and drinking maintenance or increased AB. The current findings therefore indicate that stimulation to the DLPFCs impaired inhibitory control, consistent with previous stimulation research (see Brevet-Aeby et al., 2016), however these impairments were not found to mediate *ad libitum* consumption. This may suggest that while the DLPFCs appears to modulate the extent to which individuals can exert control over prepotent responses, this capacity does not appear to be directly related to drinking behaviour. This contrasts with early suggestions by Field and colleagues (2010) but appears to be consistent with a growing body of more recent contributions (e.g., Christiansen et al., 2013; Jones et al., 2020, 2018; McNeill et al., 2018). Present (null) findings therefore appear to undermine further the notion of a causal link between inhibition impairments and loss of volitional control over actual

beverage alcohol consumption, and may therefore be more consistent with theoretical models that view inhibitory control as a more multifaceted construct that is embedded within wider cognitive processing networks (Verbruggen, 2016).

In a similar vein, the current study also failed to find a relationship between impairments in inhibitory control and AB. These results contrast with the suggestions that impaired inhibitory control may adverely impact people's ability to control attention to alcohol-related cues (Adams et al. 2012) and that alcohol-related stimuli impairs impulse control (Monk et al., 2017). The current study did evidence reduced AB following mOFC stimulation, this however did not translate into the predicted decreases in inhibition failures as measured by the Gaze Contingency Task. Furthermore, the current findings did not yield any support for the relationship between AB and craving as previously theorised (e.g., Franken, 2003; Tiffany, 1990; Tiffany & Conklin, 2000). While stimulation to the lDPFC elevated alcohol-related craving, this did not, in turn, appear to translate into increases in AB (in contrast with Lowe et al., 2018). When considered alongside meta-analyses indicating significant yet weak links between impulsivity and AB (see Luenge et al., 2017) and between craving and AB (Field, Munafò & Franken, 2009), the current research casts doubt on the notion of a simple (causal) relationship between these processes. Rather, any relationships appear likely to be nuanced and likely to be underpinned by a wider complex neural network (see Koob, 2014) which require further research scrutiny.

Further evidence of the complexity of these processes is evidenced when turning to the finding that alcohol consumption was elevated following lDLPFC stimulation, though this increase appeared to be partially mediated by changes in craving. To our knowledge, this is the first study to attempt to examine the role that lDPFC plays in

exerting control of alcohol consumption, extending previous findings in relation to wider appetitive behaviours (see Lowe et al., 2018). Moreover, by isolating craving from wider pharmacological changes associated with consumption, this research adds weight to the notion that craving may represent an important cognitive mechanism through which drinking episodes are maintained (e.g., Rose et al., 2013). Indeed, it may be suggested that craving, rather than inhibitory control (which did not appear to mediate consumption) is a more central cognitive process through which consumption is initiated and maintained. In this way, our work may provide an explanation for why efforts to train inhibitory control have not proved efficacious for reducing consumption (see Jones et al., 2016). Targeting craving may therefore be a more fruitful avenue for future exploration and may better inform interventions which seek to reduce the number of drinking episodes and may help minimise people's sense of losing control.

The current findings should be viewed with caution in light of a number of potential limitations. First, while the current sample size is similar to other TMS research in this area (e.g., Lowe et al., 2018; Lowe et al., 2017), further explorations of this kind are encouraged, particularly when seeking to unpick further the interactions between processes (inhibitory control, AB and craving) where effects may be small (for instance, the relationship between craving and AB in substance users; Field, Munafò, & Franken, 2009). Second, it should be noted that the current study began testing responses immediately post stimulation, in order to allow for competition of measures during the suggested 45 minute duration of stimulation effect (Huang et al., 2005). This has the benefit of reducing demand on participants and limits the procedural signalling which may occur where multiple stimulation sessions are utilised (i.e., one stimulation session for cognitive and questionnaire measures and a second identical stimulation for behavioural measures). It has been observed, however, that cTBS does not reach peak

efficacy till around 14-40 minutes post stimulation (ibid) and, as such, it should be noted that there may have been resultant variability in observed cognitive and behavioural changes. Finally, caution is needed when seeking to generalise the current findings, taken from a young student sample, to the populations where developmental differences may be expected in terms of prefrontal structures and impulse control. Specifically, it has been suggested that prefrontal brain regions and, consequently, impulse control continue to develop up to the age of 25 years (see Spear, 2013). Future research should therefore be expanded to older populations to examine whether the current findings apply there.

In conclusion, the current study represents an initial attempt to use TMS to isolate changes in cognitive processes (inhibitory control, attentional bias and craving) from wider pharmacological effects of alcohol. In so doing, it examined how reputedly important cognitive processes associated with alcohol behaviours interact and relate to alcohol consumption. In general, findings suggest while DLPFCs may be important in the control of prepotent responses, such changes do not manifest in increased consumption. Likewise, while the lDPFC appears to exert a degree of control over craving processes, current findings did not support the notion that heightened craving is associated with elevations in alcohol-related attentional bias. Rather, the current findings suggest that craving may be a more central (mediatory) mechanism than inhibitory control and attentional bias in the self-regulation of alcohol consumption. While we advocate for further research to unpick the complex interaction between cognitive processes and their underlying neural substrates, we tentatively suggest that future interventions may benefit from increased consideration of craving as a significant and potentially malleable mechanism to help reduce alcohol consumption and related harms.

Chapter 7: Discussion

7.1 Summary of findings

7.1.1 Study 1

The aim of the study was to unpick the anticipated from the pharmacological effects of alcohol and in so doing, assess their relative contributions to changes in cognitive processes and alcohol consumption behaviour. In a counterbalanced within participants design, participants were administered beverages (alcohol pre-load, placebo, control) followed by a battery of questionnaires (AUQ, AOES) and cognitive tasks (SST, Alcohol Dot Probe). Results demonstrated significant inhibitory control impairments following both alcohol pre-load and placebo, with greater impairments associated with alcohol pre-load. A similar pattern was observed for craving. Increases in attentional bias were detected following both alcohol and placebo, however, in this instance placebo had a greater influence in heightening attentional bias. Furthermore, increases in *ad libitum* consumption were only observed following alcohol pre-load, not placebo. Crucially, the impairments in inhibitory control did not mediate the relationship between initial intoxication and successive drinking. However, there was some evidence for changes in craving partially mediating this relationship. These findings converge to suggest that alcohol's pharmacological effects may be more critical in the driving continual drinking and the subjective sensitivities to these effects are potentially the route by which continued drinking is driven.

7.1.2 Study 2

A novel naïve alcohol administration procedure was developed and used in a randomised between participants design, aiming to disentangle the relative contribution of the pharmacological and anticipated effects of alcohol in changing cognition and driving successive consumption. The naïve alcohol condition involved deceptively

administering alcohol (.4g/kg), with participants told they are in a control condition, and this was compared with traditional alcohol pre-load, placebo and pure control conditions. Overall, findings indicated that pharmacological (rather than anticipated) effects drive subsequent alcohol consumption and result in the biggest changes in inhibitory control and craving. However, consistent with the other PhD studies these inhibitory control impairments did not mediate the relationship between the initial intoxication and *ad libitum* consumption. On the other hand, this relationship was mediated by changes in craving, specifically, that higher levels of craving were associated with heightened consumption. This is consistent with past research implicating craving changes in subsequent consumption and those suggesting these changes to be stronger predictors of drinking behaviour compared with inhibitory control impairments. With this being said, findings demonstrating the involvement of impaired inhibitory control in subsequent drinking are inconsistent, hence, research is required to further explore this complicated relationship. In the current study, the attentional bias findings are inconclusive and somewhat inconsistent with the existing literature. It is suggested that alcohol pharmacology has no impact on attentional bias, which is inconsistent with previous findings demonstrating dose dependent effects. Expressly, that low doses (comparable with current study) show a heightening effect on attentional bias, while higher doses (e.g., .8g/kg) exhibit reductions in attentional bias. Conversely, the anticipated effects appeared to amplify attentional bias for alcohol-related stimuli, however, the current study represents the first attempt to examine the effects of placebo on attentional bias. Overall, the findings of the current study suggest alcohol's pharmacological effects play a more significant role in driving successive drinking behaviours, importantly however, it is how this intoxication is experienced that is pivotal. Future research is required to further explore the subjective experiences associated with being intoxicated and how these may influence continued drinking.

7.1.3 Study 3

A counterbalanced within participants design was employed, using continuous theta burst (cTBS) transcranial magnetic stimulation (TMS) to impede functioning of the right dorsolateral prefrontal cortex (rDLPFC). A Vertex controlled design was utilised to examine the effects of cTBS to the rDLPFC in terms inhibitory control and successive alcohol consumption. First, compared with baseline and Vertex stimulation, rDLPFC stimulation significantly impaired inhibitory control as measures by the Stop-Signal Task (SST). Secondly, *ad libitum* alcohol consumption was higher following rDLPFC stimulation compared with Vertex stimulation. Importantly, however, these increases in consumption were not mediated by the inhibitory control impairments. The study signifies the first attempt to apply cTBS to the rDLPFC to isolate reduced prefrontal functioning and impaired inhibitory control comparable to those changes observed under alcohol intoxication. While findings indicated comparable inhibitory control impairment and *ad libitum* consumption, they lacked support for the assumption of a mediational relationship. This relationship is rarely observed in the alcohol administration literature, but these findings may suggest that while inhibitory control is implicated in drinking behaviour, it may not be the central mechanism by which consumption is determined. Rather, alternative processes, such as explicit craving processes, for example, may be more crucial in promoting consumption behaviours.

7.1.4 Study 4

The study utilised a randomised between participants design, deploying cTBS to inhibit the functioning of prefrontal regions (rDLPFC, left-DLPFC, mOFC) associated with alcohol-related cognitive processes (inhibitory control, attentional bias and craving). The study aimed to examine how these cortical regions and associated processes interact and specifically, how these interactions are involved in driving consumption

behaviour. The study did not yield support for an interactional relationship between the cortical regions or the cognitive processes, but cTBS to individual regions resulted in cognitive changes. Specifically, cTBS to the rDLPFC resulted in impaired inhibitory control and to the lDLPFC increases in craving. The findings for attentional bias, however, are not as clear, with explorations revealing reductions in attentional bias following mOFC stimulation. Importantly, as with study 3, inhibitory control impairments did not mediate subsequent consumption, on the other hand, craving did partially mediate this relationship. It is therefore, suggested that subjective processes play a more fundamental function in the maintenance of consumption behaviours. These recommendations may be concordant with previous research suggesting that how we subjectively experience drinking episodes may be more influential in changing patterns of consumption, when compared with changes in implicit cognitions (e.g., inhibitory control). In devising future research, the relationship between subject alcohol-related experiences and implicit processes should be given consideration and not examined in isolation.

7.1.5 Overall Summation

In a research first, the current thesis sought to explore and isolate the pharmacological from the anticipatory effects of alcohol. Alongside neuromodulation techniques, it has utilised alcohol administration procedures, including the inclusion of a novel naïve alcohol administration protocol. In so doing, it has been able to better isolate cognitive changes and their respective roles in alcohol consumption behaviour. Overall, the findings suggest that craving may be a potentially central motivational mechanism involved in driving and maintaining drinking episodes. Furthermore, it appears that transient fluctuations in craving appear to elevate consumption, while apparent losses of

control are primarily driven by alcohol's pharmacological, not anticipated effects. This has important implications for our understanding of alcohol consumption practices.

Finally, this thesis now turns to consider the overall limitations of the thesis and the potential future directions for this avenue of research.

7.2 Limitations

Throughout the course of the thesis specific limitations have been considered for each respective study. However, a number of over-arching limitations are now outlined, with suggestions for future approaches.

7.2.1 Cognitive measures

There is a potential distinction between implicit and explicit cognitions. Implicit cognition could be defined as an unconscious or automatic process (Stacy & Wiers, 2010). It has been suggested that implicit cognitions explain why people continue to engage in heightened drinking in the knowledge that they may face harms to their physical health and/or social life (ibid). The findings of the thesis suggest that changes in implicit cognitions (i.e., inhibitory control) are less associated with successive drinking compared with explicit cognitions (i.e., subjective craving). Specifically, subjective experiences of intoxication are more influential in patterns of consumption, rather than fluctuations in implicit cognitions. Nevertheless, there are a number of potential limitations to the cognitive measures used in the current thesis. These are outlined and considered below.

7.2.1.1 Attentional bias

Widely implicated in alcohol consumption behaviour and motivations to drink (see, Field & Cox, 2008), the course of research into attentional bias has resulted in the development of a number of measures. Post hoc reliability analysis of attentional bias assessed using the visual probe task (VPT) and unblocked versions of the alcohol-related Stroop suggest that these tasks may be unreliable (Ataya et al., 2012). However, Field and Christiansen (2012) went a step further in their post hoc analyses,

differentiating between reaction and dwell time in the VPT, demonstrating that dwell time compared with reaction time held superior reliability. They also, suggested that alcohol versions of VPT were less reliable than other substance versions. This is somewhat consistent with the internal reliability found in study 1, with reliability for dwell time slightly more reliable than for reaction time. More importantly, on the whole the reliability for attentional bias tasks in studies 1, 3 and 4 was unacceptable and therefore, the attentional bias findings need to be evaluated with caution. Likewise, this lack of reliability may also in part explain why some of the attentional bias findings are inconsistent with the wider literature. Specifically, in study 2, evidence has demonstrated low doses cause increases in attentional bias (e.g., Schoenmakers et al., 2008). It is imperative that future research addresses the reliability of attentional bias measures before a true understanding of attentional bias can concluded and crucially how attentional bias relates to consumption behaviours. A few suggestions have been made, including using stimulus onset asynchrony (e.g., Noël et al., 2006; Townshend & Duka, 2007; Vollstadt-Klein, Loeber, von der Goltz, Mann, & Kiefer, 2009), allowing for a more precise appreciation of the 'grabbing' potential of alcohol-related stimuli in the environment. Furthermore, the use of personalised stimuli has been advocated for (Christiansen, Mansfield, Duckworth, Field, & Jones, 2015), as this may not only improve the reliability of attentional bias measures but also the ecological validity. This extends to the issues that have long surrounded the use of abstract control stimuli (i.e., stationary as in this thesis), which has been suggested to amplify attentional bias towards alcohol-related stimuli (Field & Cox, 2008). Rather recent studies have demonstrated that drinkers show preference towards appetitive cues (i.e., alcohol, food, non-alcoholic beverages) generally (Pennington, Qureshi, Monk, Greenwood, & Heim, 2019; Qureshi, Monk, Pennington, Wilcockson, & Heim, 2019). Rather these findings suggest that attentional bias may be a more a generalised appetitive process (Pennington

et al., 2019) and as such current attentional bias tasks lack the sensitivity to detect any nuances in attentional processing between specific appetitive cues (i.e., alcohol, drugs, foods).

This evidential lack of consistency and reliability within the VPT has far reaching implications for the alcohol substance use domain. Principle among these is our inability to accurately test specific predictions of theoretical accounts of AB (e.g., Franken 2003; Robinson & Berridge, 2001), for instance the cyclical association between AB and craving as posited by Franken (2003). This lack of reliability further impairs our ability to test and compare theoretical accounts, hindering current understandings of AB. A specific example of this stems from contemporary theories that suggest AB is the result of rapid transient stimulus evaluations, sensitive to a plethora of internal and external factors (Field et al., 2016). If this is the case, such a blunt tool as the VPT likely lacks the sensitivity to detect quick momentary evaluations and associated shifts in attention. It is therefore imperative that significant attention is given to improving the reliability of VPTs and wider AB tasks. This will not only improve our understanding of the processes underpinning AB, but also enhance their clinical relevance both as diagnostic and therapeutic tool.

7.2.1.2 Inhibitory control

Inhibitory control is measured by a multitude of different measures, with the most common among these the Stop-Signal Task (SST; Verbruggen et al., 2008), Go/No-go task (GNG; Newman & Kosson, 1986) and the Stroop task. While generally the validity of these tasks is well established, a comprehensive review is beyond the remit of the current thesis (see Fillmore & Weafer, 2013). However, some differences in literature can be explained by the deployment of different inhibitory control measures

and their limitations. For instance, inhibitory control as measured by the Stroop task has been shown to mediate the relationship between acute alcohol intoxication and snack food intake (Christiansen, Rose, Randall-Smith, & Hardman, 2016) and between cTBS to the lDLPFC and food consumption (Lowe et al., 2014). Interestingly, Lowe and colleagues (2014) also took inhibitory control measures using the SST and GNG, finding no mediational relationship. This is important in the context of the current thesis as the suggestion that appetitive behaviours are mediated with inhibitory control impairments is scantly supported. Within the current research no support is provided for inhibitory control impairments mediating subsequent drinking and task differences may explain this. The Stroop task cannot really be considered a pure measure of inhibitory control, in fact some suggest the cognitive and emotional processes that underpin the Stroop task are ambiguous and include considerable attentional processes (Cox, Fadardi, & Pothos, 2006). Moreover, greater effect sizes are observed for Stroop tasks consisting of fewer blocks, with diminishing effects sizes as the blocks increase (ibid). Studies directly comparing findings from the Stroop with the SST have determined different underlying processes govern the two tasks (e.g., Khng & Lee, 2014; Verbruggen, Liefooghe, & Vandierendonck, 2004). Therefore, the different processes and larger effects may explain why mediational relationships are more readily found using the Stroop task compared with other tasks.

The SST was adopted due to the suggestion it is a 'purer' measure of (response) inhibition. The SST is predicated on the *Horse Race Model of Inhibition* (Logan & Cowen, 1984; Logan, 1985), which put simply suggests a 'race' between two competing processes; the activating (go-signals) and inhibiting (stop-signals), with the process completing first determining the behavioural outcome. Alternative tasks however, involve what may be seen as multiple somewhat conflicting components

(GNG – associative learning, Stroop – attentional allocation). More contemporary theories of cognitive behavioural regulation however, suggest that this simple binary competing processes model may be too simplistic and that impulse behavioural control is more likely the interaction between a number of basic cognitions within the executive function network (Verbruggen, 2016). With a shift away from this hierarchical structure of executive function and inhibitory control specifically, this could potentially explain the very limited evidence (including in this thesis) for the role of impairments in maintaining drinking behaviour. For instance, recent research has suggested that proactive slowing, rather than reactive control, is a better predictor of consumption in heavy drinkers (Baines, Field, Christiansen & Jones, 2020). Were this the case, conscious control or 'planning' may be more pivotal in patterns of consumption than automatic and reactive inhibition, and the importance of inhibitory control in alcohol consumption may have been hitherto overstated within the literature. It is therefore, important to develop our understanding of inhibitory control processes and developing new tasks that are more sensitive to these multifaceted models. Such successes, may however, illuminate the potential role inhibitory control plays in the maintenance of consumption.

7.2.2 Self-report data

Addiction research relies heavily on self-report data (Greenfield & Kerr, 2008) and although this is considered to be a reliable and valid method, we should continue to critically appraise this approach, and the factors influencing reporting accuracy (Del Boca & Noll, 2000). Indeed, while self-reports are commonly used establish to history alcohol involvement, it has been suggested that participants' memories about their drinking may be limited, an issue that is compounded by alcohol consumption (see Walker & Hunter, 1978). Responses may also be driven by the desire to elicit favourable self-evaluations (Davies & Best, 1996) or by the nature of the questions

themselves (see Melson, Monk, & Heim, 2016; Melson, Davies, & Martinus, 2011). This body of research raises important questions for our understanding of how these (self-reported) attitudes, belief and cognitions are associated with patterns of consumption.

The results of the current thesis must also be noted for their reliance on self-reports of alcohol-related attitudes, beliefs and cognitions. For example, the current research suggests that heightened (self-reported) subjective craving is related with increases in alcohol consumption. However, it may be questioned whether participants are motivated or even able to provide an honest representation of their alcohol-related beliefs, attitudes and cognitions (Davies, 1997). Specifically, craving has been shown to fluctuate as result of alcohol-related contexts (Field & Jones, 2017), alcohol pre-loads (e.g., Christiansen et al., 2013) and even placebo alcohol (e.g., Christiansen et al., 2017). As such these potentially sensitive temporal changes in craving are likely to fluctuate over the course of a drinking episode (e.g, Rose et al., 2013) and while the current findings implicate subjective craving in consumption, future research is required to examine both the nuances of craving itself and its relationship with drinking patterns.

Finally, it has been posited that self-reported craving is not indicative of underlying craving activation (e.g., Sayette et al., 2000). There have been further suggestions that self-report measures do not map onto theoretical or conceptual accounts of craving (e.g., Sayette et al., 2000; Kavanagh et al., 2013). Specifically, theories of craving often suggest that craving characterised by spontaneous emergence and the reorientation of alcohol-seeking cognitions (e.g., attentional biases; Tiffany, 1990), as a consequence of heightened arousal in the dorsal striatum (see Volkow et al., 2016). These concerns are allayed somewhat by findings which show that self-reported

craving is associated (albeit weakly) with activation in the reward network (nucleus accumbent [NAc] and ventral tegmental area [VTA]; e.g., Goldstein et al., 2009). Furthermore, self-reported craving has been shown to be associated with behavioural self-administration measures in the present thesis, as well in previous research (e.g., Field & Jones, 2017; Wardell, Le Foll, & Hendershot, 2018). However, as previously discussed cravings are susceptible to fluctuation and it has been argued that single self-report measures are ill equipped to examine theoretical aspects such as craving spontaneity (Kavanagh et al., 2013). It is therefore imperative that future research adopts more contextualised repeated measurements (e.g., EMA) to unpack the nuanced relationship between craving and patterns of consumption.

The issue of this association is further complicated by our dependence on self-reported, often retrospective, consumption (i.e., TLFB). Some of these concerns are alleviated by research suggesting that self-report measures of alcohol consumption correlate with more objective assessments acquired using transdermal alcohol assessment (Simons, Wills, Emery, & Marks, 2015). On the other hand, research comparing real-time with retrospective reporting has indicated an under estimation in drinking when reporting retrospectively (Monk, Heim, Qureshi, & Price, 2015). Therefore, as our methodological options for measuring alcohol *in vivo* increase and more importantly their reliability improves (Piasecki, 2019), avenues open up to unpick the role of craving in both the initiation of consumption and temporal course of drinking episodes.

7.2.3 Alcohol administration

Alcohol administration studies generally employ one of two paradigms; oral administration or a clamping procedure. Oral alcohol administration involves participants consuming volume of alcohol based on their body mass (grams of alcohol

per kilogram of body mass), over a fixed period of time, followed by an absorption period. This technique was employed within this thesis (study 1 .5-.6g/kg; study 2 .4g/kg), employing a ten-minute consumption period and twenty minutes for absorption. On the other hand, the clamping procedure involves intravenously infusing participants with an ethanol solution throughout the course of the study. This method maintains a constant breath/blood alcohol concentration, and provides a reliable intoxication window (Ramchandani, Bolane, Li, & O'Connor, 1999). This is potentially important for experimental testing as it has been found that priming doses of alcohol elicit responses in the form of an "inverted U" - with low and high doses of alcohol showing little to no effects on performance, while moderate doses elicit high effects on cognition and behaviour (Henningfield, Cohen, & Heishman, 1991). Of course, many cognitive processes and behaviours show dose dependent effects that may not always fit this curve. For example, high doses have been shown to result in decreases in attentional bias (e.g., Duka & Townshend, 2004; Weafer & Fillmore, 2013), on the other hand, higher doses demonstrate greater effect on risk-taking behaviour (e.g., Lane et al., 2004). Therefore, while alcohol pre-loading techniques are valuable tool to examine transient changes in cognition and drinking behaviour, throughout their history they have presented a number of limitations.

An issue for researchers using alcohol administration techniques to consider is that of 'priming thresholds' – the relative alcohol dose required to elicit the 'priming' effect in a sample (de Wit, 1996). Specifically, it is feasible that certain populations respond differently to comparable doses of alcohol, meaning that these thresholds may be population dependent. For instance, low doses may be sufficient to prime responses in light/social drinkers, while higher doses may be required to prime positive effects in heavy drinkers (Rose & Duka, 2006). The majority of the participants represented

within this thesis could be classified as heavy drinkers demonstrated by mean AUDIT scores >8, comparable with other studies of a similar nature and priming effects have been observed in both studies 1 and 4, at moderate and low doses respectively. This phenomenon may be explained by the sample, as while they display as acutely heavy drinkers, it is likely their drinking history is limited due to the young student based sample and as such their tolerance has yet to fully settle. Future research interested in how these 'priming thresholds' are affected by drinking history, and how they related to changes in cognition and behaviour should consider using samples from more experienced drinkers, whose patterns differ from those students.

The current body of research aimed to overcome the limitations presented by placebo-controlled designs, specifically, their inability to allow for the examination of the effect of alcohol anticipation on cognition and alcohol seeking behaviour. This constitutes one arm of the current research, to unpick the relative contributions of alcohol's anticipatory and pharmacological effects and their potential interaction in cognitive changes and driving consumption behaviour. Findings from the thesis overall support the influence of the anticipated effects on inhibitory control and craving, however, they lack support for their effect on consumption behaviour. Importantly, the research present here constitutes the first attempt to address the effects of anticipation on attentional bias, suggesting wholesale increases compared with control, however, findings around alcohol's effects are somewhat inconsistent within the literature and therefore, future research is required to examine the relationship between the pharmacological and anticipated effects on attentional bias.

In terms of disentangling the pharmacological and anticipated effects, pure controlled studies still present a limitation which must be acknowledged; they can

address the anticipated effects in isolation, but not the pharmacological. In light of research demonstrating the effects of placebo on cognitions and behaviour (e.g., Christiansen et al., 2017), it could be assumed that anticipated effects have an additive impact to those of alcohol pharmacology. Study 4 results provide some positive evidence for the relationship between pharmacology and anticipation, suggesting that alcohol's pharmacological effects are primarily responsible for driving subsequent drinking. However, anticipated effects may not have been entirely eliminated as participants reported significantly higher subjective intoxication compared with controls, but significantly lower than alcohol pre-load. Findings from the current study have highlighted the primary driving role for alcohol pharmacology over anticipation, presenting potential implications for interventions (e.g., pharmacotherapies) and as such future research should continue to examine the role of pharmacology in wider alcohol-related cognitions.

7.2.4 Sampling

The course of empirical psychological research has been marred by issues of sampling, with a heavy reliance on student samples recruited from Western universities. The use of student participants is ubiquitous within Psychological research, being primarily driven by the availability of potential subjects in the universities in which this research is being carried out. However, it has been suggested that while students represent an interesting sample within themselves, generalising from them may be problematic (Hanel & Vione, 2016). Accordingly, the research in this thesis sought to recruit from non-student samples and boost the representativeness of the data. Nevertheless, the nature of recruitments methods employed during the course of the research, specifically the use of the SONA[4] recruitment system, meant that the overall

[4] SONA is an online recruitment tool, where potential participants can see study information and make an informed decision whether or not they would like to take part. Participants can sign up to available study slots and researcher can track sign-ups.

research sample was predominately student. It is therefore appropriate to explore the concerns raised by student sampling and acknowledge how they may impact the current thesis.

A meta-analysis of social science research indicates that there are effect size differences for student compared with non-student samples and in some cases differences in the direction of the effect were also revealed (Peterson, 2001). In the domain of alcohol research, where the use of student samples is consistent area for debate (e.g., Moreira, Smith, & Foxcroft, 2009), there could be a number of reasons for this finding. The first thing to consider is the drinking patterns of student samples. Heavy episodic drinking is seemingly engrained in student culture, with high levels of hazardous and problematic drinking observed (Borsari & Carey, 2001; Karam et al., 2007; Knight et al., 2002). This may represent a number of problems for findings from research in which they are the sole or majority participants: First, there may be variability in student drinking patterns, as the timings of student drinking episodes differ from the wider population (Del Boca, Darkes, Greenbaum, & Goldman, 2004). Second, evidence has demonstrated that associated social norms surrounding student drinking are strong predictor of alcohol consumption behaviours (e.g., Lewis et al., 2011). It may therefore be possible that, irrespective of experimental manipulations implemented in the current research (e.g., alcohol pre-load administration), drinking-related social norms may affect *ad libitum* consumption tasks by driving up consumption. Future research should therefore expand sampling efforts in order to assess whether alcohol associated changes in cognition are comparable and these changes maintain a consistent relationship with drinking patterns in the general populous.

Findings from neuroscience also cast further questions onto the reliance of student testing. Indeed, it has been suggested that much of what we know about the brain and its functioning comes from samples of convenience (e.g., students; Falk et al., 2013) which may impede our capacity to generalise these findings to other populations with varying neurological structures. Specifically, it has been noted that prefrontal regions associated with impulse and attentional control are still developing into the early twenties (Spear, 2013). Studies 2 & 3, which focus on transcranial magnetic stimulation (TMS) of the prefrontal regions (i.e., right dorsolateral prefrontal cortex [rDLPFC], medial Orbital Frontal Cortext [mOFC]), should therefore be considered carefully. Indeed, it is possible that the transient changes in cognition are unrepresentative of the fully developed brain. Furthermore, it should be noted that caution is warranted before seeking to generalise the findings of studies 1 & 4 to more mature adults, where inhibitory control capacity may be more developed, making it less susceptible to such pronounced short-lived impairments. As such a number of approaches have been suggested to improve issues with sample representability including among others, integration into wider population research (as is the case of the IMEGEN study; Schumann et al., 2010) and multi-site approaches to recruitment (Falk et al., 2013). It is therefore imperative in light of issues of generalisability and replication that future research works hard to diverge from the long history of opportunity samples to more encompassing sampling strategies.

A number of reviews have observed a bias in the research towards using samples from Western, Educated, Industrialised, Rich and Democratic (W.E.I.R.D.) societies, both within the social science (Henrich, Heine, & Norenzayan, 2010) and neuroscience literature (Chiao & Cheon, 2010). Importantly however, Henrich and colleagues (2010) found research using W.E.I.R.D research exhibit different findings to comparable cross-

cultural studies. Indeed, such cultural differences have been observed in cognitive styles and control (Kitayama et al., 2019) and even personality predictors of internet addiction (Sariyska et al., 2014). Similarly, evidence from neuroscience suggests that there are a number of potential differences between W.E.I..R.D and, for example, Eastern cultures. These include including variability in brain regions that are recruited for object and facial recognition, as well as for introspective behaviour (Chiao & Cheon, 2010). Differences have also been observed in prefrontal regions, associated with attentional processing concerning judgements (Hedden, Ketay, Aron, Markus, & Gabrieli, 2008). This could have implications for the tentative conclusions of study 4, where it is suggested that the role of the mOFC in attentional bias may not translate as salience attribution. For instance, when observing cultures where drinking alcohol is forbidden either by law or religion, people impairments in inhibitory control may not culminate in a drinking episode, as their cultural belief and attitudes will more likely govern this behaviour. Therefore, future research is therefore required to explore the intersection between cognitive processes (e.g., inhibitory control, attentional bias) and cultural beliefs in relation to alcohol consumption.

7.3 Future directions

Future research should continue to unpick the how fluctuations in implicit and explicit cognitions drive alcohol consumption. However, it may benefit from more context aware approaches. For instance, a recent study using Ecological Momentary Assessment (EMA) found that fluctuations in inhibitory control during the daily course were predictive of drinking over and above that planned (Jones et al., 2018). However, craving and implementation intentions were found to be better predictors of overall daily alcohol consumption (ibid). EMA has the advantages of examining behaviour and cognitions in *in vivo,* therefore, allowing scope to study the complex and dynamic nature of alcohol consumption behaviour (Wray, Merrill, & Monti, 2014). This methodology also allows researchers to assess the potentially mediating role of social (e.g., Erskine-Shaw, Monk, Qureshi, & Heim, 2017) and environmental contexts in these processes (e.g., Monk & Heim, 2013a, 2013b). This approach may therefore present a potentially useful tool for further research which aims to understand further how real-world changes in implicit (e.g., inhibitory control, attentional biases) and explicit (e.g., craving) cognitions during a drinking episode are involved in maintaining consumption. This may also enable researchers to build on early insights which suggest that intoxication craving peaks after "three" drinks and then begins to fall (Rose et al., 2010), elucidating further the role of cognitive processes at various stages of the drinking episode. It is imperative that as technology improves that research evolves and makes every attempt to extrapolate lab-based findings into real-world context, only then can we be confident of understanding complex drinking behaviours.

Keeping in mind that research examining the relationship between process fluctuations and patterns of drinking needs to become more context aware, it must also address the issues of generalisability. Considering previous research has suggested that

younger (student) samples have limited experience on which to form their drinking related attitudes, beliefs and cognitions (McAlaney & McMahon, 2007), and to successfully examine the position of this thesis that it is the explicit rather than implicit processes driving consumption behaviour, such samples should be avoided. This extends beyond this assertion into the aforementioned research suggestions using EMA and examining group processes. There is evidence to suggest processes such as inhibitory control and attention are not fully developed in such young samples (see Peeters et al., 2014), hence, understanding daily fluctuations in those processes may still not generalise to wider drinking populations. Furthermore, the drinking cultures differentiate between student and non-student samples, for instance, evidence suggests students commonly engage in pre-loading prior to going out on a drinking occasion (e.g., Caudwell & Hagger, 2014; O'Rourke, Ferris, & Devaney, 2016). Therefore, the use of such samples may lack validity when exploring the social and group processes involved in alcohol consumption behaviour. This issue of sampling and generalisability remains a contentious issue in the alcohol literature, but one that must be addressed to make significant advances in our understanding of the processes involved in maintenance of consumption.

7.4 Implications

7.4.1 Research Implications

Existing research demonstrates a relationship between initial intoxication and changes in cognition (e.g., inhibitory control and attentional bias), craving and subsequent drinking (see Field et al., 2010). However, it has been reliant on placebo-controlled designs, neglecting the relative contributions of the pharmacological and anticipated effects of alcohol. The current thesis adds to the diminutive research which has taken this approach and its findings add weight to the notion that such research should include a pure control condition to truly unpick the association between alcohol's pharmacological and anticipated effects. Furthermore, in a novel approach, study 2 represents the first attempt to isolate alcohol's pharmacological from the anticipated effects. The current thesis therefore has implications for role anticipation of alcohol's effect may play in the maintenance of consumption, specifically, findings implicate alcohol pharmacology (not anticipation) in successive consumption. Particularly, findings have indicated more pronounced changes in both implicit (i.e., inhibitory control) and explicit (i.e., craving) cognitions following alcohol containing pre-loads, with subsequent consumption partially mediated by changes in craving. Future research may therefore benefit from the further development of such alcohol administration procedures.

The current thesis also has implications for the use of neuromodulation techniques to study the link between brain regions and behaviour (e.g., TMS, transcranial direct current stimulation [tDCS]). Specifically, existing research has indicated that different forms of TMS to the lDLPFC heightens food-related craving and *ad libitum* calorie intake (Lowe et al., 2014) and rTMS has been show to inhibit activity mOFC and reduce craving smokers (Li et al., 2017). The current research utilised

continuous theta burst (CBS) TMS to various prefrontal regions (right-, left-DLPFC, mOFC) to unpick the association between neural inhibition, cognition and behaviour. Findings yielded little support for the direct link between inhibitory control impairments and successive consumption following both right- and left-DLPFC CBS. However, changes to in craving associated with CBS to the lDLFPC was shown to partially mediate consumption. Future research may also benefit from adopting multiple neuropsychological (for example, EEG combined with *f*MRI or TMS and *f*MRI) to more accurately unpick the nuanced relationships between brain regions, cognitive processes and behaviour.

7.4.2 Therapeutic Implications

In recent years there has been an emphasis on the development of cognitive interventions to change alcohol consumption behaviours including reduction of drinking (see Jones et al., 2016) and preventing relapse (e.g., Boffo, Pronk, Wiers, & Mannarini, 2015; Gladwin et al., 2015). The current findings have real implications for the potential efficacy of the interventions. Research implicates inhibitory control in alcohol consumption behaviours, specifically, poor inhibitory control is predictive of heavy and hazardous drinking (e.g., Christiansen et al., 2012; Nederkoorn et al., 2009). Furthermore, poor inhibitory control in adolescence has been shown to be predictive of the onset of alcohol use (Wong et al., 2006) and problematic alcohol and drug use in later life (Nigg et al., 2006). However, a recent meta-analysis has revealed that inhibitory control training (ICT) has a limited effect in reduction of alcohol consumption in lab-based studies (Jones et al., 2016). Furthermore, a randomised control trial (RCT) examining the effects of wed-based ICT in heavy drinking, healthy participants found no overall effect of training (Jones, McGrath, Houben, Nederkoorn & Field., 2018). However, the findings of this thesis fail to implicate inhibitory control

changes in the maintenance of consumption behaviour, therefore, it is suggested that ICT can only have limited success in reducing consumption. It may be suggested that ICT may have some efficacy in reducing the number of drinking episodes, which in itself is a positive. On the other hand, the current findings suggest that once a drinking episode is initiated, ICT will have no effect in reducing consumption or preventing the loss of control in that episode. Therefore, to test this assumption future ICT research should track the number of drinking episodes and the volume consumption on drinking occasions. However, due to complex and dynamic nature of drinking behaviours, complex interventions are required to make more drastic improvements in patterns of consumption and while these may include ICT, explicit cognition need to be considered also.

While attentional bias has been linked with motivations to drink (e.g., Fadardi & Cox, 2008) and alcohol intoxication has been shown to alter attentional bias (e.g., Weafer & Fillmore, 2013; Duka & Townshend, 2004). The findings from this thesis were inconclusive regarding attentional bias's function in maintaining consumption behaviour. Therefore, it is difficult to shed light on the growing body of research into cognitive bias modification (CBM) to address heavy and problematic drinking (see Wiers, Boffo, & Field, 2018). However, much like ICT, the evidence for the efficacy of CBM is mixed and it may therefore be pertinent to develop a more complete understanding of the role attentional bias and cognitive biases play in driving and maintaining of drinking behaviours.

It is the contention of this thesis that explicit cognitions (i.e., craving) play a more critical role in driving alcohol consumption and as such it may be more fruitful to develop interventions targeting these processes. Furthermore, craving has been

suggested to be highly clinically relevant in terms of abstinence, relapse and overall treatment outcomes. Pharmacotherapies for the use of treating AUD have targeted craving as a mechanism for reducing drinking behaviour, however, a recent meta-analysis of Baclofen demonstrated its efficacy in increasing abstinence, but no significant effect on reducing craving (Rose & Jones, 2018). There is growing evidence for interventions targeting craving and subjective experiences in AUD. For example, a recent RCT investigated the effects of personalised cognitive behavioural therapy (CBT), demonstrated that declines in craving were associated with reductions in the number of drinking days and overall consumption (Coates, Gullo, Feeney, Young, & Connor, 2018). Moreover, neuromodulation based interventions, for example, deep brain stimulation (DBS) has shown promise in reducing craving and persisting alcohol abstinence (Salib, Ho, Sussman, Pendharkar, & Halpern, 2018). However, there is a dearth of evidence for interventions based on craving or subjective experiences in non-dependent samples. With this being said, mindfulness has been shown to attenuate cue induced craving in healthy participants, signifying promise for mindfulness based interventions (Hochster, Block-Lerner, Marks, & Erblich, 2018). Furthermore, physical exercise based interventions have shown promise in reducing craving and relapse in people recovering from AUD (see Thompson et al., 2018), offering a fruitful avenue for non-clinical alcohol reduction. Findings from the current thesis implicate explicit cognitions, and specifically craving in the onset and maintenance of alcohol consumption and therefore posits that the development of complex interventions are required to target such processes.

7.5 Conclusions

A number of overall conclusions can be drawn from the body of research presented within this thesis. First, findings indicate that alcohol's pharmacology (rather than anticipation) are responsible for maintenance of consumption. Second, changes in explicit cognition, specifically craving, are central in maintaining drinking episodes. Finally, while the current thesis demonstrates no evidence for fluctuations in implicit cognitions (inhibitory control, attentional bias) exercising direct control over alcohol consumption, we suggest this may be due to current conceptualisations of inhibitory control and attentional biases. These conclusions hold major implications for our understanding of drinking behaviour, use disorder treatment and alcohol related harm reduction.

The novel naïve alcohol administration method presented in chapter 3 provides new and exciting insights into relevant contributions to subsequent drinking made by the alcohol's pharmacology and anticipation. Findings from chapter 2 & 3 indicate elevated consumption following alcohol pre-loads (but not placebo) and we posit that pharmacological changes associated with alcohol intoxication are the primary mechanisms responsible for maintaining drinking episodes. It is important however, to recognise that theories of anticipation are not being rejected in this thesis; rather, suggesting that anticipation may initiate alcohol-seeking behaviours, but its influence does not extend beyond the commencement of drinking. This position is supported by differences between alcohol and placebo associated changes in alcohol urge and sip rate over successive drinks (Rose et al., 2013). Specifically, it is suggested here that alcohol pharmacology may alter the interactions between implicit (inhibitory control, attentional bias) and explicit (craving, expectations) cognition in the alcohol-behaviour link.

While an initial foundation of the current body of research was the postulation that transient changes in cognitions such as inhibitory control and attentional bias are processes central to the maintenance and loss-of-control over drinking (see Field et al., 2010), the thesis provides no evidence for this. Here, we are not eliminating such processes from the regulation of consumption, but we are however, rebuffing their potential as central mechanisms. A position that is hardly surprising giving the limited evidence from the ICT literature to implicate inhibitory control in reducing consumption (e.g., Jones et al., 2018) or even that ICT improving inhibitory control itself (Jones et al., 2020). It is proposed that a reconceptualisation of inhibitory control and perhaps executive functioning more broadly may afford new and valuable insights into how such processes exert control over consumption behaviours. For instance, contemporary theories of executive functioning reject its previously posited fixed, hierarchal structure in favour of more interactive and competitive model (e.g., Verbruggen, 2016). These models recognise personal experience and external factors in inhibitory processing (e.g., (Venables et al., 2018; Baines et al., 2020) and as such, future research should consider how explicit processes (e.g., craving) interact and compete with automatic processes to drive consummatory behaviour.

The principle assertion of the present thesis is that craving is central to the maintenance of drinking behaviours, with findings consistently demonstrating cravings partial mediatory role in subsequent *ad libitum* consumption (approached significance in study 1). When taken together therefore, the current findings may help provide some explanation for the poor efficacy of interventions targeting implicit cognitions, such as ICT (e.g., Jones et al., 2018) and CBM (Wier, Boffo & Field, 2018) in reducing alcohol-related harms. It would be remiss however, to suggest craving acts independently when exerting influence over drinking behaviour, particularly given the

partial nature of the mediation presented. Current theories and models of craving nonetheless require further examination to identify how and when subcomponents exert the effects and with which other cognitive processes they are interacting.

Finally, we suggest that the hierarchical and often sequential nature of existing dual-process models are inflexible and fail to explain the multifaceted reality of drinking behaviours. For instance, to suggest that alcohol-seeking tendencies are moderated by impulse control (e.g., Weirs et al., 2007; Houben & Weirs, 2009), is overly simplistic. Rather, it is posited here that the relationship between explicit and implicit processes is more dynamic, and more likely to be fuelled by past experiences (e.g., Moss & Albery, 2009). Finding from the thesis in particular, suggest a pivotal role for craving and as such future research should examine how its fluctuations in the 'preconsumption' and 'consumption' phases steer consumption.

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