Multiple Perspectives on Self-Regulation in Alcohol Use Disorder:

Executive Functioning, Neuroimaging, and Psychophysiology

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Thesis Summary

Reduced ability to regulate deleterious behaviours can lead to negative social, health, and financial outcomes. Individuals with alcohol use disorder that continue to drink despite adverse consequences from their drinking demonstrate dysregulated drinking behaviour, potentially due to difficulty in appropriate self-regulation. Identifying the factors that may be integral in appropriate regulation of responses to alcohol cues may help us better understand the underlying mechanisms involved in self-regulation in these dysregulated individuals. Elucidating the factors involved in the regulation of impulsive, motivational drives inherent in alcohol use disorder is important to inform and augment current frameworks, which do not yet adequately explain dysregulated behaviour within this complex and multifaceted disorder.

Thus, the aim of thesis was to empirically examine the regulation of responses to alcohol cues and influencing factors in alcohol use disorder. A diverse methodology of neuropsychological, psychophysiological and neuroimaging techniques was applied to comprehensively evaluate regulation across various time periods surrounding cue presentation, to assess the influence of components, such as executive functioning, in appropriate regulation, and to identify overlapping evidence of underlying regulatory processes and influencing factors in a range of dysregulated alcohol use disorder samples.

Four separate studies were conducted. The first applied an influential theoretical framework of executive functioning to demonstrate discrete executive functioning domains were uniquely associated with the regulation of alcohol cue-elicited responses as indicated by physiological indices in non-treatment-seeking drinkers. The second further investigated these associations using the same methodology in more severely dysregulated alcohol use disorder samples—individuals with alcoholic liver disease and alcohol dependence—and showed overall difficulties in regulation of responses in these samples that were not related to executive functioning ability. The third used the same dysregulated samples to examine

whether reduced capacity for incorporating previous negative feedback leads to impaired decision-making processes regarding drinking, and found reduced physiological responses to risky choices with negative outcomes and decision-making deficits in these samples. The final study used functional neuroimaging techniques to find converging reduced neural activation in prefrontal regions related to regulation of alcohol cue responses, and worse executive functioning and dysregulated drinking measures in an alcohol dependent sample.

Taken together, this thesis advances our understanding of the integral components that may underlie the progression and maintenance of alcohol use disorder. This body of work contributes to the literature involved in elucidating the role of self-regulation and influencing factors in alcohol use disorder, through a convergence of neurocircuitry and underlying neurocognitive mechanisms that is essential to advance our understanding of key processes of regulation in alcohol use disorder and better inform treatment approaches.

Statement of Authorship

I certify that the work in this thesis entitled “Multiple perspectives on self-regulation in alcohol use disorder: Executive functioning, neuroimaging, and psychophysiology” has not previously been submitted for a degree, nor has it been submitted as part of requirements for a degree to any other university or institution other than Macquarie University. I also certify that the thesis in an original piece of research and has been written by me. In addition, I certify that all information sources and literature are indicated in this thesis.

Each of the empirical chapters lists multiple authors. I, Warren Logge, am the primary author of each chapter. The contributions of the authors for each empirical chapter are as follows:

Chapter Two: As the primary author, I was responsible for the study conception and the design, experimental data collection, analysis, interpretation of the results, and preparation of the manuscript for publication. Prof Andrew Baillie provided guidance throughout these processes, including suggestions of statistical approaches, and extensive feedback on the manuscript.

Chapter Three: The participants were recruited as part of a larger trial, which was led by Dr Kirsten Morley, Prof Paul Haber and Prof Andrew Baillie. As primary author, I was responsible for the study conception and the design, experimental data collection, analysis, interpretation of the results, and preparation of the manuscript for publication. Prof Andrew Baillie provided guidance throughout these processes, and extensive feedback on the manuscript. Dr Kirsten Morley provided guidance through aspects of recruitment and data collection, and provided extensive feedback on the manuscript.

Chapter Four: The participants were recruited as part of a larger trial, which was led by Dr Kirsten Morley, Prof Paul Haber and Prof Andrew Baillie. As primary author, I was responsible for the study conception and the design, experimental data collection, analysis,

interpretation of the results, and preparation of the manuscript for publication. Prof Andrew Baillie provided guidance throughout the processes, and extensive feedback on the manuscript. Dr Kirsten Morley provided guidance through aspects of recruitment and data collection, and feedback on the manuscript.

Chapter Five: The participants were recruited as part of a larger trial, which was led by Dr Kirsten Morley, Prof Paul Haber and Prof Andrew Baillie. As primary author, I worked with Dr Kirsten Morley to design the study that formed the basis of Chapter Five. I was responsible for the construction of the tasks, experimental data collection, analysis and interpretation of results, and preparation of the manuscript for publication. Dr Richard Morris was involved with the construction of the neuroimaging protocol and provided guidance for the statistical analysis of the imaging data, and extensive feedback on the manuscript. Dr Kirsten Morley provided guidance across the processes the study and extensive feedback on the manuscript. Prof Andrew Baillie provided feedback on the manuscript.

Prof Andrew Baillie and I spent an extensive amount of time discussing ideas and themes comprising Chapter One and Chapter Six, and Prof Andrew Baillie provided conceptual and editorial feedback on these chapters. Dr Kirsten Morley proofread Chapter Three and Chapter Four, Dr Rose Chesworth proofread Chapter One and Chapter Five, and Dr Sally Fitzpatrick proofread Chapter Two.

The research in this thesis was approved by the following: the Macquarie University Human Research Ethics Committee (Medical Sciences) for the research contained in Chapter Two (Reference No: 5201400315); and the Sydney South West Area Health Service Ethics Review Committee (RPAH Zone) for research contained in Chapter Three, Chapter Four, and Chapter Five (Reference No: HREC/11/RPAH223; SSA/12/RPAH/350). Approval letters can be found in Appendix A.

Warren B. Logge Dated: 7th November, 2017

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Chapter One

General Introduction

General Introduction

This thesis investigates the mechanisms involved in self-regulation in alcohol use disorders (AUDs). Regulation can be defined as the ability of individuals to control behaviour appropriately (Heatherton & Wagner, 2011), and underpins adaptive behaviour that can lead to better health outcomes and increased lifespan. While many humans can successfully regulate several behaviours in response to environmental feedback, difficulty in appropriate self-regulation regularly occurs. For some individuals, not regulating deleterious behaviours leads to negative social, health, and financial outcomes. Understanding the factors involved in self-regulatory failure, and the mechanisms involved may help us to understand and treat common maladaptive behaviours in mental disorders.

Alcohol use disorders are a useful example to examine regulatory failure. Negative consequences that can result from alcohol use should provide feedback to individuals that drinking behaviours, such as chronic consumption, are disadvantageous—subsequently resulting in regulation. The definition of AUDs used for this thesis is provided by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), which defines the disorder as a continuous spectrum of differing severity, ranging from mild to severe, reflected by an increasing number of symptoms. The DSM-5 marked a shift in the classification of AUDs from its previous iteration which denoted two distinct disorders—alcohol abuse, and alcohol dependence (Proudfoot, Baillie, & Teesson, 2006). However, some of the empirical work in this thesis commenced before the DSM-5 (American Psychiatric Association, 2013) revision, and several measures used were based on this earlier classification. Therefore, alcohol dependence will be used interchangeably with severe AUD, but should be considered conceptually analogous.

Alcohol use disorder can be defined by: increased tolerance of the effects of alcohol; withdrawal related to cessation of alcohol consumption; continued desire to consume alcohol;

impaired control over drinking; and continued consumption of alcohol, despite the adverse effects from drinking (American Psychiatric Association, 2013). This set of symptoms are identifiers of an incapability to regulate behaviour appropriately. However, AUDs are associated with significant negative outcomes. Alcohol-related harm is a significant worldwide health issue, accounting for 5.1 % of global disease and injury burden (World Health Organization, 2014), with an estimated 4.3% of the Australian population experiencing an alcohol use disorder in Australia in 2007, and 22.1% within their lifetimes. (Teesson et al., 2010). AUDs are therefore a considerable health and community burden, and can lead to deleterious outcomes from both acute and chronic use, including serious physical harm and death (Litten et al., 2015; Schuckit, Smith, Anthenelli, & Irwin, 1993). Yet, given that some individuals continue to drink despite experienced or potential negative consequences, severe AUD may be considered as an inability to appropriately self-regulate consumption. By comprehensively examining multiple indicators of regulation in a wide range of drinkers, including severely dysfunctional drinkers and those will less severe problems associated with drinking, this thesis investigates a convergence in regulatory mechanisms and associated factors that may underpin dysregulated drinking in AUD.

Self-regulation is a broad concept that is ill-defined, but can be generally described as an individuals capacity to appropriately control and direct goal-specific behaviours, thoughts, and emotions (Posner, Rothbart, Sheese, & Tang, 2007). Individuals with severe AUD are a good example of a significantly dysregulated group that characterise the difficulty required in appropriate self-regulation. That is, they have consistent difficulty controlling or changing their behaviour appropriately (i.e., alcohol consumption) according to environmental feedback from their situation, particularly if consequences are known to be adverse. This is often referred to as self-regulatory "failure": the repeated incapacity to appropriately to self-correct deleterious behaviour, despite the negative feedback and potential negative outcomes

(Baumeister, Heatherton, & Tice, 1994; Sayette, 2004; Steel, 2007). This deleterious behaviour can be elicited by cues in the environment previously associated with alcohol that signal or prompt various physiological, biological, and psychological responses within AUD individuals (Koob & Le Moal, 2008; Tiffany, 1990; Tiffany & Carter, 1998). These responses are involved in driving urges toward the behaviour, such as dysregulated alcohol consumption (Bechara, 2005; Goldstein & Volkow, 2002; Koob, Everitt, & Robbins, 2008; Koob & Le Moal, 2008; Koob & Volkow, 2009). The strength of these alcohol-related cues, and their capability to elicit responses is a key part of the regulatory challenge for individuals with AUD, who must self-regulate appropriately when exposed to these eliciting cues (Sayette, 2004).

Therefore, I am interested in evaluating the potential mechanisms that may underlie regulation, through examination of dysregulated AUD individuals who consistently demonstrate difficulties in regulation of alcohol consumption. This thesis aimed to advance our understanding of mechanisms involved in self-regulation in AUD. A diverse range of quantitative methodologies were applied to measure regulation of responses across various time periods surrounding cue exposure, including reactive responses during exposure to alcohol cues, regulation of these responses after cues are removed, and anticipatory responses to cues that indicate impending reinforcement and potentially negative outcomes. Additionally, I examined cognitive processes that may subserve appropriate regulation, such as executive functions, to determine if they are a significant component in self-regulation in AUD. This first chapter provides an overview and context that establish the theoretical framework for the empirical chapters, including problems associated with drinking, conceptual models of dysregulation in AUD, the role of cognitive processes in regulation, and determining the factors and timescale of regulation that will be examined through several novel and comprehensive methods implemented in my program of research. The next section

of this chapter will present a review of the literature on regulation in AUDs and an outline of the aims and structure of the thesis will be established.

Problems from Drinking

Alcohol has a diverse range of negative effects that can arise from consumption. These can be acute, sometimes resulting from a single occasion of alcohol intake, including (but not exhaustive): physical effects, such as headaches, nausea, or hangovers; personal injury, due to risky behaviours such as drink driving, accidents, violence, and risky sexual behaviour (Rehm et al., 2003; Taylor et al., 2010); psychological feelings of guilt or remorse (Muraven, Collins, Morsheimer, Shiffman, & Paty, 2005); and social, interpersonal, financial, or employment impacts (Klingemann & Gmel, 2001; Rehm, 2011). Continued and/or regular consumption can lead to chronic problems involving: more severe occurrences or compounding of acute consequences (Rehm et al., 2003; Taylor et al., 2010); significant health problems, such as brain and organ damage (including the liver, heart, and pancreas; Butterworth, 1995a; Irving, Samokhvalov, & Rehm, 2009; Patra et al., 2010; Rehm et al., 2003; Samokhvalov, Irving, & Rehm, 2010), and weakening of the immune system (Cook, 1998; Goral, Karavitis, & Kovacs, 2008); significant financial and employment problems; and psychosocial issues, such as the loss of interpersonal relationships with family and friends (Casswell & Thamarangsi, 2009; Klingemann & Gmel, 2001). These types of consequences are largely reflected in various screening and diagnosis instruments for clinical identification of AUD (e.g., the Alcohol Dependence Scale; Skinner & Allen, 1982), and measures specifically identifying the occurrence and frequency of drinking consequences (e.g., the Drinkers Inventory of Consequences (Miller, Tonigan, & Longabaugh, 1995). Alcohol consumption is thus clearly associated with several negative consequences, and experiencing these may predicate regulation of behaviour to avoid the development of more significant alcohol problems in the future.

However, alcohol is also associated with positive outcomes. Similar to other substances of abuse, alcohol use has several initial neuropharmacological effects on the body, occurring through interaction with the reward and reinforcement systems via several neuroreceptor targets within the brain, including the dopaminergic, serotonergic, opioid, glutamatergic, and gamma-amino-butyric acid-ergic pathways (for reviews, see Chastain, 2006; Gilpin & Koob, 2008; Lovinger, 2008). This can lead to positive emotional states, such as pleasure and alcohol-induced euphoria, which are generally accepted as key motivating factors in early stages of alcohol use, and for people who develop AUD (Gilpin & Koob, 2008). For example, drugs of abuse typically produce euphoria through activation of brain pleasure and reward centres, leading to the increase of extracellular dopamine in areas such as the nucleus accumbens, although receptor action (e.g., the D2 receptor) is also a key component (Volkow, Fowler, Wang, & Swanson, 2004). Alcohol also has significant positive psychosocial outcomes. It is attributed as a social lubricant that can reduce preoccupation regarding rejection, and lead to social rewards (Fairbairn & Sayette, 2014). Alcohol can also increase positive mood, either through intoxication effects, or through reducing negative affect related to the removal of negative effects of alcohol withdrawal experienced by chronic drinkers due to adaptations from persistent alcohol exposure (Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Heinz et al., 2003; Koob & Le Moal, 2001; Siegel, 1983). Taken together, alcohol has a range of positive outcomes that may arise from initial use or due to chronic exposure, and occasion further continued consumption.

Given that alcohol use is associated with both positive and negative effects, drinkers are faced with the problem of how to appropriately regulate consumption below risky levels, or avoid risky patterns of consumption. For example, the most recent guidelines for safe drinking levels in Australia (proposed by the National Health and Medical Research Council) suggest restricting intake to no more than two standard units (SD: one SD = 10 g ethanol) a

day for healthy adults (National Health and Medical Research Council, 2009). Drinking above this level, or drinking more than four standard units in one session—regarded as acute harm (i.e., binge drinking)—can be considered as risky drinking. Regulation of drinking behaviour would therefore involve restricting impulses or desires to consume alcohol, in order to limit consumption below risky levels and/or to avoid negative consequences. Herein lies the challenge of appropriate self-regulation in AUD, as problem drinkers are regularly exposed to high-risk situations that may compromise their capacity to maintain or abstain from drinking.

However, AUD is a complex, multifaceted disorder that has significant heterogeneity (Dick & Kendler, 2012). Similar to several mental disorders, the mechanisms and experiences that underpin AUD within individuals stem from a multitude of neurobiological and environmental factors. The unique interaction of these factors manifest in varying patterns, including: levels and frequency of consumption; severity of alcohol use problems; and stages of regulated drinking, such as cycles of abstinence and relapse. Indeed, subphenotypes have been continuously categorised and updated across the decades of alcohol research (Litten et al., 2015), with one recent classification identifying dysregulated drinking behaviours occur across the continuum of severity, and are exhibited with several subphenotypes of AUD (Moss, Chen, & Yi, 2007). The range of negative consequences linked to consumption is weighed against the positive aspects of alcohol use, which should be considered by individuals with AUD who continue to consume at risky levels, or those who continue to consume alcohol despite significant experienced negative drinking consequences. This thesis will focus upon the dysregulated negative consequences associated with drinking outcomes as a measure of severity in AUD. Moreover, I will evaluate what processes may underlie appropriate self-regulation of responses to alcohol cues, which allow most individuals who drink alcohol to effectively control their intake and reduce aversive outcomes.

Conceptual Frameworks of Dysregulation in AUD

Several models of self-regulation have been developed to explain why individuals with AUD have difficulties regulating responses elicited by motivational alcohol cues. These models have common themes that relate to successful regulation of behaviour, including: (a) an increased salience of eliciting cues; (b) an "impulsive" system comprising motivational networks and reward pathways that respond to these cues, and increases subsequent motivational drive toward cues; (c) a regulatory "reflective" system that should successfully monitor or control the reactions elicited by the reward and motivational neurocircuitry. These will be described in further detail below in the context of the program of research.

The strength of salient alcohol-related cues: key drivers of responses to alcohol.

The emergence of these motivational impulses related to alcohol can be triggered by various related environmental cues. A neurobiological model of addiction (Koob & Le Moal, 2001, 2008; Koob & Volkow, 2009) provides a framework to demonstrate the strengthening of cues in the generation of motivational, impulsive system responses toward alcohol. Initially, the reinforcing effects of alcohol consumption establishes an association between the rewarding properties of alcohol (e.g., euphoria) and alcohol-related cues in the environment. These cues will primarily relate to features of alcohol per se, such as the taste, smell, or visual (e.g., drink colour, effervescence) associations (Tiffany, 1990). Repeated exposure strengthens the eliciting power of the environmental cues, leading to the sensitisation of the motivational incentive neurocircuitry, and shifting from an initial "liking' to "wanting" of the drug (Robinson & Berridge, 1993). Negative reinforcement is also a factor, for decreased levels or cessation of alcohol within the system can initiate withdrawal though several physiological mechanisms (Koob & Le Moal, 2008). This can lead to craving—defined as the conscious desire for a drug (Drummond, 2000)—and motivation to consume alcohol thus occurs to alleviate negative affect (Koob et al., 2008). Solomon and Corbit's (1974) opponent

process theory of motivation explains this inverse relationship, proposing that experienced emotional, affective or hedonic states are automatically suppressed by the central nervous system, through several mechanisms that counter the valence of these states.

This suppression (or inhibition) of the central nervous system can be demonstrated in the regulation of these states, as reflected through physiological indices (such as heart rate) in response to stressors in the environment. Appropriate regulation of responses within an organism in response to dynamic external cues is key for adaptability and flexibility to environmental demands. For example, Thayer and Lane's (2000) neurovisceral integration model proposes that both the central and peripheral nervous systems comprise a "super-system", that incorporates both external and internal information to produce an adaptive, contextually relevant physiological response and elicit motivational drives. This is reflected in heart rate variability (HRV), the beat-to-beat changes in heart rate that are driven by the sympathetic and parasympathetic autonomic nervous systems, and can provide information of underlying processes of regulation within the organism (Thayer & Lane, 2009).

Of particular interest is the parasympathetic system, as it can exert a relatively rapid high-frequency temporal effect on heart rate via the vagal access through top-down processes signalled from the brain (Malliani, Montano, & Pagani, 1997). High-frequency HRV is therefore a potential index of an adaptive, flexible organism capable of reacting to potential cues and stressors in the environment (Thayer & Brosschot, 2005). In the context of AUD, maladaptive regulation may be evidenced through these parasympathetic indices providing information of motivational responses to alcohol-related cues. For example, reduced parasympathetic HRV activity during alcohol cue exposures in AUD individuals corresponds with elevated responses (or feelings) to eliciting cues (Ingjaldsson, Thayer, & Laberg, 2003) resulting in a heightened state of arousal in expectation of a drinking situation or alcohol reinforcement.

The emergence of these feelings or states that may be triggered by drug-related cues in the environment can also elicit positive affect associated with pharmacological, physiological, and psychological drug effects, and/or negative affective states as drug use progresses—all which influence drug-seeking behaviour, and potentially leading to compulsive drug use (Koob & Le Moal, 2008). Additionally, physiological and neurobiological changes through repeated drug use—such as altered neurotransmitter levels and receptor expression within the brain—can also shift the homeostatic (i.e., optimal) level of functioning of the organism, so that further drug intake may be sought to maintain the altered level of functioning within the system and compensate for these changes. This is a termed an "allostatic state"— as a state of persisting divergence of regulatory systems that maintain the normal homeostatic functioning of an organism to a new level or set point (Koob & Le Moal, 2001). Subcortical structures involved in reward and motivation are activated in the initial stages of alcohol and drug use, and through repeated, chronic use the normal function of these structures is altered, driving subsequent drug use to compensate for persistent neurochemical and neurobiological changes (Koob & Le Moal, 2001). The "hijacking" of the reward and motivational pathways (also known as the mesocorticolimbic pathway) explains how individuals can be drawn to consume abused substances (Kalivas & Volkow, 2005; Nesse & Berridge, 1997). Furthermore, a system that is not able to adjust accordingly to demands of the environment, or that is inflexible or "stuck" in a particular pattern is considered maladaptive (Koob & Le Moal, 2001), and may be reflected in physiological indices such as heart rate variability as per the neurovisceral integration model (Thayer & Lane, 2000). This thesis will therefore examine these changes and patterns in individuals with AUD as indices of maladaptive regulatory responses to alcohol cues. Furthermore, I will implement various neuropsychological, psychophysiological and neuroimaging techniques to determine whether these mechanisms involved in regulation of

these affective states are critical in the progression and maintenance of AUD, and whether maladaptive regulation of responses to alcohol-related cues may thus be key to this disorder.

Regulation of impulsive responses to alcohol cues: the interaction of two competing systems.

Dual-process models of addiction are a framework that has been developed to explain the interaction of competing systems in substance use disorders (Bechara, 2005; Lubman, Yücel, & Pantelis, 2004; Wiers & Stacy, 2006b). Dual-process models comprise two processes responsible for behaviour: the "impulsive" system, which involves relatively automatic, impulsive drives; and the "reflective" system, which monitors and regulates these impulses (Bechara & Damasio, 2005; Strack & Deutsch, 2004). In alcohol dependence, the impulsive system response to alcohol-specific cues is strengthened through several related—but distinct—mechanisms, including: incentive sensitisation (Robinson & Berridge, 1993), habit-formation (Everitt & Robbins, 2005; Koob & Volkow, 2009) and negative reinforcement (Koob & Le Moal, 2008), which result in an overactive impulsive system. The role of the reflective system, therefore, should be maintaining and regulating the urge to consume alcohol driven by the impulsive system: either indirectly, through the inhibition of the impulsive system; or directly suppressing the urges to consume alcohol.

There has been some criticism of general dual-process models, concerning their over-simplification of complex behavioural phenomena potentially limiting consideration of other significant factors, and the inconsistency between researchers regarding conceptual definitions of these models (Keren & Schul, 2009). This, in part, may be due to the underlying perspectives that stem from their field of development, such as neuropsychological (Bechara, 2005), neurobiological (Lubman et al., 2004), or social-psychological (Strack & Deutsch, 2004) foundations (see Wiers & Stacy, 2006b). However, while recognising that these processes do not exclusively determine output of behaviour and have many overlapping

functional components (Gladwin, Figner, Crone, & Wiers, 2011), dual-process models arguably still provide a useful theoretical framework to conceptualise specific complex behaviours such as AUD, a considerably heterogeneous disorder that potentially involves a multitude of determining neurobiological and environmental factors. This thesis attempted to comprehensively capture these interacting components at several levels, using a range of measurement techniques across various stages of cue presentation, to better identify these processes within dysregulated individuals with AUD.

Failure to self-regulate behaviours, therefore, results from the net effect of these systems. For example, Heatherton and Wagner (2011) suggest individuals have difficulty with appropriate self-regulation due to an imbalance in motivational (i.e. impulsive) and regulatory (i.e. reflective) systems, and emphasises the role of key factors that shift the balance toward the reward/motivational system outputs. In AUD, strong impulses or drive toward a behaviour or substance requiring self-regulation are triggered by salient alcohol-related cues. Alternatively, the regulatory system that should appropriately control these impulses may be impaired, underactive, or overwhelmed by the strength of this impulsive drive (Bickel et al., 2007), and thus unable to self-regulate appropriately. It is the interaction of these competing systems in the presence of alcohol-related cues eliciting impulses that may lead to dysregulated drinking behaviours, and capturing this interplay is central to this thesis.

Individuals with AUD will be regularly exposed to high-risk situations containing various alcohol-related cues that may challenge their capacity to self-regulate, and these impulsive drives may lead to disadvantageous drinking outcomes (e.g., excessive consumption, relapse) and result in negative consequences that could be both acute and/or chronic. The regulatory "reflective" system (hereafter referred to as the reflective system; Strack & Deutsch, 2004) defined in dual-process models is proposed to encompass cognitive processes that regulate impulsive urges and drives that may be disadvantageous. This includes

executive functioning—an umbrella term that encapsulates several cognitive functions that guide complex adaptive and goal-directed behaviours during novel situations, including: planning, targeted and sustained attentional processes, response inhibition, cognitive flexibility, and reasoning (Crews & Boettiger, 2009; Miyake & Friedman, 2012; Miyake et al., 2000). Executive functions are generally considered to be involved in the control and regulation of more basic cognitive functions such as visual and spatial perception, psychomotor abilities (e.g., response speed), and nonselective attention (Alvarez & Emory, 2006). According to the dual-process model of addiction, continued and/or chronic consumption in alcohol dependence is the outcome of the reflective system inadequately regulate impulsive urges to consume alcohol (Wiers & Stacy, 2006a). This reduced capacity of the reflective system to appropriately regulate responses may rely upon sufficient executive functioning ability, and thus impairment in executive functions may be a key factor in the progression to, and the maintenance of, severe AUD.

Comprehensive identification of specific executive functioning deficits in AUD samples and the potential role in regulation of alcohol cue-elicited responses is a key theme that is investigated in my thesis. However, it is important to note that other cognitive processes are also posited to comprise the reflective system, which often have overlapping constructs and utilities that accord with components of executive functioning—such as working memory (Deutsch, Gawronski, & Strack, 2006)—which is beyond the scope of this thesis. For the purposes of this thesis, I restricted investigation to the defining role of executive functioning capacity in AUD, and the relationship between executive functioning and regulation of alcohol cue-elicited responses in explaining the continuation of drinking in the face of adverse consequences evident in this population of dysregulated individuals.

The Role of Executive Functioning in Regulation in Alcohol Use Disorder

There is substantial evidence of cognitive impairment in AUD in treatment-seeking samples, both with complicated aetiologies (e.g., Wernicke-Korsakoff's syndrome from thiamine deficiencies, Oscar-Berman, 2012; alcohol dementia, Ridley, Draper, & Withall, 2013) and comparatively "typical" severe AUD (Le Berre, Fama, & Sullivan, 2017; Oscar-Berman et al., 2014; E. V. Sullivan, Harris, & Pfefferbaum, 2010); as the latter is the focus in my thesis, we excluded individuals experiencing separate syndromes such as Wernicke-Korsakoff's syndrome within our AUD samples. Executive functioning is a key neuropsychological functional domain that is impaired in AUD, but other domains are affected, including domains of memory, visuospatial cognition, emotional and psychosocial skills, and psychomotor abilities (Oscar-Berman et al., 2014). However, executive functioning has a significant role subserving higher-order cognitive processes of goal-directed behaviour such as decision-making and reasoning—cognitive processes which are key in making choices leading to dysregulated alcohol behaviours such as chronic consumption (Le Berre et al., 2017). Accordingly, while I acknowledge that impairment in other cognitive domains may have an impact in AUD, I restrict the focus in this thesis to investigation of executive functioning domains and associations as a key factor in regulation in AUD.

There is considerable evidence of executive functioning impairment in AUD. Research suggests that executive functions are most vulnerable to alcohol-induced deficits (Nixon, 2006; Parsons, 1998). Studies employing extensive batteries of standardised neuropsychological tests have demonstrated specific executive functioning deficits compared to healthy controls in recently detoxified alcoholics (Ratti, Bo, Giardini, & Soragna, 2002; E. V. Sullivan, Rosenbloom, Lim, & Pfefferbaum, 2000), including no deficits to non-executive functions (Noël et al., 2001). While some recovery of executive functioning impairment is evident, executive functioning impairments have been shown to be the most pervasive

alcohol-related cognitive deficits, and take longer to recover than other cognitive domains (Bates, Pawlak, Tonigan, & Buckman, 2006; Oscar-Berman & Marinković, 2007; Zinn, Stein, & Swartzwelder, 2004), with a recent meta-analysis revealing long-term deficits are evident across executive functioning domains at one year of abstinence (Stavro, Pelletier, & Potvin, 2013). Impairment is also seen in non-treatment-seeking heavy drinker samples, demonstrating wide-ranging executive functioning deficits relative to consumption (Houston et al., 2014; Montgomery, Fisk, Murphy, Ryland, & Hilton, 2012), although there is some conflicting evidence (S. Smith & Fein, 2010). Results may be mixed according to several factors, including: measures of pre- and post-abstinence, adequately controlling for practice effects inherent in various standard neuropsychological measures, the difficulties involved in prospective studies that capture pre-drinking cognitive performance, and may thus provide the link between progression of AUD (Schulte et al., 2014). Impairment identification in non-treatment-seeking samples is important, considering only an estimated 15-25% ever seek treatment for AUD in Australian or American contexts (Teesson, Baillie, Lynskey, Manor, & Degenhardt, 2006), and thus clinical treatment samples may not fully reflect the heterogeneity of AUD and range of dysregulated drinking patterns. Taken together, it is apparent that executive functioning deficits are present in non-treatment-seeking and clinical drinker samples, and impairment may be pervasive, persisting even after abstinence is achieved. In order to best capture the breadth of dysregulated drinking behaviours and consumption patterns, as well individual differences in executive functioning ability, this thesis implements both treatment-seeking and non-treatment-seeking samples.

To assess the extent that separable executive functioning component processes may uniquely influence dysregulated drinking and self-regulation in AUD, the concept of executive functioning needs to be deconstructed. Miyake and Freidman's (Miyake & Friedman, 2012; Miyake et al., 2000) influential unitary/diversity model of executive

functions supplies a theoretical framework to extend the conceptualisation of the cognitive construct, outlining three underlying components or subdomains. They demonstrated through a series of elegant latent-variable analyses that commonly applied neuropsychological tasks engage one, or more, of three subdomains that are both unified and separable: a common executive functioning component, comprising maintenance of low level processing toward goal-oriented tasks (originally response inhibition); a set-shifting component, the capacity to switch between new task-set representations, often referred to as cognitive flexibility; and an updating-specific component, the capacity to renew short-term, task-relevant stored information (Miyake et al., 2000). Tasks measuring these domains have identified domain-specific deficits in several clinical AUD samples (Chanraud et al., 2007; Oscar-Berman et al., 2009; Oscar-Berman et al., 2014; Ratti et al., 2002; Zinn et al., 2004) and non-treatment-seeking heavy drinkers (Montgomery et al., 2012). However, the discrete contribution of these domains to regulation has not been extensively assessed, particularly when AUD individuals are exposed to tangible alcohol cues. The empirical study presented in Chapter Two of this thesis will apply the unitary/diversity framework (Miyake et al., 2000) to examine whether these executive functioning domains are varyingly associated with appropriate regulation of cue-elicited responses during a laboratory cue presentation task in regular drinkers.

Structural targets for executive functioning: overlapping neurocircuitry.

Executive functions are generally linked to frontal cortex of the brain, primarily the prefrontal cortex and surrounding connective networks; although the extent to which executive functioning are regulated by the frontal lobes is still disputed (Miyake et al., 2000; Stuss & Alexander, 2000; Welsh, 2002). This contention stems partly from the development of the construct from a largely clinical neuropsychological and neurocognitive testing foundation (Stuss & Alexander, 2000), coupled with converging—though sometimes

inconsistent—evidence of reduced performance from patients with lesions in prefrontal areas. For example, Alvarez and Emory's (2006) meta-analysis examining the links between executive functioning and the frontal cortex in lesion studies found inconsistent evidence associating deficits in three regularly used complex executive functioning tasks (e.g., Verbal Fluency, Wisconsin Card Sorting Task, Stroop Interference Task) and prefrontal structural targets. While the examination of complex executive functioning tasks that employ multiple subdomains may limit the sensitivity of the effects within the studies investigated (Miyake et al., 2000), these findings suggest a functional diversity of executive functioning within the prefrontal cortex. More recently, corroborating evidence has been augmented through functional imaging research in healthy individuals (Yuan & Raz, 2014), which better account for executive functioning task-specific brain activity than lesion studies alone.

The prefrontal cortex is also increasingly implicated in addiction. This has been driven by a wealth of preclinical evidence (Mansouri, Tanaka, & Buckley, 2009), and more recent advances in brain imaging technology (notably magnetic resonance imaging [MRI] techniques) (Goldstein & Volkow, 2011; Koob & Volkow, 2009). This allows for specificity in mapping functional constructs to anatomical structures in the human brain, through correlational physiological indices of brain activity (e.g., blood oxygen level dependent [BOLD] activity) signalled within neural regions that accord with events during imaging adaptations of traditional neuropsychological tasks (Goldstein & Volkow, 2011; Koob & Volkow, 2009; E. V. Sullivan et al., 2010). Structural imaging studies have identified links with alcohol consumption and changes to overall brain morphometry largely reflecting grey and white matter volume reductions (Fein et al., 2002; Jernigan et al., 1991; Pfefferbaum et al., 1992). However, the prefrontal cortex appears to be particularly vulnerable, with decreased grey matter volume specific to frontal lobes identified with structural MRI in a range of AUD samples including: treated alcohol dependent patients (O'Neill, Cardenas, &

Meyerhoff, 2001), chronic older alcoholics in treatment (Pfefferbaum, Sullivan, Mathalon, & Lim, 1997), and non-treatment-seeking heavy drinkers (Cardenas, Studholme, Meyerhoff, Song, & Weiner, 2005). White matter tracts serving prefrontal areas are also affected, with volume reductions in adult samples (Harris et al., 2008; Pfefferbaum, Rosenbloom, Rohlfing, & Sullivan, 2009) and within younger samples of binge drinkers (K. W. Smith et al., 2017) and alcohol dependent adolescents and young adults (De Bellis et al., 2005). Both white and grey matter are therefore significantly affected in AUD, with the prefrontal cortex particularly vulnerable to brain morphometry changes.

Considering the overlap of localisation of executive functioning in the prefrontal cortex and its sensitivity to brain changes in AUD, it corresponds that brain morphometry changes in AUD have also been associated with cognitive impairment in discrete regions of the prefrontal cortex. Prefrontal brain volume loss in alcohol dependent patients in areas such as the middle frontal gyrus (MFG) were associated with worse neuropsychological executive functioning task performance, while social and somatic functioning remained relatively unaffected (Chanraud et al., 2007). Worse performance in a spatial working memory task which corresponded with prefrontal brain volume differences (e.g., MFG) in alcohol dependent patients when compared to healthy controls (Chanraud, Pitel, Rohlfing, Pfefferbaum, & Sullivan, 2010), and reduced volume in the rostral middle frontal cortex predicted worse executive functioning performance in alcohol dependent patients (Nakamura-Palacios et al., 2014). Thus, there is an association between prefrontal cortical brain morphometry changes in AUD and corresponding executive functioning deficits.

A significant linkage of structural brain changes and AUD is therefore emerging. These changes are primarily due to physical insult caused by alcohol, which has a toxic effect directly upon the brain at a cellular, neurotrophic, and neuronal level (Butterworth, 1995a; Harper, 2009; Harper & Matsumoto, 2005); indirectly through damage to the liver (e.g.,

hepatic encephalopathy; Butterworth, 1995b), and from nutritional deficiencies (e.g., thiamine deficiency leading to Wernicke-Korsakoff syndrome; Martin, Singleton, & Hiller-Sturmhöfel, 2003). Moreover, this alcohol-related brain damage is directly associated with cognitive impairment including executive functioning deficits (Harper & Matsumoto, 2005). Taken together, alcohol has diverse structural impacts upon the brain of heavy drinkers, and can occur through various mechanisms, with the prefrontal cortex—and by proxy, executive functioning—particularly vulnerable.

Functional correlates of cognitive functioning and alcohol use disorder.

Employing functional imaging methods to identify brain regions involved in cognitive functioning and AUD poses some problems, primarily due to widespread structural impacts from chronic alcohol consumption. Moreover, imaging presents some limitations in administration of traditional neuropsychological tests, due to both the physical restrictions of the equipment (e.g., MRI bore size, use of non-ferrous materials) coupled with measurement of functional responses (e.g., movement artefacts, time-course of the haemodynamic response function) impeding the presentation procedure of some tasks. Drawing inferences from patterns of activation is complex due to the indirect measurement of brain activity, such as BOLD activity in functional (f)MRI. Additionally, the prefrontal cortex is considerably functionally heterogeneous, demonstrating cognitive flexibility and neuroanatomical plasticity, making it difficult to localise functional processes to subregions of the brain (Goldstein & Volkow, 2011). Despite these challenges, effective sampling controls, computational advances in imaging techniques, and novel solutions for task presentation using MRI and positron emission topography (PET) techniques have enabled us to identify differences in brain activity within prefrontal areas during completion of neuropsychological executive functioning tasks in several substance-use samples. (Goldstein, Moeller, & Volkow, 2011).

As outlined by their impaired response inhibition and salience attribution (I-RISA) model in a seminal functional imaging review, Goldstein and Volkow (2002) argue that prefrontal cortex malfunction is a primary contributing factor in the increased prominence of subcortical and limbic reward and motivational circuits during addiction, due to impairments in frontal regions to effectively control and regulate responses, particularly when challenged with salient drug-related cues. Conceptually, this parallels with dual-process models of addiction, and further emphasises the prominent role of cues in eliciting of responses. Distinct functional regions associated with executive functioning in drug addiction have consequently been identified during executive functioning tasks completed within imaging modalities (i.e. fMRI, PET) comparing drug use samples and healthy controls, with and without drug administration (Goldstein et al., 2011; Goldstein & Volkow, 2011). These regions include the dorsolateral prefrontal cortex (DLPFC), the ventromedial prefrontal cortex (VMPFC), the orbitofrontal cortex (OFC), and the cingulate cortex (Goldstein et al., 2011)—regions significantly compromised in AUD (Oscar-Berman et al., 2014). Overall, a general pattern of task-related hypoactivity in the prefrontal cortex has been identified (Goldstein & Volkow, 2011). Hyperactivation of these regions has also been evidenced, but is generally related to compensatory recruitment to counter impaired functioning of principal regions associated with adequate performance, indicating task-specific areas need to be accounted for when inferring from imaging data (Wetherill, Squeglia, Yang, & Tapert, 2013).

Fundamentally, there is considerable conceptual overlap between the regulatory components of the super-system proposed by the neurovisceral integration model and the reflective system espoused by dual-processes models of addiction. This is further evidenced by a commonality of these models' governing neural structures, such as the medial frontal and anterior cingulate cortices (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012), which are also critical structures in addiction model networks for representation of internal and external

contexts and consequent control processes. However, the convergence of these models have only been partially tested, and it is unclear whether this commonality in their neurocircuitry is reflected in maladaptive regulation of responses within dysregulated AUD individuals. This thesis attempted to clarify whether these regions share commonality through the convergence of the underlying neurocircuitry of some of these models in the regulation of responses in AUD in Chapter Five, which applies an imaging cue presentation task to identify overlapping neural correlates of regulatory processes.

Investigating the Mechanisms and Influencing Factors of Self-regulation in Alcohol Use Disorder

In summary, several theoretical models posit key themes in self-regulation in AUD, namely the interaction of the motivational impulsive system reacting to salient alcohol cues and the subsequent regulation of these impulses by the reflective system, thus reducing deleterious drinking behaviours. However, while the reflective system assumedly has a prominent role in the appropriate self-regulation in AUD, the extent of this relationship is still unclear. Several overlapping components have emerged through this brief conceptual overview of various neurocognitive and neurobiological models that attempt to explain self-regulation in AUD. Identifying the factors that may be integral for appropriate regulation of responses to drinking cues may help us better understand the underlying mechanisms involved in successful self-regulation in these dysregulated individuals. Subsequently, elucidating the extent to which these components are involved in the regulation of impulsive, motivational drives inherent in AUD may inform and augment current frameworks, which do not yet adequately explain dysregulated behaviour within this complex and multifaceted disorder.

Therefore, this thesis will address the following questions: 1) Is the inability of the reflective system to regulate responses to salient cues a major component predicating

dysregulated drinking behaviour in AUD? 2) Do cognitive processes such as executive functioning play a role in the capacity of the reflective system to appropriately regulate impulsive responses to alcohol, and are the executive functioning domains differently involved? 3) What is the timescale of regulation, and at which stages surrounding cue presentation is regulation apparent? 4) Is there a convergence in the neurocircuitry implicated in regulatory frameworks evident in dysregulated drinkers, particularly in prefrontal regions? The aim of this programme of research was to empirically investigate the potential mechanisms that may underlie self-regulation through the examination of dysregulated AUD individuals. To achieve this, a diverse methodology of neuropsychological, psychophysiological and neuroimaging techniques were employed to comprehensively evaluate regulation across various time periods surrounding cue presentation (e.g., cue reactivity during cue exposures, recovery periods after cue offset, and anticipatory responses prior to reinforcement) to assess the relationship of components such as executive functioning in appropriate regulation, and elucidate underlying regulatory processes in a range of dysregulated drinking samples.

Methodological Considerations

Identifying the timescale of regulation.

Successful regulation involves controlling the drives and urge to drink signalled by the impulsive system that are elicited by salient environmental cues. However, individuals are exposed to numerous types of eliciting stimuli in social and environmental contexts that are often situationally specific (Tiffany & Conklin, 2000). Measurement of these specific responses is consequently complex, and can be affected by multiple factors that may be competing (e.g., anxiety-provoking situations) and/or complimentary (e.g., other arousing cues such as sexual or appetitive cues). Eliciting these responses to individual cues in a controlled environment is therefore required to isolate the drug-specific impact of the cues

(Carter & Tiffany, 1999). Laboratory paradigms that present salient stimuli to individuals allows for control of external parameters, and thus maximises the specificity and reliability of measurement of regulation of responses to cues in real-time.

This thesis attempts to delineate the timescale of regulatory processes through assessment of responses surrounding cue presentation. This includes reactivity during exposure to cues; the recovery effect after cue offset, whereby elicited responses should be regulated; and anticipatory responses prior to cue presentation where reinforcement is expected. The following section describes the varying methodologies that are employed in this thesis, and the diverse range of techniques to capture indices of regulation, such as self-report, neuropsychological, psychophysiological and neuroimaging outcomes.

Cue reactivity—cue present.

It is important to establish whether alcohol cues elicit the expected responses in dysregulated AUD individuals (referred to as cue reactivity) as an indication of impulsive system activity. This can be initiated using the cue reactivity task (also referred to as the cue exposure task; Drummond & Glautier, 1994) . The cue reactivity task is a laboratory paradigm involving presentation of tangible alcohol cues to elicit and measure subjective (e.g, alcohol craving), physiological (e.g., heart rate variability, skin conductance response), biological (e.g., neuro-endocrine changes such as cortisol) and behavioural (e.g., consumption) responses evoked by the cues. An extensive literature exists of cue reactivity tasks employed in alcohol use research (Carter & Tiffany, 1999) and has informed several theoretical frameworks that refer to the strengthening of initially neutral alcohol-related stimuli and incentive-salience associations previously outlined. Several modalities of drug-related stimuli can be used (visual, tactile, olfactory, gustatory; or a combination) to elicit motivational impulsive responses and are compared to a baseline, or control stimuli, which

can be neutral (e.g., affectively neutral images), or appetitive (such as water or novel beverages, high-caloric food).

Several studies have been conducted assessing participants' subjective craving for alcohol via self-report, but there have been mixed results of self-reported craving and the strength of its association with behavioural drinking outcomes of dysregulation. For example, when assessing relapse in abstaining clinical AUD samples, several studies observed no connection between reported alcohol craving and relapse (Grüsser et al., 2004; Litt, Cooney, & Morse, 2000; Reich, Below, & Goldman, 2010; Rohsenow et al., 1992), while other studies found evidence of a positive correlation (Bottlender & Soyka, 2004; Cooney et al., 1997; Heinz et al., 2005). This may be partly due to demand characteristics inherent in treatment-seeking samples, for whom reporting of craving may indicate failure in patients' perceived treatment goals, resulting in denial of feelings associated with alcohol (Tiffany & Carter, 1998). Alternatively, lack of recognition may be due to impaired interoception, impeding comprehension of experienced impulses and affective states related to alcohol (Verdejo-Garcia, Clark, & Dunn, 2012).

However, studies examining psychophysiological responses due to alcohol-related cues have demonstrated stronger relationships to drinking behaviours, such as skin conductance response (Drummond & Glautier, 1994), cardiovascular indices (Garland, Franken, & Howard, 2012; Ingjaldsson, Laberg, & Thayer, 2003), salivation (Roshenhow, 1994), and neural targets using functional imaging (Braus et al., 2001; Filbey, Claus, & Hutchison, 2011; Grüsser et al., 2004). Furthermore, psychophysiological indices can also provide information on underlying regulatory processes controlling impulsive system responses, and advances in psychophysiological measurement techniques, such as functional imaging (fMRI, PET), has seen an increase in the application and versatility of the cue

reactivity task for several drugs of abuse (for review, see Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014). Some of these indices will be discussed briefly.

Cardiovascular indices of cue regulation.

Heart rate variability reflects differences in the length of beat-to-beat changes of heart rate, and is a useful psychophysiological marker for examining regulation, as it is reactive to emotionally salient cues in the environment, and can provide information on the interplay between the sympathetic and parasympathetic influences of the autonomic nervous system (Porges, 2009; Thayer & Lane, 2009). The role of parasympathetic system is of interest as it is responsible for regulating heart rate in response to emotional cues and returning the organism to homeostasis (Malliani, Pagani, Montano, & Mela, 1998). In particular, measuring high-frequency HRV during a cue reactivity task allows us to index the parasympathetic system activity in response to eliciting environmental cues, reflective of an organism's ability to adaptively react to potential cues and stressors in the environment (Thayer & Brosschot, 2005). Furthermore, a system that is not able to adjust accordingly to demands of the environment, or that is inflexible or stuck in a particular pattern is considered maladaptive as it cannot adjust to dynamic environmental demands—potentially reflecting an allostatic state of altered functioning (Koob & Le Moal, 2001).

Physiological indices such as HRV can therefore provide an indirect measure of reactivity of salient alcohol-cue responses. This has been demonstrated in research measuring HRV during cue reactivity tasks, with alcohol cue exposure increasing high-frequency HRV in alcohol dependent patients when exposed to an alcohol-cued script (Ingjaldsson, Laberg, et al., 2003), and high-frequency HRV predicting probability of relapse in treated alcohol dependent patients who demonstrated greater high-frequency HRV to stress-primed alcohol cues prior to relapse (Garland et al., 2012). However, a combined laboratory and field study revealed no evidence of different high-frequency HRV responses to alcohol advertisement

cues in detoxified alcoholics compared to control soft drink advertisements at baseline measurement, or relationships with relapse, but this may be due to the diffuse strength of the eliciting cues (Witteman et al., 2015). Overall, HRV provides a reliable, low-intensity, non-invasive index of underlying regulatory processes comprising the dynamic output of autonomic nervous system activity.

Accordingly, Chapter Two and Chapter Three of this thesis include a cue reactivity task to measure the reactivity to cues in different samples of AUD participants. I employ a multimodal cue reactivity task that exposes participants to tactile, visual and olfactory appetitive alcohol beverage cues. Additionally, water will be administered as a neutral control to accommodate for appetitive characteristics intrinsic to alcohol cues (Monti et al., 1987). Cue reactivity will be assessed through both psychophysiological indices of arousal and parasympathetic responses (e.g., HRV) and self-reported behavioural measures of motivational responses (e.g., alcohol craving), where it is expected that elevated responses to the alcohol-related cues relate to greater AUD severity. Furthermore, as executive functioning is posited to play a significant role in reflective system regulation of impulsive system responses, I will examine whether worse executive functioning performance relates to heightened cue reactivity responses in AUD individuals.

Neural correlates of cue reactivity: alcohol cue-elicited activation.

Recent application of the cue reactivity paradigm within a functional imaging context—which allows for associations between functional activity of motivational responses and structural localisation—has seen a resurgence of studies investigating cue exposure in drug use (Jasinska et al., 2014) and AUD (Heinz, Beck, Grüsser, Grace, & Wrase, 2009). Several studies have identified brain regions activated by alcohol cue presentations, employing various modalities across AUD samples of differing severity (Schacht, Anton, & Myrick, 2013), including mapping neurocircuitry involved in psychological indicators, such

as craving response, and behavioural outcomes, such as vulnerability to relapse (Heinz et al., 2009). Differences in alcohol cue-elicited brain activation in prefrontal cortical areas have been associated with several outcomes of dysregulated alcohol use, including higher consumption in adolescents (Tapert, Cheung, Brown, & et al., 2003), greater severity of alcohol use problems (Claus, Ewing, Filbey, Sabbineni, & Hutchison, 2011; Filbey et al., 2007; Sjoerds, van den Brink, Beekman, Penninx, & Veltman, 2014), alcohol-related craving (George et al., 2001; Heinz et al., 2005; Seo et al., 2011), and relapse (Beck et al., 2012; Braus et al., 2001; Grüsser et al., 2004; Seo et al., 2011). A recent brain-coordinate-based meta-analysis by Schacht, Anton, and Myrick (2013) identified mesocortical neurocircuitry which was consistently activated within AUD samples, including the striatum, and prefrontal regions including the anterior cingulate cortex (ACC) and medial prefrontal cortex. These regions are implicated within reward pathways of drug abuse, indicating increased engagement of this circuitry by alcohol cues. Interestingly, differences in activation between control and AUD samples were not as evident in these same regions, although this may be due to limitations to the meta-analytic quantification approach in distinguishing cue-elicited response effects in alcohol dependent samples over and above activity exhibited by control samples (who may also find these cues rewarding and/or novel), leading to mixed results in these regions (Schacht, Anton, & Myrick, 2013). Moreover, several studies focused upon reward circuitry per se, whereas prefrontal brain activity may reflect effective regulation of motivational, impulsive responses to alcohol cues.

Despite this, few studies investigate the relationship between individual differences in cognitive functioning and appropriate regulation of these cues using functional imaging techniques during cue exposure. Wrase et al. (2007) found alcohol dependent patients exhibited hyperactivity in the OFC and thalamus during anticipation of loss/gain reinforcement during an fMRI monetary incentive delay task, but no differences in limbic

activation to reward compared to control participants. However, alcohol cue-elicited reactivity was demonstrated in expected mesocortical areas, suggesting engagement of subcortical reward structures is specific to alcohol compared to other reward processing, which may require recruitment of prefrontal regions (Wrase et al., 2007). Vollstädt-Klein et al. (2012) found associations with alcohol cue-induced activation and increased attention to alcohol cues during a visual attentional bias task in a network including frontal, temporal and subcortical regions. Overall, limited research has examined how cognitive processes such as executive functioning may be implicated in regulation during an fMRI alcohol cue reactivity task, and whether this is exhibited in patterns of brain activation of prefrontal regions. Chapter Five will therefore investigate neural correlates of executive functioning and alcohol cue-elicited activation in alcohol dependent patients, and what role executive functioning may have relative to regions associated with regulation of motivational responses to cues.

Regulation after cue offset and the recovery effect.

While the studies that implement cue reactivity tasks outlined above demonstrated that psychophysiological indices such as HRV are sensitive to alcohol cue reactivity, these studies largely do not account for regulatory processes that return the autonomic nervous system to baseline after cues are removed. This period after cue offset may be key in observing the timescale of regulation in a cue reactivity paradigm, as the parasympathetic system should actively recover from the regulatory challenge presented by the salient alcohol cues. The sensitivity of this "recovery effect" has been demonstrated in healthy participants, whereby lower vagal tone, indicated as reduced "resting" high-frequency HRV at baseline, was associated with delayed return to baseline levels after physical and cognitive stressors (Weber et al., 2010). Persistent autonomic system activity after an emotional stress task has also been demonstrated in undergraduate samples related to increased trait rumination (Key, Campbell, Bacon, & Gerin, 2008), and greater state-related worry (Verkuil, Brosschot, de

Beurs, & Thayer, 2009). Additionally, an inflexible system that is not responding to environmental demands may be revealed through a lack of overall change in parasympathetic response during the cue reactivity task, even when presented salient cues that should elicit impulsive responses. This lack of change may indicate a system that is operating at a consistently maladaptive or dysregulated level, suggesting evidence of an allostatic state (Koob & Le Moal, 2001). High-frequency HRV therefore can provide substantial information of regulation through parasympathetic responses and evidence of a recovery effect after cue offset.

However, there is a paucity of research that investigates this recovery effect using alcohol cue reactivity tasks. Monti et al. (1999) applied a recovery period after water and alcohol cue presentations, but employed psychophysiological measures that only capture gross arousal (e.g., heart rate) and stress (cortisol) response that lack sensitivity for parasympathetic autonomic activity. Garland (2011) found alcohol dependent inpatients demonstrated reduced high-frequency HRV recovery after a visual alcohol cue exposure task, but as this was a path-analysis study primarily investigating individual effects of mindfulness, it is unclear what level of parasympathetic system recovery was experienced. Furthermore, aversive pictures were used as a visual control, but only change scores between baseline–alcohol cue exposure and alcohol cue exposure–recovery were reported; whether this was alcohol-specific or related to general physiological arousal is unclear. A related pilot study (Garland, Gaylord, Boettiger, & Howard, 2010) investigating the effect of a mindfulness intervention in previously treated alcohol dependent participants observed decreased HRV during recovery after the same cue exposure task for the participants completing a mindfulness intervention, compared to those completing an evidence-based alcohol support group treatment. This apparently conflicting outcome was attributed to active regulation strategies employed during the recovery period, as well as appropriate HRV patterns during

the stress and alcohol cue task. However, the omission of a recovery period between stress and alcohol cues was a major limitation of this study, as the recovery cannot be cannot be demarcated specifically to either set of arousing stimuli (Garland et al., 2010). While the conclusions were unclear, this study demonstrates the versatility of HRV as a physiological index of underlying regulation.

This thesis will integrate the recovery effect demonstrated by psychophysiological indices after cue offsets within the cue reactivity paradigm. This will allow us to assess whether parasympathetic system regulation occurs, as levels of motivational responses to alcohol cues should return to baseline levels. Crucially, respective recovery periods following cue offsets (control water cue, alcohol cue) will be included to ascertain whether recovery effects are generalised to appetitive arousal, or alcohol cue-specific recovery is evidenced. Chapter Two and Chapter Three will employ this cue reactivity task adaptation, completed by samples with different profiles of dysregulated drinking. Furthermore, considering that severity of AUD should reduce the regulatory capacity of the system, this should be reflected in samples with increasing alcohol severity exhibiting reduced physiological indices of parasympathetic response. Finally, as executive functioning ability should reflect better regulation capacity, worse neuropsychological executive functioning task performance is expected to be associated with reduced or delayed recovery effects after cue offsets.

Skin conductance response and decision-making: anticipation of risky choices with negative outcomes.

AUD is characterised by impaired control of drinking, and continued consumption despite negative consequences. These symptoms may be due to poor decision-making surrounding drinking choices. Decision-making is a higher-order cognitive process that involves a selection of one option from available choices (Bechara, 2005; Crews & Boettiger, 2009). Appropriate decision-making is influenced by several factors, including: cognitive

capacity (such as executive functioning) to weigh up the risks and benefits of associated options, knowledge of the ratio of risk/benefit, the capacity to retrieve this information from memory, and working memory to actively compare/contrast these options (Séguin, Arseneault, & Tremblay, 2007). Furthermore, emotional "hot" decision-making includes emotional and affective responses to available options, which may be influenced by past experiences or the salience or eliciting nature of options (Séguin et al., 2007). Individuals with AUD are regularly faced with several choices regarding drinking that may lead to positive or negative outcomes. However, the strength of alcohol-related cues can elicit significant emotional and affective responses that may influence decision-making toward disadvantageous choices (such as continued or excessive alcohol consumption), rather than longer-term options (such as regulated drinking or abstinence) that may lead to beneficial future outcomes (Bechara, 2005).

Neuropsychological tasks that simulate real-world decision-making demonstrate substance-use disorder participants show a preference toward short-term gratification reward rather than avoiding negative consequences through long-term advantageous choices (Bechara & Damasio, 2002; Buelow & Suhr, 2009), known as delayed discounting (Green, Fry, & Myerson, 1994). AUD participants have shown delayed discounting with poorer performance in the Iowa Gambling task (IGT), a card game which simulates delayed discounting through offering choices for short and long-term rewards that also have greater or lower negative outcomes, respectively (Bechara, Damasio, Damasio, & Anderson, 1994). This has been exhibited by alcohol dependent patients in long-term treatment (Dom, De Wilde, Hulstijn, Van Den Brink, & Sabbe, 2006), and long-term abstinent alcoholics demonstrating deficits in IGT compared to non-drinker participants (Fein, Torres, Price, & Di Sclafani, 2006). Worse IGT performance was also associated with maladaptive drinking outcomes such as relapse (Bowden-Jones, McPhillips, Rogers, Hutton, & Joyce, 2005), and was predictive of future

heavy consumption patterns in nonclinical drinkers (Goudriaan, Grekin, & Sher, 2011). The IGT can therefore be used to identify decision-making deficits within AUD populations to non-alcoholic rewards such as money, as opposed to alcohol-associated cues.

However, the IGT can also be used to identify autonomic psychophysiological indices related to choice outcomes, such as somatic arousal signalled by skin conductance response (SCR). When measuring SCRs during the IGT during anticipation of reinforcement (i.e., presentation of reward/punishment), Bechara et al. (2001) identified that a subgroup of alcohol- and substance-dependent patients with impaired IGT behavioural performance also exhibited reduced anticipatory SCRs for risky choices with potentially significant negative outcomes prior to receiving reinforcement, compared to unimpaired substance users and non-drinkers. Anticipatory SCRs are assumed to indicate affective evaluation processes involved in different choice options (Figner, Murphy, Schulte-Mecklenburg, Kuehberger, & Ranyard, 2012). Interestingly, anticipatory SCRs to non-risky, advantageous choices and SCRs after reward and punishment did not differ to other participants, suggesting a specificity of impaired somatic responses reflecting the expectation of reinforcers for choices with potentially negative outcomes (Bechara et al., 2001).

In AUD, reduced psychophysiological anticipatory responses to risky choices may thus reflect learning or memory deficits that may preclude impaired choices: individuals should learn that risky choices can have negative consequences and thus self-correct their behaviour. However, AUD individuals who continue to drink at risky levels despite experienced negative consequences may demonstrate impaired decision-making and/or reduced anticipatory responses. This may be reflected in real-world situations where AUD individuals are faced with behavioural decisions involving short-term gratification through alcohol consumption (likely initiated by salient cues) or avoiding consumption to achieve longer-term goals including self-regulation and/or abstinence (Le Berre et al., 2017). Chapter

Four will explore whether potential impairments in IGT performance and anticipatory SCR to risky choices (as an index of reduced expectation of negative reinforcement) are exhibited in a sample of severely dysregulated drinkers that demonstrate an inability to self-regulate consumption, even when faced with significant negative consequences from drinking.

Implementation of a range of dysregulated drinker samples.

A broad range of drinkers exhibiting a variety of dysregulated drinking behaviours were recruited in this thesis to investigate regulatory processes in AUD, in order to account for the heterogeneity of the disorder and allow for identification of the maximal potential differences in regulation. However, a restricting factor in the assessment of executive functioning is the possibility for significant alcohol-related brain damage resulting from chronic drinking (Butterworth, 1995a; Harper, 2009), limiting the capacity for elucidating associations between impaired regulation and discrete executive functioning domains. Moreover, as previously identified, clinical samples of treatment-seeking drinkers may not accurately self-report craving, potentially due to demand characteristics related to achieving treatment goals (Tiffany & Carter, 1998). Therefore, recruitment of clinical and non-clinical samples, both non-treatment-seeking and treatment-seeking, with a wide range of AUD severity and experienced drinking consequences and controlling for consumption between samples allowed for evaluation of mechanisms that may be key to appropriate self-regulation in AUD.

One candidate subgroup recruited for this thesis that is ideal for investigating regulation in AUD are individuals with alcoholic liver disease (ALD). ALD is a long-term negative consequence resulting from a dose-response relationship of increasing risk of ALD with escalating chronic alcohol consumption, typically over several years (Corrao, Bagnardi, Zambon, & Torchio, 1998; Lelbach, 1975). ALD is a primary cause of liver disease globally, accounting for two thirds of liver disease cases in men and half of the cases in women in more

economically developed countries (World Health Organization, 2004). Inconsistency in measuring the direct relationship between ALD and mortality suggests prevalence may be underestimated (World Health Organization, 2004). The proportion of liver diseases from alcohol is expected to rise—no interventions for ALD have demonstrated significant clinical efficacy, whereas other causes of liver disease are increasingly more effectively managed (Guirguis et al., 2015). Despite this, ALD individuals that continue to drink despite the knowledge of alcohol-related risks, or the availability of salient, negative biological feedback attributable to the disease potentially demonstrate self-regulatory failure to control intake—even when end-stage outcomes can be fatal.

ALD drinkers are thus useful in examining regulation in severe AUD as a significantly dysregulated subsample. However, ALD patients are at risk of alcohol-related brain damage, both from chronic drinking , and disease-specific insults such as hepatic encephalopathy (Butterworth, 1995b). This poses some issues regarding measurement of executive functioning and associations with regulatory processes. Considering the vulnerability of the frontal lobes to alcohol-related insult impacting upon brain morphometry, and at the neuronal and cellular levels, this may impact normal executive functioning that—while not entirely functionally associated with the frontal cortex—comprises sub-processes that may critically rely prefrontal areas. To counter this, I recruited an alcohol dependent sample, that exhibited similar levels and periods of sustained chronic alcohol consumption without ALD, as a drinking control group for ALD patients in this thesis.

The studies presented in this thesis recruited three samples in order to capture a range of drinkers representing a wide variety of dysregulated drinking behaviours and drinking-related consequences, while also attempting to match for alcohol consumption and severity of alcohol problems as reliable control comparison groups. The first study (Chapter Two) recruited non-treatment-seeking regular drinkers (at least once a week) who demonstrated a

wide range of drinking behaviours and severity of alcohol problems, but did not represent the chronic drinking profile of alcohol dependent drinkers. Therefore, they are less likely to suffer from alcohol-related brain damage, allowing for comprehensive assessment of domains of executive functioning and regulation of alcohol responses. The second sample comprised treatment-seeking drinkers with alcoholic liver disease within a drug treatment trial (Morley, Leung, Baillie, & Haber, 2013), who represent a severely dysregulated subsample of chronic drinkers with significant negative experienced drinking consequences. Additionally, a control comparison group of treatment-seeking alcohol dependent drinkers was recruited, who demonstrated similar consumption patterns to the ALD patients but may not have developed the severe negative outcomes experienced by those with ALD, such as pain, jaundice, bloating, or vomiting blood (Madhotra & Gilmore, 2003). This enabled for the examination of potential differences in regulation of responses alcohol cues related to overall executive functioning (described in Chapter Three) as well as assessing whether impairments in decision-making and anticipatory responses for expected reinforcers may predicate the incapacity of ALD to regulate their drinking (described in Chapter Four). The last sample comprised a larger sample of the treatment-seeking alcohol dependent participants and healthy controls who do not regularly drink (i.e. less than once a week), which allowed for examination of alcohol cue-induced brain activation in a fMRI study whereby the potential for alcohol-related brain damage in ALD would be a major confounding factor.

Thesis Structure

This thesis comprises six chapters, four of which are self-contained empirical chapters. This chapter has provided an overview of the main issues that will be addressed in the following chapters. Chapter Two implements the unitary/diversity theoretical framework of executive functioning (Miyake & Friedman, 2012; Miyake et al., 2000) to examine whether executive functioning domains are differentially associated with regulation of responses to

alcohol in a sample of non-treatment-seeking drinkers. A cue reactivity task with a water control and alcohol beverage cues is employed, and physiological indices of regulatory activity such as HRV are measured during cue presentation, as well as after cue offset, to investigate whether there are differences in cue reactivity and recovery associated with previous dysregulated drinking history or executive functioning ability represented by domain-specific neuropsychological task performance. The primary hypotheses were: (a) heavier drinkers would exhibit reduced high-frequency HRV at baseline during the cue reactivity task; (b) participants with more dysregulated drinking problems would show reduced cardiovascular activity during recovery after cue offset; (c) executive functioning ability would be associated with regulation of cue-elicited responses.

Chapter Three applies the cue reactivity experimental methodology to further examine the relationship of executive functioning and dysfunctional regulation of responses in a subsample of treatment-seeking ALD patients (who represent a severely dysregulated clinical sample of drinkers) compared with a subsample of treatment-seeking participants with alcohol dependence, to control for consumption and severity of alcohol problems. Overall executive functioning measures and dysregulated drinking history are measured, as well as associations with cue reactivity and recovery effects during the cue reactivity task, to determine whether still-drinking ALD patients demonstrate greater regulatory deficits due to significant biological negative feedback related to their disease compared to otherwise-healthy alcohol dependent drinkers. The primary hypotheses were: (a) ALD participants would show greater alcohol cue reactivity, and (b) reduced recovery effects after cue offsets, both indexed by psychophysiological indices; (c) executive functioning would be associated with reduced regulation in these dysregulated drinker samples across the cue reactivity task.

As findings from Chapter Three revealed similar patterns of dysfunction in regulation between ALD and alcohol dependent groups, the study in Chapter Four employs a

different experimental paradigm, the IGT (simulating real-world decision-making processes) to examine whether ALD patients demonstrate greater decision-making deficits that may reflect poorer drinking outcomes than alcohol dependent participants. Furthermore, novel measurement approaches of physiological indices of somatic arousal (skin conductance response) during key trial components of the IGT are used to assess whether deficits in anticipation of expectancy of negative outcomes from risky choices may explain why ALD patients fail to regulate their drinking even when confronted with negative biological feedback. The study hypotheses were: (a) ALD patients would demonstrate worse behavioural IGT performance, and (b) exhibit reduced anticipatory skin conductance responses to disadvantageous choices reflecting negative outcomes., while other responses remain intact (i.e., advantageous choices, and reward and punishment outcome responses); (c) anticipatory responses to disadvantageous choices will be associated with a greater history of dysregulated drinking measures.

Chapter Five applies fMRI techniques to elucidate neural correlates of alcohol cue-elicited responses identified in earlier chapters, using an fMRI visual cue reactivity task to examine brain activity. Alcohol cue reactivity is assessed in sample of alcohol dependent patients compared to healthy controls, measuring BOLD activity to alcohol-related versus control images during an alcohol cue-activation task. Furthermore, associations between alcohol cue-induced activation with executive functioning task performance and dysregulated drinking measures are explored within the alcohol dependent patients, to determine whether there is a convergence in brain activity in structures related to regulation of responses to alcohol cues, executive functioning ability, and history of dysregulated drinking. The study hypotheses were: (a) alcohol dependent patients will show more alcohol cue activation than controls; (b) within alcohol dependent participants, those worse executive functioning performance and/or greater dysregulated drinking problems will show greater alcohol cue-

activation in key mesocorticolimbic brain areas; (c) there will be a convergence in areas of greater alcohol cue activation related to executive functioning ability and previous dyregulated drinking history.

In summary, this thesis investigates the potential mechanisms that may underlie self-regulation through examination of various samples of dysregulated AUD individuals. Using these diverse empirical methods to evaluate regulation to eliciting cues across several stages surrounding cue presentation in these dysregulated drinking populations, this thesis extends the existent literature by seeking to confirm convergence, and enhancing our understanding of the factors that may underlie appropriate self-regulation in this population of dysregulated AUD individuals, and distinguish the timescale of regulation to better inform frameworks that attempt to characterise self-regulation in this disorder.

Chapter Two

Executive Functioning and Dysregulated Drinking History are Associated with Regulation of Alcohol Cue Responses in Non-Treatment-Seeking Drinkers

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WBL designed the study, developed the methodology, collected the data, performed the analysis, and wrote the manuscript. AJB provided feedback for the manuscript.

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Abstract

Previous research has implicated executive functioning in the regulation of motivational responses to environmental alcohol cues. However, much of this research only employs clinical samples or only applies one complex neuropsychological task that may lack sensitivity to domain-specific executive functioning. This study implements domain-specific executive functioning tasks based on a comprehensive model of executive functioning (Miyake et al., 2000) and measures physiological indices during an alcohol cue reactivity task to examine regulation of cue-elicited responses in a non-treatment-seeking drinker sample. We hypothesised that, among participants with greater dysregulated drinking history, reduced regulation of cue-elicited responses after alcohol cue-offset will be demonstrated, and executive functioning domains will be differentially related to regulation of cue-elicited responses. Sixty non-treatment-seeking drinkers were administered domain-specific executive functioning (common executive functioning/response inhibition, set-shifting, updating) tasks and a cue reactivity task with appetitive control (water) and alcohol exposures, with subsequent recovery periods for examining regulation of cue-elicited responses after cue-offset (recovery effect). A key comparison was the recovery effect after alcohol cue exposure. Subjective alcohol craving and physiological indices (heart rate, heart rate variability) were recorded during the cue reactivity task, and dysregulated drinking measures of alcohol use disorder severity and experienced drinking consequences. Physiological reactivity to cue exposures and subsequent regulation during recovery periods were observed for heart rate and heart rate variability indices. No reduced recovery effects after alcohol cue-offset were seen. Executive functioning domain-specific measures were differentially associated with physiological reactivity and regulation during a cue reactivity task. Common executive functioning domain task performance related to overall elevated heart rate variability during the cue reactivity task, and was associated with better overall recovery effect after cue offset

observed in heart rate variability for participants with greater alcohol use disorder severity. Executive functioning has a potential role in the regulation of cue-elicited responses to environmental appetitive cues in non-treatment-seeking drinkers, although this regulation may not be specific to alcohol.

Executive Functioning and Dysregulated Drinking History are Associated with Regulation of Alcohol Cue Responses in Non-Treatment-Seeking Drinkers

Many people drink alcohol without any apparent problems, while others experience negative consequences and subsequently regulate drinking. However, a significant number continue to drink after experiencing negative consequences (Heilig et al., 2010). This difficulty in self-regulation may be central to alcohol use disorder (AUD) as it demonstrates a failure of adaptive functioning. Dual-process models of addiction have been proposed to explain AUD (Bechara, 2005; Lubman et al., 2004; Wiers & Stacy, 2006b)—incapacity to appropriately regulate alcohol consumption is due to an overactive impulsive system (involving relatively automatic, impulsive drives such as craving), an underactive reflective system (which monitors and regulates these impulses), or a combination. This paper describes an experimental manipulation of both water and alcohol cues and subsequent recovery periods to non-treatment-seeking drinkers and concurrent measurement of their subjective and physiological indices to examine the role of executive functioning in the regulation of cue-elicited responses.

The reflective system encapsulates cognitive processes such as executive functioning that regulate impulsive urges and drives that may lead to disadvantageous consequences. Executive functioning is a concept encompassing several cognitive domains that guide complex behaviours, such as planning, attentional processes, decision-making, response inhibition, and reasoning (Crews & Boettiger, 2009). According to the dual-process model of addiction, severe AUD (or alcohol dependence) is the outcome of the reflective system failing to regulate impulsive urges to consume alcohol (Wiers & Stacy, 2006b). Therefore, executive functioning may have an integral role in the progression to, and the maintenance of AUD.

Existing evidence suggests executive functioning impairment in alcohol dependent samples of differing severity. Executive functioning impairments are most vulnerable to alcohol-induced cognitive impairment (Nixon, 2006; Parsons, 1998), with recently abstaining chronic drinkers showing specific executive functioning deficits compared to healthy controls, with non-executive functions unaffected (Davies et al., 2005; Noël et al., 2001). Executive functioning deficits are the most pervasive, and take longest to recover, with deficits apparent after one year of abstinence (Stavro et al., 2013).

However, a major issue when assessing executive functioning deficits in these samples is the confound of potential alcohol-related brain damage from chronic consumption (Harper, 2009). Non-treatment-seeking drinkers who demonstrate detrimental drinking behaviours—but may not have the chronic drinking profile of alcohol dependent samples and fewer consequent executive functioning deficits—provide a solution for investigating executive functioning in AUD. Yet studies employing these samples have yielded inconsistent results.

Influential conceptualisations of executive functioning have demonstrated that several standardised executive functioning measures are complex tasks that tap into several multiple executive functioning domains (Miyake et al., 2000). Moreover, a systematic review of social drinker studies found all implemented only a single, complex executive functioning task involving several executive functioning subdomains that may lack sensitivity to elucidate specific deficits, particularly if these deficits are not severe (Montgomery et al., 2012). Using latent variable analyses, Miyake et al. (2000) identified three executive functioning domains, that are both separable and share a unitary executive functioning construct: common-executive functioning, encompassing maintenance of low-level processing towards goal-oriented tasks; shifting-specific, the ability to switch to new task-set representations; and updating-specific, the ability to actively update short-term stored information. Montgomery et al. (2012) employed this framework in a subsequent experiment and observed heavy social

drinkers performed worse than lighter drinkers in executive functioning domain-specific tasks. However, the study did not address if these domains uniquely relate to alcohol craving responses in real-time.

Though still poorly understood, cue-elicited craving—defined as the conscious experience of a desire to take a drug (Drummond, 2000)—is an important factor in the maintenance of addiction and can still manifest after abstinence, leading to detrimental outcomes such as relapse (Anton, 1999). Inability to control cue-elicited craving and subsequently restrict alcohol consumption therefore represents a regulatory failure for alcohol dependent individuals. An alcohol cue reactivity task is a real-time laboratory paradigm that elicits motivational responses using tangible appetitive, but non-addiction-related cues (such as water) and alcohol-specific cues, while simultaneously measuring participants' subjective craving and biophysiological activity (e.g., heart rate) as indices of cue-elicited responses (Monti et al., 1987). The observed relationship between subjective craving elicited by laboratory cue reactivity tasks and subsequent alcohol outcomes has been relatively modest, whereas physiological indices of regulatory response have demonstrated positive relationships with behavioural outcomes such as relapse (Tiffany & Conklin, 2000).

Heart rate variability (HRV) is a psychophysiological index that is reactive to emotionally salient cues, and can inform of the interplay between sympathetic and parasympathetic influences of the autonomic nervous system (Thayer et al., 2012; Thayer & Lane, 2000). The parasympathetic system is involved in heart rate modulation and returning the organism to homeostasis (i.e., an optimal level of functioning; Pagani et al., 1997). As this system can exert a relatively rapid high-frequency temporal effect on heart rate (via the vagus nerve), variable, high-frequency HRV is thus a potential index of an adaptive, flexible organism that is responsive to eliciting environmental cues and stressors and regulates accordingly (Thayer & Brosschot, 2005). Invariable high-frequency HRV, however, suggests

a maladaptive system that is inflexible or "stuck" in a pattern, unable to adjust accordingly to environmental demands. In alcohol dependent drinkers, this may represent an "allostatic state" (Koob & Le Moal, 2001), whereby chronic alcohol consumption shifts an individual's optimal level of functioning (i.e. homeostasis) to a new set point to accommodate for the regular presence of alcohol within the system.

Previous studies demonstrated that alcohol cue exposure increased high-frequency HRV in alcohol dependent individuals when exposed to an alcohol-cued script (Ingjaldsson, Laberg, et al., 2003) and higher levels of high-frequency HRV to stress-primed alcohol cues during a spatial attentional bias task predicted earlier relapse in treated alcohol dependent patients (Garland et al., 2012). Furthermore, reduced baseline high-frequency HRV has been associated with delayed return to baseline after physical and cognitive stressors (Weber et al., 2010), and prolonged autonomic response and/or reduced return to baseline levels may signify failure to regulate responses to eliciting stressors or cues after they removed, potentially from prolonged focus upon eliciting stimuli (Key et al., 2008; Verkuil, Brosschot, de Beurs, et al., 2009). As alcohol cues elicit a conditioned arousal response in regular drinkers (Robinson & Berridge, 2008), this study will examine whether there is a parasympathetic system "recovery effect" after eliciting cues are removed (cue offset), evidenced by a return to baseline high-frequency HRV levels after alcohol exposure. Reduced return to baseline levels, or reduced overall parasympathetic activity during alcohol cue presentation may reflect an incapacity of the parasympathetic system to regulate responses to cues appropriately and return to baseline levels after cue offset.

This study examines whether subjective craving and a range of physiological responses during an alcohol cue reactivity task relate to dysregulated drinking in a non-treatment-seeking regular drinker sample, and if executive functioning is implicated in these relationships. As reduced high-frequency HRV is associated with a maladaptive regulatory

system, we hypothesise that heavier drinkers will exhibit reduced high-frequency HRV at baseline during the cue reactivity task. We predict that participants with a greater history of dysregulated drinking will demonstrate reduced cardiovascular activity (e.g., HRV) after the alcohol cue is removed, indicating decreased parasympathetic system capacity to return to baseline levels. Finally, we employ neuropsychological tasks measuring the executive functioning domains outlined by a comprehensive empirical framework (i.e., unitary-diversity framework; Miyake & Friedman, 2012) to examine whether poorer executive functioning performance is associated with dysregulated drinking history, and differentially related to responses during the cue reactivity task. We hypothesise that executive functioning will be associated with regulation of cue-elicited responses, specifically those participants with more severe AUD and adverse drinking consequences, as behavioural and/or historical indicators of AUD dysregulation. This will be evidenced in these participants by reduced HRV across the cue reactivity task and reduced recovery effects after alcohol cue offset.

Materials and Method

Design and Participants

A sample of non-treatment-seeking drinkers were assessed on executive functioning measures, then exposed to water and alcohol cues during a cue reactivity task (baseline; water cues; recovery 1; alcohol cues; recovery 2) while subjective and physiological responses were recorded. Sixty adults participated: 31 were undergraduate first-year psychology students from Macquarie University (age range: 18–51, M = 23.33, SD = 8.44) participating in exchange for course credit, and 29 were community volunteers (age range: 18–45, M = 27.03, SD = 8.68) recruited through advertisements who were reimbursed AU$30. Advertisements for both samples targeted a range of drinkers, from infrequent (at least once a week) to drinking heavily several times a week. Seventy-two individuals made contact and eligibility was assessed by phone. Participants were required to drink alcohol at least once a week, be a

minimum 18 years old, speak fluent English and have normal or corrected-to-normal eyesight. Exclusion criteria were any history of AUD (diagnosis, referral, or treatment of a drinking problem; none were excluded) and any previous traumatic or acquired brain injury. Participants with pre-existing heart conditions (n = 1) or taking medications that could affect heart rate, and those with consistently elevated (n = 1) or reduced heart rate (n = 1) were also excluded. One participant was excluded for failing to correctly identify any incongruent Stroop trials. Participants with high self-reported anxiety were asked to reconfirm their participation as required by the ethics committee, and all agreed to continue. The final sample comprised 60 participants (See Table 1 for sample characteristics); all gave informed consent. The study was approved by the Macquarie University Human Research Ethics Committee (Medical Sciences; Ref: 5201400315; see Appendix A).

Measures

Neuropsychological measures of executive functioning domains.

Updating-specific: adapted letter memory (Rogers and Monsell, 1995) task involves a sequence of letters presented individually in serial order on screen, each for 2500 ms. Participants had to correctly say out loud the last three letters. They were instructed to say the last three letters in the sequence out loud after each letter presentation, ensuring continuous updating occurred. Letter sequences were randomly presented in varying lengths (five, seven, or nine letters) to ensure participants were updating using the instructed strategy. Participants completed one practice trial per sequence length before completing 12 test trials (four trials per sequence length). A higher proportion of letters correctly recalled indicated better updating ability.

Table 1

Descriptive statistics, dysregulated drinking behavioural measures of the student and community samples, and the total sample

Measure	Student (*n* = 31)	Community (*n* = 29)	p-value [a]	Total (*N* = 60)
Age (years)	22.86 ± 7.94 (18.07–51.39)	27.03 ± 8.69 (18.15–45.11)	.057	24.88 ± 8.5 (18.07–51.39)
Sex: *n* (%) female	20 (64.51)	16 (55.75)	.460	
TLFB mean drinks per drinking day	6.18 ± 3.94 (1.2–18.77)	6.19 ± 3.66 (1.47–14.4)	.994	6.19 ± 3.77 (1.2–18.77)
TLFB mean drinks per week	15.41 ± 11.16 (1.8–33.68)	12.59 ± 12.52 (2.2–59.65)	.896	14.04 ± 11.82 (1.8–59.65)
ADS	9.68 ± 6.08 (0–21)	9.38 ± 7.02 (0–31)	.861	9.53 ± 6.5 (0–31)
DrInC:				
Total score	12.84 ± 8.87 (0–32)	13.9 ± 9.04 (0–35)	.649	13.35 ± 8.89 (0–35)
DrInC Subscales			-	
Impulse control	3.27 ± 2.16 (0–7)	3.69 ± 2.7 (0–9)	-	3.47 ± 2.43 (0–9)
Interpersonal	2.03 ± 1.79 (0–7)	2.28 ± 2.07 (0–7)	-	2.15 ± 1.92 (0–7)
Intrapersonal	2.23 ± 2.49 (0–8)	2.28 ± 2.03 (0–7)	-	2.25 ± 2.26 (0–8)
Physical	3.7 ± 1.7 (0–7)	3.79 ± 2.04 (0–8)	-	3.75 ± 1.86 (0–8)
Social Responsibility	2.03 ± 2.04 (0–6)	1.86 ± 1.77 (0–7)	-	1.95 ± 1.9 (0–7)
PACS	9.58 ± 4.91 (0–19)	10.79 ± 5.19 (1–22)	.356	10.17 ± 5.04 (0–22)
DASS 21: Anxiety	7.77 ± 8.74 (0–36)	5.86 ± 7.33 (0–32)	.364	6.85 ± 8.08 (0–36)

Note. Means and *SD*s with range (minimum – maximum) shown in brackets. TLFB = Timeline followback; ADS = Alcohol Dependence Scale; DrInC = Drinkers Inventory of Consequences; PACS = Penn Alcohol Craving Scale; DASS = Depression, Anxiety and Stress Scales.
[a] Chi square tests and *t*-tests conducted where appropriate.

Set-shifting: number letter task was adapted from Miyake et al. (2000). A number-letter pair (e.g., A7) was presented in one of four quadrants of a square: if the number-letter pair target was presented in the top half, participants used keys to indicate whether the letter was a vowel or consonant; if the target was presented in the bottom half, participants indicated whether the number was odd or even. The target was presented only in the top half during the first block (32 trials), only in the bottom half during the second block of (32 trials), and presented clockwise around the four quadrants during the third block (128 trials). Thus, while the first two blocks required no rule switching, the third block required participants to switch between the categorisation rules. Twelve practice trials preceded each test block. Errors were indicated with a black 'X' replacing the target for 150 ms. A switch cost was calculated as the difference between the average of trials in the third block where the internal rule shift was required (top-left, bottom-right quadrants) and the average of the first two blocks without rule switches required. A lower switch cost reflected better performance through capable internal shifting.

Common executive functioning: Stroop (Stroop, 1935) task was an automated original colour version similar to that used by Houben and Wiers (2009). Participants indicated the colour (red, green, blue or yellow) of the text on a screen using coloured keys. Participants first completed a 20-trial practice block for key familiarisation, indicating the colour of a rectangle. The following test block, comprised three trial types: control trials, with symbols "####", "%%%%", "&&&&", or "****" presented in the four colours; congruent trials, with words "red", "green", "blue" or "yellow" presented in corresponding coloured text; and incongruent trials, where the text meaning and presented text colour were incompatible (e.g., the word "red" coloured in blue text). The test block comprised 84 trials, with each trial type presented seven times per colour. Stimuli were presented in random order, and stimuli were not immediately consecutively presented in the same colour. A Stroop

interference score was calculated by subtracting the mean response latencies of the control trials from incongruent trials, where a higher score indicated worse performance from greater Stroop interference.

Measures of dysregulated alcohol consumption.

Timeline followback interview (TLFB; Sobell & Sobell, 1992) measures the number of standard drinks consumed per drinking day in the preceding 30 days, and has demonstrated reliability and validity. Participants were actively prompted to recall number of drinks; mean drinks per drinking day (henceforth TLFB drinks) was used.

Alcohol Dependence Scale (ADS; Skinner & Allen, 1982) is a 25-item self-report measure of alcohol dependence, with high levels of consistency and reliability (Ross, Gavin, & Skinner, 1990). The total score was used as an index of the severity of alcohol dependence.

Drinkers Inventory of Consequences (DrInC) Lifetime (Miller et al., 1995) is a 50-item questionnaire measuring whether physical, emotional and social consequences related to alcohol use have ever been experienced, and is a reliable and valid measure. The total score was used as an index of the negative feedback received by participants about their drinking.

Penn Alcohol Craving Scale (PACS; (Flannery, Volpicelli, & Pettinati, 1999) is a 5-item self-report measure regarding the frequency, intensity and duration of craving for alcohol over the last week. It has a high degree of internal consistency and good convergent and divergent validity.

Alcohol Urge Questionnaire (AUQ; (Bohn, Krahn, & Staehler, 1995) is an 8-item self-report measure of current craving or urge to drink obtained after each stage of the cue reactivity task. The AUQ has demonstrated reliability and convergent/discriminant validity, indicative of a high degree of construct validity (Drummond & Phillips, 2002).

T*he *Depression Anxiety Stress Scales is the short form (21 items) of Lovibond and Lovibond's (1995) self-report measure of depression, anxiety, and stress. Each scale contain

seven items assessing the severity of the respective dimensions of emotional disturbance, with good reported convergent and discriminant validity and reliability (Henry & Crawford, 2005). The anxiety scale (DASS-A) is used in this study to measure autonomic arousal and situational anxiety, which can impede accuracy of physiological indices.

Procedure

Telephone screening for past alcohol-related diagnoses, history of traumatic brain injuries, and drinking behaviour was conducted prior to test day. Participants were instructed to avoid drinking alcohol from the night preceding test, and to avoid caffeine and nicotine for four hours prior to test session. Testing was conducted so the cue reactivity task was completed between 12–5 pm. Participants were breathalysed prior to session, with the intention that a BAC above .000 would have excluded them from testing, but none were. They then completed the executive functioning tasks (Stroop, number letter, letter memory) presented using Inquisit 4.0.5.0 software (Millisecond Software LLC, 2014), with order counterbalanced between participants using a latin-square design to minimise task carryover effects.

Participants sat in an armchair and faced a 66 cm television attached to a wall 2 m away used for video presentation. The cue reactivity task was conducted in same order (baseline; water cues; recovery 1; alcohol cues; recovery 2; see Table 2) as counterbalancing has been found to mask potential alcohol cue effects (Monti et al., 1987). For the baseline and recovery periods, participants were instructed to concentrate on a video of neutral animal scenes with classical music for three minutes. Cues were either a bottle of water or a bottle containing an Australian standard drink (10 g alcohol) of participants' preference out of lager, red or white wine, placed in front of participants with a water glass, beer schooner glass, or wine glass. An audio script was played to enhance craving for beverage type (see Appendix B), which the participant was instructed to imagine as vividly as possible. They were then

Table 2

Timeline of the cue reactivity task and planned contrast coefficients of key stages

	Baseline 3 min	Water 3 min	Recovery 1 3 min	Alcohol 3 min	Recovery 2 3 min
Stimuli	Nature video	Water beverage + control audio script	Nature video	Preferred alcoholic beverage + alcohol audio script + model bar cues	Nature video
Measures	HR HRV AUQ (at end)	HR HRV AUQ (at end)	HR HRV AUQ (at end)	HR HRV AUQ (at end)	HR HRV AUQ (at end)
Contrasts:					
Baseline vs. cues	-1	0.5	–	0.5	–
Water cue vs. alcohol cue	0	-1	–	1	–
Cues vs. recovery periods	0	-0.5	0.5	-0.5	0.5
Alcohol cue vs. recovery 2	0	–	–	-1	1

Note. HR = Heart rate; HRV = Heart rate variability; AUQ = Alcohol Urge Questionnaire.

instructed to pour, hold and smell the beverage for three minutes. To diversify alcohol-related cues during alcohol exposure, participants were seated adjacent to a simulated bar comprising: a wooden bar with alcohol glasses; and alcohol, sports, and gambling posters. A curtain obscured the bar and was removed prior to alcohol exposure, and replaced post-exposure to reduce carryover cue effects. Heart rate was continuously recorded during each cue reactivity stage: a three-lead electrocardiogram (ECG) with two disposable Ag/Cl electrodes (ADInstruments, Sydney, Australia) was placed on the arms slightly above the cubital fossa and a ground electrode on the non-dominant inner wrist. A PowerLab 4/25 System (ADInstruments, Sydney, Australia) connected to a PC operating Labchart Pro 7.3.7 software (Alvarez & Emory, 2006) sampled ECG at 1000 Hz. R-wave data were automatically calculated per 3-min stage. The AUQ was completed after each stage. Following the cue reactivity task, ADS, DrInC, and PACS questionnaires were completed. All questionnaires were presented using Qualtrics online survey interface (www.qualtrics.com). Participants were debriefed at session end.

Data Transformations

The reaction time (RT) distributions for Stroop and number letter were skewed and/or kurtotic, requiring transformation to produce normality. A two-stage trimming procedure for outliers was employed. Firstly, RTs outside cut-off criterion values were omitted (Stroop: 200–3000 ms, 4.12% of total RTs; number letter: 200–4000 ms, 2.67% of total RTs). The Median Absolute Deviation method (Leys, Ley, Klein, Bernard, & Licata, 2013) was then applied, a within-subjects procedure that excluded outliers outside three median absolute deviation units (Stroop: 3.7% of total RTs; number letter: 7% of total RTs). Letter memory proportion correct raw scores had an expected negative skew and were arcsine transformed to produce normality. Table 3 presents raw and transformed proportion scores, but only transformed scores were used and hereafter is termed “proportion correct score”.

HR and HRV per cue reactivity stage were processed and analysed using Kubios 2.2 HRV analysis software (Biosignal Analysis and Medical Imaging Group, 2012), with each sample manually examined for artefacts and a low-pass filter applied to interpolate identified artefacts. Trend components were removed using the Smoothness priors method with $\lambda = 500$ (Tarvainen, Ranta-Aho, & Karjalainen, 2002). Two HRV indices were calculated: (a) RMSSD, the square root of mean squared differences between successive R-R intervals per stage; (b) spectral analysis was performed with Kubios, employing a Fast Fourier transformation for HRV in the frequency band 0.15-0.40 Hz to calculate the high-frequency HRV in normalised units. The means per stage for both indices were positively skewed and natural log-transformed for normality.

Table 3

*Executive functioning task performance for student (*n *= 31), community (*n *= 29), and total (*n *= 60) samples*

Measure	Student	Community	*p*	Total
Stroop interference score: Incongruent-Control	79.75 ± 88.89 (-75.07–323.94)	82.8 ± 96.8 (-30.77–400.69)	.899	81.23 ± 92.02 (-75.07–400.69)
Number letter: Switch cost	301.4 ± 149.02 (-86.8–563.89)	370.66 ± 156.58 (-9.43–666.03)	.084	334.87 ± 155.39 (-86.8–666.03)
Letter Memory proportion correct:				
Raw scores	0.83 ± 0.15 (0.53 - 1)	0.86 ± 0.13 (0.56 - 1)	.296	0.84 ± 0.14 (0.53 - 1)
Arcsine transformed	68.34 ± 13.47 (46.59 - 90)	71.71 ± 12.89 (48.19 - 90)	.327	69.96 ± 13.19 (46.59 - 90)

Note. Means, *SD*s with range (minimum – maximum) shown in brackets. *p* = p-value.

Statistical Analysis

Models were conducted using IBM SPSS v.20.0 (IBM Corp, Armonk, U.S.A.). Standardised scores were used: executive functioning task scores (Stroop interference score; number letter switch cost, letter memory proportion correct score); alcohol use severity (ADS), history of drinking experiences (DrInC), and craving (PACS); and trait-anxiety

(DASS-A). Separate multiple regression models assessed associations of executive functioning tasks (Stroop, number letter, letter memory) with TLFB drinks, ADS scores, and DrInC scores. Control covariates sex, age, and clinically relevant covariates (craving: PACS; trait-anxiety: DASS-A) were also added. Variance inflation factor was examined to assess potential multicollinearity issues with the separate variable.

Linear mixed model (LMM) analyses were implemented to assess relationships between performance per executive functioning task with AUQ scores, and with regulatory indices heart rate, RMSSD, and high-frequency HRV during the cue reactivity task. A random intercept-only model per planned contrast was fitted to compare regulatory activity during key cue reactivity stages whilst controlling for baseline responses per subject (see Table 2): (a) baseline versus appetitive exposures (water, alcohol), (b) water exposure versus alcohol exposure, (c) cue exposures versus recovery periods after cue offset; (d) alcohol exposure versus recovery 2 period assessed specificity of the drug response and recovery effect. Fixed variables executive functioning tasks, ADS, and DrInC scores were added, then covariates related to cue reactivity (sex, age, DASS-A). Two-way interactions of respective contrast with each executive functioning task were added assessing associations with AUQ and regulatory indices, and similarly for contrasts with ADS and DrInC. Lastly, three-way interactions of contrast, executive functioning tasks, and ADS or DrInC tested whether executive functioning performance influenced regulatory activity across the cue reactivity task for those with differing alcohol severity and/or history of dysregulated drinking. Final model fits were assessed using likelihood ratio tests.

Results

Confirming the Sample Covered a Range Of Dysregulated Drinking and Executive Functioning Task Performance

The sample showed a wide range of alcohol consumption with TLFB; 20 participants (33.3%) had consumption levels outside Australian safe drinking recommendations of 14 standard drinks per week (National Health and Medical Research Council, 2009), and a wide range of negative drinking consequences by lifetime DrInC (See Table 1). When applying a cut-off score of 9 (Ross et al., 1990), 30 participants (50%) were alcohol dependent on the ADS. There were no significant differences between the student and community subsamples (*p*'s > .05).

Mean scores of executive functioning tasks are shown in Table 3. No significant differences between the student and community subsamples were observed (*p*'s > .05) so only overall sample results are addressed. Paired samples *t*-tests demonstrated a significant Stroop effect, as colour-naming was slower during the incongruent trials (M = 926.21 ms, SD = 185.30) compared to control trials (M = 844.98 ms, SD = 144.47), $t(59) = 6.83$, $p < .001$.

For the number letter task, participants' mean latencies for the switch trials (M = 652.18 ms, SD = 211.83) were significantly slower than the average latencies of the non-switch blocks (M = 574.23 ms, SD = 139.51), indicating a significant switch cost, $t(59) = 16.69$, $p < .001$. A one-sample *t*-test demonstrated significantly higher letter memory proportion correct than chance (raw score: .5, or 50%), $t(59) = 18.75$, $p < .001$. The range of executive functioning scores across the sample was therefore sufficient for hypothesis testing.

The Relationship between Executive Functioning and Drinking Behaviour

Table 4 provides descriptive information across cue reactivity stages, and Table 5 presents the separate regression model parameters. Letter memory proportion correct scores (p = .039) was significantly related to ADS score, where participants with lower letter

memory proportion correct scores had higher ADS scores. Other executive functioning domains were not significant (*p*'s > .05). Regarding covariates, ADS scores significantly decreased with increasing age ($p = .001$), and participants with higher reported PACS scores had higher ADS scores ($p = .001$). No significant associations with any executive functioning tasks or covariates for DrInC scores (*p*'s > .05), or with TLFB drinks (*p*'s > .05) were found.

Table 4

Subjective craving and cardiovascular measures of total sample during cue reactivity stages

Stage	Baseline	Water cue	Recovery 1	Alcohol cue	Recovery 2
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
AUQ	20.10 (9.13)	25.89 (12.83)	23.75 (12.72)	31.64 (13.43)	24.97 (13.17)
HR	72.38 (11.13)	74.81 (10.87)	72.68 (10.38)	73.81 (10.02)	71.98 (10.26)
RMSSD	3.67 (0.59)	3.73 (0.63)	3.62 (0.61)	3.79 (0.60)	3.63 (0.58)
HF HRV	3.74 (0.51)	3.50 (0.58)	3.55 (0.54)	3.46 (0.60)	3.54 (0.57)

Note: AUQ: Alcohol Urge Questionnaire; HR = heart rate, beats per min; RMSSD = square root of mean squared differences between successive R-R intervals, natural log transformed; HF HRV = high-frequency heart rate variability, normalised units, natural log transformed.

Confirming Subjective Craving during Cue Reactivity Task

Table 4 presents AUQ scores per cue reactivity stage. A LMM of all cue reactivity stages demonstrated that, overall, AUQ scores changed across the cue reactivity task, $F(1,233.89) = 13.73$, $p < .001$. Planned contrasts showed participants reported significantly higher AUQ during cue exposures compared to baseline, $F(1,105) = 24.64$, $p < .001$, and higher AUQ during alcohol exposure compared to water exposure, $F(1,105) = 5.19$, $p = .025$. Furthermore, recovery was evidenced post-cue offset: participants reported lower AUQ during recovery periods compared to the cue exposures, $F(1,227.46) = 16.42$, $p = .001$. Participants reported reduction in AUQ during recovery period 2 after alcohol cue offset $F(1,105) = 4.98$, $p = .028$. Thus, we are confident that the exposure sufficiently

Table 5

Multiple linear regression models assessing relationships between drinking behaviours and executive functioning tasks

	B	*SE* B	β	*t*	*p*
Alcohol severity (ADS) [a]					
Stroop: interference score	1.40	0.74	0.22	1.9	.063
Number letter: switch cost	-0.32	0.71	-0.05	-0.45	.658
Letter memory: proportion correct	**-1.46**	**0.69**	**-0.23**	**-2.12**	**.039**
Sex	0.84	1.39	0.06	0.61	.548
Age (years)	**-0.32**	**0.09**	**-0.42**	**-3.69**	**.001**
PACS	**2.52**	**0.74**	**0.39**	**3.39**	**.001**
DASS-A	0.35	0.75	0.05	0.46	.646
Drinks per drinking day (TLFB) [b]					
Stroop: interference score	0.74	0.51	0.2	1.46	.149
Number letter: switch cost	0.30	0.48	0.08	0.62	.536
Letter memory: proportion correct	-0.90	0.47	-0.24	-1.90	.063
Sex	-1.22	0.96	-0.16	-1.27	.209
Age (years)	-0.07	0.06	-0.15	-1.13	.263
PACS	0.80	0.51	0.21	1.57	.122
DASS-A	-0.88	0.52	-0.23	-1.70	.095
Alcohol-related consequences (DrInC) [c]					
Stroop: interference score	0.098	1.3	0.01	0.08	.941
Number letter: switch cost	-0.25	1.24	-0.03	-0.2	.843
Letter memory: proportion correct	-1.44	1.21	-0.16	-1.19	.241
Sex	0.54	2.45	0.03	0.22	.828
Age (years)	-0.01	0.15	-0.01	-0.03	.978
PACS	1.95	1.31	0.22	1.49	.142
DASS-A	-0.66	1.32	-0.08	-0.50	.618

Note. ADS = Alcohol Dependence Scale; TLFB = Timeline followback; DrInC = Drinkers Inventory of Consequences; PACS = Penn Alcohol Craving Scale; DASS-A = Depression, Anxiety and Stress Scales—anxiety scale. Significant factors indicated by bold text with *p*-value < .05.

[a] R^2 = .446, N=60.

[b] R^2 = .214, N=60.

[c] R^2 = .070, N=60.

elicited cue reactivity and consequent regulation. There was a main effect of sex on AUQ: males reported higher overall AUQ during the cue reactivity task, $F(1,70.33) = 5.28$, $p = .025$, but this did not change across contrasts (no contrast interactions, *p*'s >.05). Sex was thus added as a covariate to subsequent models to identify any sex differences in autonomic

nervous system response indices. No meaningful relationships were found between the executive functioning tasks and AUQ across any of the contrasts (*p*'s > .05).

Baseline Indicators of Parasympathetic Dysregulation and Alcohol Consumption

Descriptive information for multiple regression models for TLFB drinks and baseline HRV indices are presented in Table 4; Table 6 presents regression parameters. Heavier drinkers showed elevated baseline RMSSD compared to lighter drinkers (*p* = .02). Males demonstrated significantly elevated baseline RMSSD compared to females (*p* = .029), and younger participants exhibited higher baseline RMSSD compared to older participants (*p* = .029). Neither TLFB drinks nor relevant covariates significantly related to baseline high-frequency HRV (*p*'s > .05).

Table 6

Multiple Linear Regression Models of the relationship between alcohol consumption and cue reactivity baseline HRV indices

Index	*B*	*SE B*	β	*t*	*p*
RMSSD [a]					
TLFB Drinks per drinking day	**.04**	**.02**	**.3**	**2.38**	**.021**
Sex	**.31**	**.14**	**.27**	**2.24**	**.029**
Age (years)	**-.02**	**.01**	**-.27**	**-2.24**	**.029**
PACS	-.03	.07	-.06	-.45	.654
DASS-A	-.11	.08	-.20	-1.50	.139
HF HRV [b]					
TLFB Drinks per drinking day	-.00	.02	-.03	-.21	.832
Sex	.22	.14	.21	1.58	.119
Age (years)	-.01	.01	-.21	-1.58	.121
PACS	.01	.07	.02	.14	.890
DASS-A	.03	.07	.05	.36	.722

Note: RMSSD = square root of mean squared differences between successive R-R intervals, natural log transformed; HF HRV = High-frequency heart rate variability, normalised units, natural log transformed; TLFB = Timeline followback; PACS = Penn Alcohol Craving Scale; DASS-A = Depression, Anxiety and Stress Scales: anxiety scale. Significant factors indicated by bold text: $p < .05$.

[a] $R^2 = .24$, N=60.

[b] $R^2 = .097$, N=60.

Physiological Reactivity during Cue Reactivity Task Exposures

Table 4 reports mean physiological indices per stage of the cue reactivity task. Planned contrast LMMs showed participants demonstrated significantly higher heart rate during the cue exposures compared to baseline, $F(1,105) = 31.34$, $p < .001$. For HRV, the same pattern of increased autonomic activity during cue exposures were observed for both RMSSD, $F(1,105) = 6.33$, $p = .013$, and a decrease in high-frequency HRV, $F(1,105) = 10.81$, $p = .001$, indicating reduced parasympathetic activity. Older participants exhibited lower overall RMSSD compared to younger participants, $F(1,105) = 6.48$, $p = .014$. There was a contrast and age interaction for heart rate, with younger participants demonstrating a greater heart rate increase during exposures than older participants, $F(1,51) = 7.12$, $p = .009$, and a contrast and sex interaction for RMSSD, with females demonstrating less change from baseline to exposures compared to males, $F(1,105) = 6.06$, $p = .015$.

When comparing water cue versus alcohol cue exposures for heart rate and HRV indices, there were no overall sample differences from water versus alcohol cues for heart rate, RMSSD, or high-frequency HRV (p's > .05), indicating similar levels of overall autonomic activity across water and alcohol cue presentations, yet alcohol did not elicit a different magnitude of cue reactivity.

Physiological Regulation during Recovery after Cue Presentations

The recovery periods should demonstrate dynamic parasympathetic system regulation, through baseline return after cue offset. There were significant overall decreases from exposure to recovery periods for all participants for heart rate, $F(1,225.33) = 28.04$, $p < .001$, and RMSSD levels, $F(1,225.59) = 22.82$, $p < .001$, but no overall differences observed for high-frequency HRV ($p > .05$). This suggests general autonomic activity after water and alcohol cue offsets, but parasympathetic responses as reflected by spectral high-frequency HRV did not elucidate overall regulation after offset of eliciting cues.

Physiological Regulation during Recovery After Alcohol Cue

A key hypothesised index of specific dysregulation to alcohol cues was delayed recovery after alcohol cue offset. All participants showed an overall reduction during recovery compared to alcohol exposure for both heart rate, $F(1,105) = 6.15$, $p = .015$, and RMSSD levels, $F(1,105) = 17.012$, $p < .001$; but no contrast differences for the overall sample were observed for high-frequency HRV ($p > .05$). This suggests autonomic activity changes, but this may not be related to parasympathetic response after the initial alcohol cue reactivity demonstrated during alcohol cue presentation.

Executive Functioning is Related to Overall Dysregulation of Physiological Responses during the Cue Reactivity Task

Participants with less Stroop interference demonstrated higher overall heart rate across cue reactivity compared to those with greater interference, $F(1,53.5) = 6.14$, $p = .016$. Regarding HRV, participants with greater Stroop interference demonstrated elevated overall RMSSD during cue reactivity compared to those with less interference, $F(1,56) = 5.18$, $p = .027$. There were no significant overall differences in heart rate or RMSSD for other executive functioning domains, and no significant main effects of executive functioning and high-frequency HRV across overall cue reactivity were observed (p's >.05). When comparing heart rate during exposures versus baseline, there was a trend for a contrast and Stroop interaction, $F(1,51) = 3.57$, $p = .062$, whereby participants with greater Stroop interference had higher heart rate during cue exposures than those with low interference scores. For high-frequency HRV there was a trend for water and alcohol exposure contrast and number letter performance interaction, $F(1,105) = 3.61$, $p = .060$, whereby high-frequency HRV reduced from water to alcohol exposure for better performing participants with a lower number letter switch cost, while high-frequency HRV increased from water to alcohol exposure for participants with a higher switch cost.

Previous history of dysregulated drinking associated with overall parasympathetic recovery effects.

There were no overall main effects across cue reactivity stages for measures of dysregulated drinking, either for ADS or DrInC scores (*p*'s >.05). Some associations with key contrasts for RMSSD were seen. A significant two-way interaction was observed for contrast comparing cue exposures and recovery periods with DrInC scores, $F(1,226.21) = 4.47$, $p = .036$, whereby participants with lower DrInC scores (reflecting fewer experienced drinking consequences) exhibiting a RMSSD reduction from cue exposures to recovery periods, compared to those with higher DrInC scores. There was a trend for an interaction of the same contrast and ADS score, $F(1,225.51) = 3.11$, $p = .079$, whereby participants with higher ADS scores (greater alcohol use severity) demonstrated a greater reduction in RMSSD levels from cue exposures to recovery when compared to those with lower ADS scores.

Better executive functioning was associated with greater overall recovery effect after cue exposure for those with greater dysregulated drinking history.

A key hypothesis concerned whether a greater previous history of dysregulated drinking was associated with poorer regulation of cue responses as reflected in HRV indices, and whether executive functioning might be implicated in these relationships. High-frequency HRV results revealed a significant three-way interaction during contrast comparing cue exposures and recovery periods, ADS score, and Stroop interference score, $F(1,255.86) = 4.11$, $p = .044$. To aid interpretation, Figure 1 presents the estimated mean high-frequency HRV levels for -1 *SD*/+1 *SD* of the mean Stroop interference score (better/poorer performance), and -1 *SD*/+1 *SD* of mean ADS score (lower/higher alcohol severity), across the overall level of other covariates. Participants with higher ADS scores, but better Stroop performance demonstrated greater general cue reactivity, followed by a greater overall recovery effect after cue offsets compared to those with worse Stroop performance (but

similar ADS scores); while participants with lower ADS scores exhibited less overall cue reactivity and high-frequency HRV, likely due to fewer alcohol problems. This suggests that, within individuals with greater alcohol-related problems, common executive functioning capacity relates to increased parasympathetic system regulation after cue offset. There were no 3-way interactions for cues versus recovery contrast, alcohol exposure versus alcohol recovery contrast, DrInC, or executive functioning tasks (*p*'s > .05).

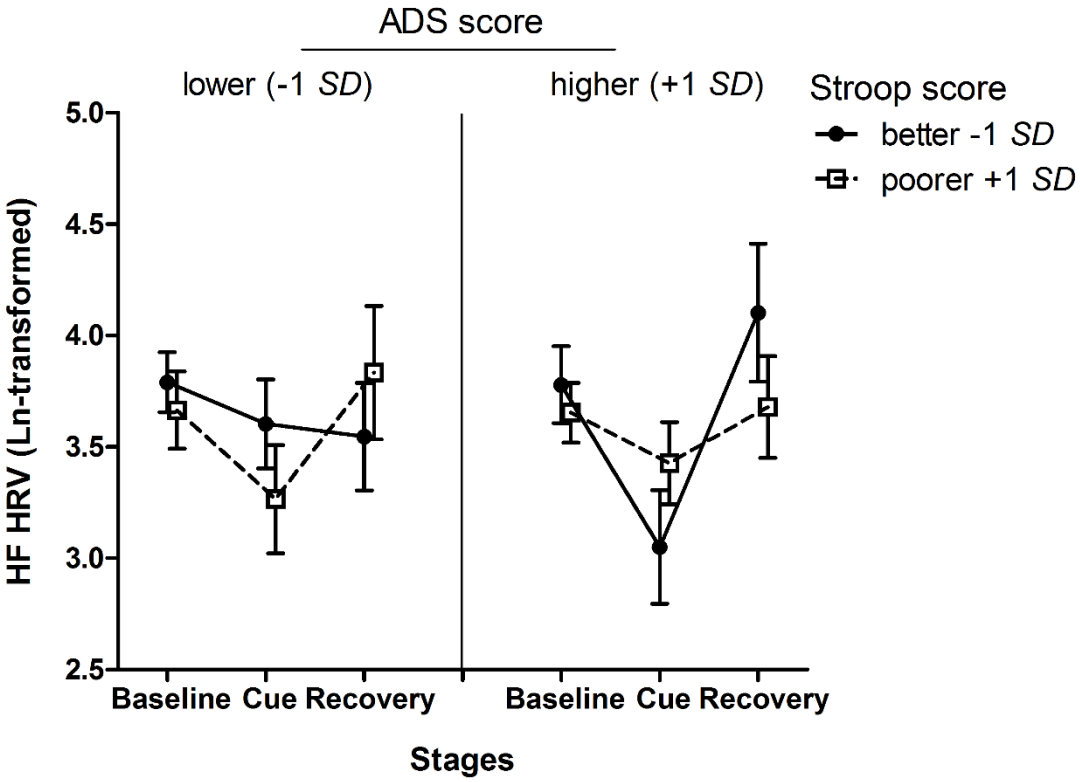

Figure 1. Estimated marginal means of high-frequency heart rate variability (HF-HRV) during the cue reactivity task for contrast cue exposures versus recovery stages, for -1 *SD*/+1 *SD* of the mean Stroop interference score (better/poorer performance), and -1 *SD*/+1 *SD* of mean ADS score (lower/higher alcohol use disorder severity), across the overall level of other covariates controlling for main and interaction effects of age, sex, and DrInC, and executive functioning task scores (number letter, letter memory). Higher HF HRV indicates greater parasympathetic activity. Error bars represent ± 1 *SEM*. Points are offset horizontally so that error bars are visible.

Discussion

This study examined whether a greater history of dysregulated drinking and executive functioning deficits would relate to poorer regulation of cue responses, observed in HRV indices during cue reactivity and reduced recovery effects. An association between Stroop performance, AUD severity and overall cue recovery effect was observed in high-frequency HRV, whereby participants with better Stroop performance and greater AUD severity (thus representing more dysregulated drinkers) demonstrated an overall recovery effect, reflecting better parasympathetic system response than those with similar levels of alcohol problems but worse Stroop performance.

The study results showed the cue reactivity task sufficiently initiated overall craving during cue exposures. Participants' alcohol craving increased during cue reactivity for both cue exposures compared to baseline, with reductions during respective recovery periods. Importantly, alcohol-specific craving was observed, with craving reductions demonstrated in subsequent recovery periods. We hypothesised executive functioning domains are differentially associated with regulation of responses to alcohol, and drinking behaviours. Poorer letter memory performance (associated with the updating executive functioning domain) related to greater severity of alcohol problems in this sample. We hypothesised heavier drinkers would demonstrate lower HRV at baseline, as evidence of a dysfunctional regulatory system. However, the reverse association was observed, with heavier drinkers exhibiting higher RMSSD.

Cue reactivity during the cue reactivity task was observed, with increased autonomic nervous system activity indicated by cardiac indices for cues overall—but this was a general response to cues, with no specific alcohol cue reactivity demonstrated above responses to water. The sample exhibited an overall recovery effect after water and alcohol cue offsets for heart rate and RMSSD indices, but not high-frequency HRV, and presented the same pattern

of overall alcohol-specific recovery effect for these indices. Regarding the role of executive functioning in alcohol cue reactivity and recovery effects, we observed associations with worse Stroop performance, and higher heart rate and RMSSD levels during the cue reactivity task.

We hypothesised executive functioning domains are differentially involved in regulatory systems that, in turn, may influence drinking behaviour. Poorer letter memory performance, associated with updating-specific executive functioning, related to greater alcohol severity in this sample. Townshend and Duka (2005) demonstrated similar associations, whereby female binge drinkers (but not males) performed worse than lighter drinkers in the spatial memory component of a standardised neuropsychological test battery (CANTAB). However, neither common executive functioning or set-shifting performance were associated with drinking measures in the current study, providing further support for Miyake and Freidman's (2012) unitary/diversity model advocating some separability between subdomains. We hypothesised heavier drinkers would demonstrate reduced HRV during baseline, indicating a dysfunctional regulatory system (Thayer et al., 2012; Weber et al., 2010). However, we observed the reverse: heavier consumption was associated with higher baseline RMSSD. Lower baseline HRV should signify a more dynamic, adaptive regulatory system per se, but as we obtained baseline psychophysiological measurements after executive functioning task completion the executive functioning tasks may have acted as a stressor for some participants (Weber et al., 2010). Thus, our intended baseline may inadvertently reflect a level of arousal, so heavier drinkers' higher baseline HRV may instead indicate increased parasympathetic activity to return to baseline post executive functioning "stressor". HRV was not recorded before executive functioning tasks, so this cannot be corroborated; pre- and post-measurement of these tasks would remedy this in future studies.

Executive functioning ability was hypothesised to relate to reduced cue reactivity during the cue reactivity task, and improve consequent regulation of responses. Results showed worse Stroop performance was associated with higher overall heart rate and RMSSD across the cue reactivity task. While higher baseline RMSSD levels should indicate a more adaptable system, uniformly elevated HRV across the cue reactivity task may signify a maladaptive system already operating at an allostatic state, and less able to respond dynamically to eliciting stimuli (Koob & Le Moal, 2001; Thayer & Sternberg, 2006). Regarding other executive functioning domains, a trend for participants with better number letter task performance demonstrating high-frequency HRV reduction from water to alcohol exposures was seen. This parasympathetic system high-frequency HRV reduction during alcohol exposure is expected, due to the arousal-eliciting properties of alcohol cues (Garland et al., 2010). However, participants with poorer number letter performance demonstrated little change, potentially indicating a system inflexible to environmental cues.

A primary study finding was the association observed between Stroop interference and dysregulated drinking measures in regulation of cue-elicited responses during the cue reactivity task. Specifically, for participants with greater alcohol-related problems (identified by higher ADS scores), a more marked overall recovery effect to the cue exposures was observed for those with better Stroop performance. According the neurovisceral integration model (Thayer & Lane, 2000), this suggests a stronger parasympathetic system response to return to baseline levels after cue offsets. The Stroop requires active response inhibition during incongruent trials to override the prepotent tendency to identify the word meaning, and instead correctly name the text colour (MacLeod, 1991), and taps into the common executive functioning subdomain (Miyake & Friedman, 2012). Thus, better response inhibition may increase the capacity of participants with greater alcohol severity to attend away from impulsive urges and thoughts of eliciting stimuli, and may have a protective role in regulating

cue-elicited responses after offset. Several studies have demonstrated deficits in response inhibition tasks in AUD samples (Noël et al., 2005; Ratti et al., 2002) including Stroop performance (Noël et al., 2001). Stronger attentional disengagement during a visual dot-probe task was associated with better high-frequency HRV recovery effects after alcohol cue reactivity in inpatient-treated, abstinent, alcohol dependent patients (Garland, 2011), and heavier social drinkers demonstrated similar biases toward alcohol cues (Townshend & Duka, 2001). Therefore, Stroop performance may be index the capacity to inhibit responding to cues for those with greater alcohol-related problems in this sample, and thus be better able to regulate responses appropriately; as has been demonstrated prospectively in high-risk adolescents (Nigg et al., 2006). Future studies would benefit from examining whether executive functioning deficits are a vulnerability factor for those with more alcohol-related problems.

This study implemented separate recovery periods after the control and alcohol cue offsets to try capture alcohol-specific recovery effects beyond general appetitive responses. However, we only observed an overall recovery effect to cues. This may be due to the water cue as a neutral stimulus inadvertently eliciting appetitive responses that may be associated with alcohol (such as hydration) due to the sensitisation of contextual cues which may signal a drinking situation. Similar HRV levels during the exposures may be due to relatively weak drug-related activation, over and above the appetitive-evoking properties intrinsic to both cues. Physiological arousal (e.g., heart rate, skin conductance) of alcohol dependent participants to alcohol have been shown to be modest compared to marked subjective craving, and largely attributed to appetitive characteristics (Reid, Flammino, Starosta, Palamar, & Franck, 2006). Indeed, studies investigating overall appetitive response have found general, rather than specific regulation for alcohol and high calorie food cues (Naqvi et al., 2015). Use of a novel, neutral appetitive stimulus (e.g., lychee juice, Claus et al., 2001) may reduce the

generalisability inherent in water cues. However, we still observed significant differences in physiological responses between the cues and their respective recovery periods, and significant subjective craving specific to alcohol exposure, suggesting a unique effect of alcohol sufficient for assessing regulation to environmental cues in this study.

Relatedly, the timescale of regulation required to significantly identify an alcohol recovery effect and associations with executive functioning or dysregulated drinking measures may exceed the three minute period applied for this study (generally the minimum time period required for high-frequency HRV spectral analysis; Berntson et al., 1997), and potentially was insufficient to differentiate alcohol-specific recovery effects. Considering we observed cue reactivity reflected in high-frequency HRV for the sample, but no specific alcohol recovery effect, regulation after alcohol cue-offset may not have occurred at a sufficient magnitude. Significant associations between high-frequency HRV recovery after an emotionally stressful speech task and rumination were evident after a 10 minute period (Key et al., 2008). Applying a longer cue reactivity stage assessment period may better capture this alcohol-specific recovery effect. Moreover, the use of mean HRV during our recovery period measures the degree of recovery, rather than the time course of recovery (Garland, 2011), which can vary within samples and require more complex measurement of HRV (e.g., ambulatory monitoring, momentary assessment) to capture a true resting baseline (Pieper, Brosschot, van der Leeden, & Thayer, 2010).

Some discrepancies between RMSSD and high-frequency HRV were seen in this study, with inverse patterns of activity during cue reactivity task. While RMSSD largely successfully filters out sympathetic system fluctuations to capture parasympathetic activity, some sympathetic activity is still represented, and RMSSD is also influenced by basal (i.e. baseline) HRV levels (Berntson, Lozano, & Chen, 2005), whereas spectral techniques that determine high-frequency HRV more accurately capture parasympathetic activity (Berntson et

al., 2005; Malik, 1996). Incorporating a sympathetic arousal index (e.g., skin conductance response) that is distinct from cardiovascular measures may better identify specific system processes reflected by these indices of autonomic nervous system activity in future studies.

The study was limited in power attributed to a small sample size, potentially limiting identification of the predicted relationships of executive functioning and cue reactivity regulation, and particularly the magnitude of the alcohol recovery effect after cue offset. However, some overall effects of domain-specific executive functioning and regulation of responses were seen, supporting the unitary-diversity framework (Miyake & Friedman, 2012), and indicates discrete neuropsychological tasks provide specificity and sensitivity for measuring alcohol reactivity and regulation. Employing these measurement techniques with a more severe sample of AUD individuals may demonstrate stronger observable responses to alcohol cues to sufficiently observe differences related to executive functioning.

In conclusion, this study employed cue reactivity that initiated alcohol craving, and we examined regulation of water and alcohol cue-elicited responses in a non-treatment-seeking drinker sample. Physiological reactivity to cue exposures, and regulation during recovery was observed for heart rate and HRV indices, but we did not observe the expected reduced recovery effect related to previous dysregulated drinking. Differences in physiological reactivity and recovery effects during cue reactivity were associated with executive functioning domain-specific measures. There was an elevated HRV system profile related to common executive functioning Stroop performance across the cue reactivity task, but not other domains. Furthermore, better Stroop performance related to an overall improved recovery effect for participants reporting greater AUD problems. Taken together, this association between executive functioning and better parasympathetic activity, as indexed by high-frequency HRV, indicates a relationship between executive functioning and regulation of responses to real-time environmental alcohol cues in non-treatment-seeking regular drinkers.

Chapter Three

Regulation of Alcohol Cue-elicited Responses in Alcoholic Liver Disease and Alcohol Dependent Drinkers during a Cue Reactivity Task

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WBL designed the study, developed the methodology, collected the data, performed the analysis, and wrote the manuscript. KCM and AJB provided feedback for the manuscript.

*This work has been submitted for publication.

Abstract

Individuals with alcoholic liver disease are a subset of chronic drinkers that typify an inability to regulate their alcohol intake despite salient physical disease consequences and biological feedback. Few studies have investigated whether drinkers with alcoholic liver show poorer regulation of responses to alcohol cues compared to alcohol dependent individuals who are otherwise healthy. An alcohol cue reactivity task was employed to examine subjective psychophysiological responses to salient alcohol cues, and whether executive functioning is associated with appropriate regulation of cue-elicited responses. We expected alcoholic liver disease patients would have worse executive functioning performance, greater subjective alcohol craving and reduced regulation of cue-elicited responses compared to alcohol dependent participants during the cue reactivity task, evidenced by greater cue reactivity and reduced return to baseline after alcohol cue-offset (recovery effect). Seventeen treatment-seeking alcoholic liver disease patients and 19 alcohol dependent treatment-seeking participants completed neuropsychological executive functioning measures (Stroop task; Trail making test: Parts A and B), and the cue reactivity task, whereby control (water) and alcohol beverage cues were presented followed by respective recovery periods. Subjective alcohol craving and physiological measures (skin conductance level; heart rate variability) were recorded across the task. Alcoholic liver disease patients performed worse in executive functioning tasks compared to alcohol dependent participants. Overall cue reactivity and consequent recovery after cue offset during the cue reactivity task was observed, and the alcoholic liver disease group demonstrated a reduced overall recovery effect. Better Stroop performance related to greater overall and alcohol-specific cue reactivity for alcohol dependent participants, but there were no group differences in recovery effects during the cue reactivity task according to neuropsychological executive functioning performance. ALD patients showed reduced overall regulation of responses to eliciting cues, and executive

functioning was associated with magnitude of responses during cue exposures, but there were no differences in regulation between alcoholic liver disease and alcohol dependent groups after cue exposures related to executive functioning. Capturing a sample of regulated alcoholic liver disease patients may better represent regulatory processes in this subsample.

Regulation of Alcohol Cue-elicited Responses in Alcoholic Liver Disease and Alcohol Dependent Drinkers during a Cue Reactivity Task

For those with alcohol use disorder, individuals with alcoholic liver disease (ALD) are a subset of chronic drinkers that typify an inability to regulate their alcohol intake. ALD is a significant long-term adverse consequence of prolonged chronic drinking. Alcohol is a major cause of liver disease worldwide (O'Shea, Dasarathy, McCullough, Practice Guideline Committee of the American Association for the Study of Liver Diseases, & the Practice Parameters Committee of the American College of Gastroenterology, 2010). Half of all global liver cirrhosis deaths are related to alcohol (World Health Organization, 2014), and ALD accounts for a significant portion of global disease burden and attributable deaths (Rehm, Samokhvalov, & Shield, 2013). People with alcohol dependence who chronically drink, therefore, represent a severe stage of alcohol use disorder, and due to their extensive chronic alcohol consumption, typically over several years (O'Shea et al., 2010), represent a subset of drinkers that consistently fail to regulate their alcohol consumption appropriately.

Most ALD patients are less severely alcohol dependent than patients receiving alcohol treatment (Howard & Fahy, 1997). As drinkers who do not initially show symptoms of severe alcohol dependence may not initially seek treatment, they are at greater risk of developing ALD as they can sustain moderate alcohol consumption untreated over many years (Wodak, Saunders, Ewusi-Mensah, Davis, & Williams, 1983). However, ALD patients who continue to drink, despite the increasing deleterious health consequences of chronic consumption demonstrate difficulties in regulating drinking behaviour appropriately. Considering the salience and immediacy of disease-related negative feedback (e.g., pain, jaundice, bloating, vomiting blood) for ALD patients (Madhotra & Gilmore, 2003), this feedback should precipitate appropriate regulation of drinking behaviour. Patients with ALD regularly report a desire to change their drinking behaviour, and they are motivated by their health situation

(Gish et al., 1993). Abstinence is essential in reducing the progression of ALD and improving the survival of patients, and central to disease management (Tilg & Day, 2007). However, a significant proportion of ALD patients relapse: one study reported 13% of ALD transplant patients severely relapsed (Perney et al., 2005), while another longer-term study observed 10% of ALD transplant participants significantly relapsed at follow-up (Everson et al., 1997). This indicates a marked inability to regulate alcohol consumption, even when the outcomes can be fatal.

Several frameworks attempt to capture the underlying processes involved in regulation of chronic alcohol consumption. Dual-process models of addiction (Bechara, 2005; Lubman et al., 2004; Wiers & Stacy, 2006b) posit two processing systems that regulate drinking behaviour: an "impulsive" system which can be hypersensitised by chronic consumption and drive impulses to drink signalled by eliciting alcohol cues; and a "reflective" system, which governs and controls these impulses. The reflective system is proposed to comprise cognitive processes such as executive functioning to sufficiently regulate intake. Executive functioning is an umbrella term that conceptualises several cognitive processes involved in complex cognition and goal-motivated behaviour, such as cognitive flexibility, inhibiting proponent responding, attentional processes, and reasoning (Miyake et al., 2000). Reduced ability of ALD patients to regulate alcohol intake appropriately may therefore be due to executive functioning deficits that affect the capacity of the reflective system to reduce impulsive system drives to consume alcohol.

Cognitive deficits in ALD patients may be due to several sources: alcohol-related brain damage from chronic drinking (Butterworth, 1995a); hepatic encephalopathy (i.e., decreased brain function from alcohol toxicity) resulting from severe liver damage (Butterworth, 2007); or pre-existing vulnerabilities that may compromise the capacity to control drinking and lead to future alcohol problems (Brown & Tapert, 2004). However, there

is inconclusive evidence detailing the relationship of ALD and executive functioning deficits. Arria, Tarter, Starzl, and Thiel (1991) assessed alcoholic liver cirrhosis patients using standardised neuropsychological tests pre- and post-liver transplant (at one year), who exhibited lasting memory and executive functioning impairment, though some post-transplant recovery was seen. While participants all reported successful abstinence at both time points, prior excessive alcohol use was not considered. McCrea, Cordoba, Vessey, Blei, and Randolph (1996) showed executive functioning deficits in both alcohol- and non-alcohol-related cirrhosis patients compared to matched healthy controls, but did not control for alcohol intake. Additionally, Sorrell, Zolnikov, Sharma, and Jinnai (2006) found that when controlling for disease severity, end-stage liver disease patients reporting previous alcohol problems had worse executive functioning performance during standardised battery RBANS and the Trail making test, compared to patients with no reported alcohol problems. However, when directly comparing discrete RBANS task performance between liver disease patients with excessive prior alcohol use versus those with no alcohol use history, those with significant use showed memory-related deficits, but no specific executive functioning deficits (Hart, Gibson, Bean, & Fisher, 2012). Therefore, there is evidence of executive functioning deficits in ALD, but there are mixed results. This may be as studies either investigate liver disease patients only, or compare them with healthy control participants that do not control for the effect of alcohol consumption and related drinking consequences that could be achieved through comparison with severe clinical samples, such as individuals with alcohol dependence.

While associations between ALD and executive functioning deficits have been seen, there is limited research investigating a potential relationship between appropriate regulation of responses to salient alcohol cues and executive functioning in ALD individuals, which may be an important factor in continued chronic consumption in this sample. A cue reactivity task

can be used to elicit specific responses to salient alcohol cues in a controlled laboratory environment compared with responses to a control cue, such as a water beverage (Drummond, Tiffany, Glautier, & Remington, 1995). These alcohol-related cues can elicit a range of psychological (e.g., subjective craving) and psychophysiological responses (e.g., changes in heart rate; skin conductance level, SCL), as well as behavioural outcomes (e.g., increased alcohol unit consumption).There have been inconsistent results regarding the relationship between self-reported subjective craving during cue reactivity tasks and drinking outcomes such as relapse (Carter & Tiffany, 1999). However, physiological indices such as heart rate variability (beat-to-beat changes in heart rate; HRV) can be particularly informative for underlying regulation of cue-elicited responses.

HRV is reactive to emotionally valent cues and stressors in the environment, and the parasympathetic autonomic nervous system can apply a relatively rapid high-frequency temporal downstream effect on heart rate (via the vagal access) in response to eliciting contextual stimuli (Berntson et al., 1997). High-frequency HRV can provide information on an individual's capacity to effectively mobilise resources according to environmental demands (Thayer & Brosschot, 2005). Therefore high-frequency HRV is a potential index of responses to emotionally-imbued cues such as alcohol (Malliani et al., 1997). Additionally, measurement responses after cues are removed (cue offset) can potentially indicate appropriate regulation of these cue-elicited responses to baseline levels (i.e., homeostasis) during the period of recovery after cue offset. Reduced or delayed return to baseline HRV levels (henceforth the 'recovery effect') have been shown after an emotional stress task in an undergraduate sample related to negative rumination (Key et al., 2008), and after a cognitive stressor related to trait worry (Verkuil, Brosschot, de Beurs, et al., 2009). Considering contextual alcohol cues trigger associated conditioned responses in drinkers, observing a

recovery effect of high-frequency HRV via a return to baseline levels after alcohol cue offset may be an index of appropriate reflective system regulation of cue-elicited responses.

Previous studies employing cue reactivity tasks have found relationships between alcohol cues and HRV in clinical alcohol dependent samples. Exposure to an alcohol-cued script increased HRV in alcohol dependent participants compared to healthy controls (Ingjaldsson, Laberg, et al., 2003), and earlier relapse in alcohol dependent patients was predicted by greater high-frequency HRV to stress-primed alcohol cues during a spatial attentional bias paradigm (Garland et al., 2012). Cue reactivity induced greater high-frequency HRV to alcohol advertisements in alcohol dependent patients, although cue reactivity did not predict relapse (Witteman et al., 2015). Finally, high-frequency HRV during recovery after alcohol cues related to better trait mindfulness in alcohol dependent participants applying a median sample split, attributed to better cognitive control (Garland, 2011). However, no studies to our knowledge have employed the cue reactivity task with ALD patients, or examined associations between regulation and executive functioning in this sample.

This study investigated whether ALD patients have difficulties appropriately regulating their responses to alcohol, which may affect control of their drinking behaviour. We implemented an alcohol cue reactivity task and measured indices of these responses to determine whether ALD patients differ in reactivity to salient alcohol cues compared to alcohol dependent participants and whether there is a systemic return to baseline levels. We hypothesised that ALD patients will experience greater alcohol cue reactivity, indexed by elevated subjective reported craving and psychophysiological (SCL, HRV) responses. We predicted ALD participants would also show reduced recovery effects after cue presentation, evidenced by a reduced return to baseline levels of these indices compared to alcohol dependent participants. Additionally, as ALD patients may have significant executive

functioning deficits, we will extend this association and examine whether executive functioning is related to appropriate response regulation. If executive functioning ability is associated with processes underlying the regulation of alcohol cue-elicited responses, we expect participants with worse executive functioning performance will evidence reduced regulation during key cue reactivity task stages.

Method

Design

Two groups of dysregulated drinkers, patients with ALD, and otherwise healthy alcohol dependent participants completed executive functioning measures, and were then exposed to water and alcohol cues with subsequent recovery periods (baseline; water cues; recovery 1; alcohol cues; recovery 2) while measures of subjective alcohol craving and physiological response indices were obtained.

Participants

Twenty-two ALD (age range: 18–51, *M* = 23.33, *SD* = 8.44) and 21 alcohol dependent adults (age range: 18–45, *M* = 27.03, *SD* = 8.68) participated. They were initially recruited for the BacALD study at Royal Prince Alfred Hospital, Sydney (Morley et al., 2013), examining the efficacy and biobehavioural basis of baclofen (a gamma-amino-butyric $acid_B$ receptor agonist) as a pharmacoptherapy for alcohol dependence in ALD patients. Participants were randomly allocated in this double-blind randomised controlled trial to three treatment conditions: low-dose (30mg/day), high-dose (75mg/day) or a placebo (sugar pill). Comprehensive recruitment strategies and full inclusion/exclusion screening criteria have been detailed elsewhere (Morley et al., 2013); the central criteria for this study are summarised below. Participants were recruited as outpatients through the hospital for alcohol-related admissions, and through online advertisements requesting participants with alcohol problems seeking treatment. Diagnostic interviews conducted by researchers identified

alcohol dependence and markers of ALD, with further formal assessment for ALD conducted by medical specialists where required.

Inclusion and Exclusion Criteria

The inclusion criteria for the trial were: 1. Alcoholic liver disease (ALD), defined as the presence of symptoms and/or signs referable to liver disease or its complications, with or without cirrhosis, in which alcohol use is considered to play a major aetiological role. Alcohol use had to exceed an average of 60 g/day in women and 80 g/day in men for 10 years. 2. Alcohol dependence according to the ICD-10 (World Health Organization, 1990) criteria. 3. Aged between 18–75. 4. Adequate cognition and English language skills to give valid consent, complete research interviews, and perform cognitive tasks. 5. Abstinence from alcohol for between 48 hours and 28 days. 6. Resolution of any clinically evident alcohol withdrawal identified using the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar: score <10; J. T. Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989).

Exclusion criteria were: 1. Any active major mental disorder associated with psychosis or significant suicide risk. 2. Concurrent use of any psychotropic medication (other alcohol pharmacotherapy to cease within three months of trial commencement) apart from antidepressants (provided that these are taken at stable doses for at least two months). 3. Unstable substance use other than nicotine. 4. Clinical evidence of persisting hepatic encephalopathy (drowsiness, sleep inversion or asterixis).

Alcohol dependent participants were matched based on the average age and gender of the ALD patients and were subject to the same inclusion/exclusion criteria, except also requiring the absence of liver disease. As HRV was an index of autonomic nervous system activity, participants with pre-existing heart conditions or taking medications that could affect heart rate, and those with consistently elevated or reduced heart rate were excluded as outliers (alcohol dependent: $n = 2$). A recording issue during Stroop led to some incomplete data

(alcohol dependent: n = 1, ALD: n = 2), and one ALD patient failed to identify any incongruent Stroop trials correctly, and these participants were excluded. One ALD patient was marginally above a blood alcohol concentration (BAC) of .05 and thus excluded. Baseline liver injury markers were not obtained for some patients (alcohol dependent: n = 3, ALD: n = 3). The final sample (N = 36) comprised 19 alcohol dependent (4 females; age: M = 48.26, SD = 10.95) and 17 ALD (6 females; age: M = 52.18 SD = 7.85) participants (see Table 7 for final sample characteristics). All participants gave informed consent, and participants were reimbursed $50AUD for their participation. The study was approved by the Human Ethics Review Committee of the Sydney Local Health District (Ref: X11-0154; HREC/11/RPAH/223).

Measures

Markers of severity of liver injury.

Maddrey's Discriminant Function (Maddrey et al., 1978) was initially developed to predict mortality risk for alcohol hepatitis and adequacy for corticosteroid treatment. Objective measures of prothrombin time and bilirubin levels are applied in the following calculation (4.6 × [prothrombin time (PT) in seconds − control PT)] + serum bilirubin in mg/dL). Higher scores relate to poorer outcomes such as mortality and decreased survival likelihood.

Model End-Stage Liver Disease (MELD) score (Forman & Lucey, 2001) is calculated using objective parameters based on the aetiology of liver disease: serum bilirubin, serum creatinine, and international normal ratio of blood coagulation (INR). These are logarithmically transformed and multiplied by several factors, improving the accuracy of cirrhosis diagnosis compared to the Child Pugh score (Pugh, Murray-Lyon, Dawson, Pietroni, & Williams, 1973). Greater MELD scores indicate greater severity and decreased survival for

Table 7

Clinical characteristics, drinking measures and neuropsychological executive functioning task performance of alcohol dependent and alcoholic liver disease groups.

	AD (*n* = 19)	ALD (*n* = 17)	*p*-value [a]	Total (*N* = 36)
Age (years)	48.26 ± 10.95 (29–68)	52.18 ± 7.85 (38–65)	.231	50.11 ± 9.68 (29–68)
Sex, *n* (%) Male	13 (68.4)	13 (76.5)	.290	26 (72.2)
TLFB mean units	11.45 ± 3.57 (7–18.48)	17.41 ± 9.86 (6–40)	.022	14.35 ± 7.83 (6–40)
Alcohol Dependence Scale (ADS)	20.32 ± 9.3 (4–42)	19.47 ± 12.44 (5–47)	.818	19.92 ± 10.74 (4–47)
Drinkers Inventory of Negative Consequences (DrInC)	30.11 ± 7.44 (14–43)	31.82 ± 12.04 (4–44)	.606	30.92 ± 9.77 (4–44)
Penn Alcohol Craving Scale (PACS)	16.68 ± 7.54 (0–29)	16.35 ± 7.31 (5–29)	.895	16.53 ± 7.32 (0–29)
Chronic Liver Disease Questionnaire (CLDQ)	141.79 ± 28.44 (88–190)	123.35 ± 35.52 (45–187)	.093	133.08 ± 32.86 (45–190)
EF task performance				
Trail making test (Trails):				
Part A (Non-EF)	26.82 ± 9.16 (16.08–45.42)	35.18 ± 16.03 (19.2–89.89)	.060	30.77 ± 13.36 (16.08–89.89)
Part B (EF)	60.18 ± 16.64 (39.38–109.34)	84.9 ± 36.66 (37.62–183)	.012	71.85 ± 30.22 (37.62–183)
Trails difference score	33.36 ± 12.45 (18.66–63.92)	49.73 ± 26.96 (5.54–110.58)	.023	41.09 ± 21.92 (5.54–110.58)
Stroop interference score	83.73 ± 124.51 (-27.21–457.03)	136.75 ± 117.84 (-40.24–336.28)	.200	108.77 ± 122.64 (-40.24–457.03)

Note: Means, *SD*s with range (minimum – maximum) shown in brackets unless specified otherwise. AD = alcohol dependent; ALD = alcoholic liver disease; TLFB = Timeline followback; EF = executive functioning.

[a] Mann-Whitney *U* tests, *t*-tests and Pearson chi-square tests conducted comparing groups, where appropriate.

the disease, with demonstrated validity in the prognosis of decompensated cirrhosis in several clinical populations (Kamath & Kim, 2007) and scores of 21 or greater considered an appropriate threshold for consideration of patients for therapeutic agents (Dunn et al., 2005). The modified MELD score is used here.

Chronic Liver Disease Questionnaire (CLDQ) (Younossi, Guyatt, Kiwi, Boparai, & King, 1999) comprises 29 items on a seven-point Likert scale (i.e., '1 = all the time', and '7 = none of the time') for six subscales addressing various symptoms of liver disease: fatigue, activity, abdominal symptoms, systemic symptoms, emotional function, and worry. The CLDQ has demonstrated appropriate reliability and validity, with lower total scores indicating higher frequency of symptoms and thus poorer health-related quality of life.

Neuropsychological measures of executive function.

Trail making test (Trails): A and B (Reitan & Wolfson, 1993) requires participants to connect a series of circles in order as quickly as possible. Part A involves joining circles with consecutive numbers only. Part B requires connecting circles of numbers and letters alternately in the correct order. Both parts involve motor speed and dexterity, and visual scanning ability. Part B is further regarded as a measure of executive functioning, specifically set-shifting flexibility, alternating attention, and inhibition (Strauss, Sherman, & Spreen, 2006). A difference score calculated by the difference in the completion time of the parts (Trails B – Trails A) is considered to reflect executive functioning ability.

Stroop task (Stroop, 1935) was an automated original colour version similar to that of Houben and Wiers (2009). The Stroop was selected due to the consistency of the interference effect. Participants indicated the colour of the printed text using keys, with 3 trial types: a control trial type, with symbols '####' '%%%%,' '&&&&' '****' presented in the colours red, green, blue or yellow; congruent trials, where the words 'red', 'green', 'blue' or 'yellow' were presented in the corresponding text colour (e.g., the word 'red' coloured in red text); and

incongruent trials, where the word text meaning and text colour were incompatible (e.g., the word 'red' coloured in blue text). A Stroop interference score was calculated by subtracting the mean response latencies of the control trials from the mean response latencies of the incongruent trials, where a higher score indicated worse performance due to greater Stroop interference.

Measures of dysregulated alcohol consumption.

Timeline followback interview (TLFB) (Sobell & Sobell, 1992) was used to measure the number of Australian standard units (10 g ethanol) per drinking day (henceforth TLFB units) in the preceding 30 days. Participants were actively prompted to recall number of drinks consumed. The TLFB has demonstrated reliability and validity (Sobell, Brown, Leo & Sobell, 1996).

Alcohol dependence scale (ADS) (Skinner & Allen, 1982) is a 25-item self-report measure of alcohol dependence which has demonstrated high levels of consistency and reliability (Ross et al., 1990). The total score was used as an index of the severity of alcohol dependence, with higher scores indicating greater severity.

Drinkers Inventory of Consequences (DrInC) Lifetime (Miller et al., 1995) is a 50-item questionnaire measuring if physical, emotional and social consequences related to alcohol use have ever been experienced. The total score was used as an index of the negative feedback received by participants about their drinking.

Penn Alcohol Craving Scale (PACS) (Flannery et al., 1999) is a 5-item self-report measure regarding the frequency, intensity and duration of craving for alcohol over the last week, with the total score reflecting greater craving. It has a high degree of internal consistency and good convergent and divergent validity (Flannery et al., 1999).

Alcohol Urge Questionnaire (AUQ) (Bohn et al., 1995) is an 8-item self-report measure of current craving or urge to drink that was taken after each stage of cue reactivity

task. The AUQ has demonstrated reliability (Bohn et al., 1995) and convergent/discriminant validity, indicative of a high degree of construct validity (Drummond & Phillips, 2002). The total score is used to assess state craving and urge to drink.

Procedure

Participants underwent a structured interview and medical consultation on day 0 of the BacALD trial to assess eligibility for the trial and medical markers of liver disease. Medical markers identified by laboratory evaluations included bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose, urinalysis, urine toxicology and human chorionic gonadotropin (β-HCG) (see Table 8) . Based on the medical assessment, participants were allocated to either ALD or alcohol dependent groups, and randomly allocated to treatment condition as determined by an independent service in fixed blocks of 15 (1:1:1 allocation ratio; see Morley et al., 2013). Baseline questionnaires ADS, DrInC, and TLFB were administered at this time.

Participants were instructed to avoid drinking alcohol the night preceding the test session and on session day and to avoid caffeine and nicotine for 4 hrs before the test session. Testing was conducted 7 (± 4) days after enrolment, with the cue reactivity task administered between 10:30 am and 3 pm. Participants were breathalysed before the session, with a BAC above .05 excluding them from testing. Participants sat in an armchair throughout the session, facing a 58 cm monitor used for Stroop and video presentation for the cue reactivity task. All questionnaires were administered with pen and paper. A face-to-face interview was first conducted to obtain drinking over the past week with a TLFB, cardiac history and exposure to alcohol in the previous week. Participants then completed Trails A and B. The Stroop was then completed on a PC using Inquisit 3.0.5.0 software (Millisecond Software LLC, 2009), followed by questionnaires unrelated to this study to reduce cognitive load effects of the

executive functioning tasks on subsequent physiological baseline recordings. Table 7 reports participant demographics, and drinking and neuropsychological task measures.

Table 8

Baseline markers of liver function for alcohol dependent and alcoholic liver disease groups

Measure	AD (*n* = 16) [a]	ALD (*n* = 14) [a]	*p* [b]
Creatinine (µmol/L)	75.07 ± 9.12 (57–87)	65.71 ± 14.64 (44–86)	–
Bilirubin (µmol/L)	8.36 ± 3.75 (4–14)	18.5 ± 20.55 (4–81)	–
Albumin (g/L)	47.79 ± 2.19 (44–51)	42.79 ± 5.77 (31–49)	–
Alkaline Phosphatase (U/L)	65.36 ± 21.5 (39–109)	118.07 ± 64.79 (59–294)	–
γ glutamyltransferase (U/L)	81.21 ± 81.39 (15–311)	426.36 ± 649.43 (26–2083)	–
Alanine aminotransferase (U/L)	32.57 ± 15.08 (15–61)	63.21 ± 34 (23–115)	–
Aspartate aminotransferase (U/L)	29.64 ± 16.78 (17–78)	86.64 ± 63.17 (24–229)	–
International normalised ratio (INR)	0.99 ± 0.06 (0.9–1.1)	1.11 ± 0.24 (1–1.9)	–
Maddrey's Discriminant Function [b]	6.54 ± 3.10 (2.59–12.31)	12.22 ± 11.87 (4.72–50.28)	.047
MELD score [b]	3.32 ± 1.86 (.94–6.16)	6.27 ± 4.92(.94–19.5)	.058

Note: Means, *SD*s with range (minimum – maximum) shown in brackets unless specified otherwise. AD = alcohol dependent; ALD = alcoholic liver disease; *p* = *p*-value; MELD = Model End-Stage Liver Disease.
[a] Measures not obtained for AD: *n* = 3, ALD: *n* = 3.
[b] Mann-Whitney *U* tests conducted comparing groups, where appropriate.

The cue reactivity task was conducted in the same order (baseline; water cues; recovery 1; alcohol cues; recovery 2; see Table 9) as counterbalancing cues has been found to mask potential effects of the alcohol cue (Monti et al., 1987). For the baseline and recovery periods, participants were instructed to concentrate on a video of neutral animal scenes set to classical music for five minutes. Cues were either a bottle of water or a bottle containing an Australian standard drink (10g alcohol) of participants' choosing: lager, red or white wine, or spirits. This was placed in front of participants with a water glass, and beer schooner glass, wine glass or spirits tumbler. An audio script was played to enhance craving for the drink stimulus (see Appendix B), which the participant was instructed to imagine as vividly as possible. Participants were then instructed to pour, then hold and smell the beverage for five

Table 9

Timeline of cue reactivity task and planned contrasts of key stages, with contrast coefficients

Stage	Baseline 5 min	Water cue 5 min	Recovery 1 5 min	Alcohol cue 5 min	Recovery 2 5 min
Stimuli	Nature video	Water beverage + control audio script	Nature video	Preferred alcoholic beverage + alcohol audio script	Nature video
Measures	SCL HRV AUQ (at end)	SCL HRV AUQ (at end)	SCL HRV AUQ (at end)	SCL HRV AUQ (at end)	SCL HRV AUQ (at end)
Contrast coefficients:					
Baseline vs. cues	-1	0.5	–	0.5	–
Water cue vs. alcohol cue	0	-1	–	1	–
Cues vs. recovery	0	-0.5	0.5	-0.5	0.5
Alcohol cue vs. recovery 2	0	–	–	-1	1

Note. SCL = Skin conductance level; HRV = Heart rate variability; AUQ = Alcohol Urge Questionnaire.

minutes. Physiological indices of heart rate and HRV were continuously recorded during each cue reactivity task stage using a three-lead electrocardiogram with two disposable Ag/Cl electrodes (ADInstruments; Sydney, Australia) placed on the arms slightly above the cubital fossa and a ground electrode on the non-dominant inner wrist. Skin conductance data were recorded with MLT117F GSR Electrodes (ADInstruments; Sydney, Australia) fitted to the second and third middle phalanges of the non-dominant hand, with the signal amplified via a FE116 GSR Amplifier (ADInstruments; Sydney, Australia), and heart rate data amplified by an ML408 Dual Bioamp/Stimulator (ADInstruments; Sydney, Australia) both connected via the PowerLab 8/25 System (ADInstruments; Sydney, Australia) to a PC operating LabChart Pro 7.3.7 software (ADInstruments, 2012). The sampling rate was 1000 Hz. R-wave data were calculated using the software's automated procedures continuously for each 5-min stage. Subjective craving was measured with AUQ after each stage. Participants were then debriefed at session end.

Data Transformations and Statistical Analysis

The Reaction Time (RT) distributions for the Stroop task were skewed and/or kurtotic, and required trimming to produce normality (Miyake et al., 2000). A two-stage trimming procedure for outliers was employed. Cut-off criterion values were first established whereby RTs outside the values were omitted: the lower and upper criteria were 200ms and 3000ms (4.12% of total RTs). The second stage of trimming utilised the Median Absolute Deviation method (Leys et al., 2013), a within-subjects procedure that identified and excludes outliers of any value 3 Median Absolute Deviation units from the median (3.7% of remaining RTs).

Skin conductance data was manually inspected for movement artefacts and processed per cue reactivity task stage using LabChart Pro, and mean SCL was calculated per stage in microsiemens (μS). Heart rate and HRV raw data per task stage were processed and analysed using Kubios 2.2 HRV analysis software (Biosignal Analysis and Medical Imaging Group,

2012) with each sample manually examined for artefacts and low pass-filter applied to interpolate identified artefacts. Trend components were removed using the Smoothness priors method with $\lambda = 500$ (Tarvainen, Ranta-Aho, & Karjalainen, 2002). Mean RMSSD per stage were positively skewed and natural log-transformed to achieve normality. For high-frequency HRV, spectral analysis was performed in Kubios employing a Fast Fourier transformation to calculate the high-frequency HRV in the frequency band 0.15-0.40 Hz, to produce mean high-frequency HRV in normalised units. High-frequency HRV means per stage were positively skewed and natural log-transformed for normality.

Standardised scores for measures were used for all model analyses, including: executive functioning tasks (Trails difference score; Stroop interference score); consumption in TLFB units; dysregulated alcohol consumption, including alcohol severity (ADS) and history of dysregulated drinking experiences (DrInC); and subjective alcohol craving (PACS). Participants did not differ in age or sex between groups, so these covariates were not included in subsequent analyses to increase parsimony of the models.

Linear mixed model (LMM) analyses were conducted examining the relationships between performance on discrete executive functioning tasks with AUQ craving scores, and with regulatory indices of SCL, RMSSD, and high-frequency HRV during the cue reactivity task. A random intercept-only model was fitted first for all cue reactivity task stages. Fixed variable disease group (alcohol dependent, ALD) was added in the next step. Baclofen treatment condition (placebo, low-dose, high-dose) was then entered as a covariate, and two-way interactions with cue reactivity task stages to examine any drug effects on model outcomes. As there were observed significant effects within the models for some indices when assessing model fits (log-likelihood ratio tests using maximum likelihood estimation), treatment condition was included in subsequent hypothesis testing analyses to control for treatment effect.

Planned contrasts were fitted first as separate models to compare psychophysiological activity during key cue reactivity task stages (see Table 9): (a) baseline versus appetitive exposures (water, alcohol); (b) water exposure versus alcohol exposure; (c) cue exposures versus recovery periods after cue offset; (d) alcohol exposure versus recovery 2 period assessing specificity of the alcohol response and consequent regulation. Fixed variable disease group was added in a further step, followed by disease group and contrast interactions. Treatment group was similarly added in the next step. Executive functioning task scores were then added. Two-way interactions of cue reactivity task contrasts and executive functioning scores were added to examine relationships with craving and regulatory indices across key cue reactivity task stages. Finally, three-way interactions of contrast, executive functioning tasks, and disease group were added to test whether executive functioning performance related to regulatory activity across the cue reactivity task for the alcohol dependent versus ALD groups.

Results

Cognitive Task Performance

There was a trend for ALD patients (M = 35.18 s, SD = 16.03) taking longer than alcohol dependent participants (M = 26.82 s, SD = 9.16) to complete the Trails A, $t(34) = -1.95$, $p = .060$. ALD patients (M = 84.90 s, SD = 36.66) were significantly slower completing Trails B compared to alcohol dependent participants (M = 60.18 s, SD = 16.64), $t(34) = -2.65$, $p = .012$. ALD (M = 49.72 s, SD = 26.96) and had significantly higher Trails difference scores than the alcohol dependent group (M = 33.36, SD = 12.45), $t(34) = -2.38$, $p = .023$, indicating worse executive functioning performance.

A paired samples t-test showed a significant Stroop effect for overall sample, with colour-naming slower during incongruent trials (M = 1123.17 ms, SD = 367.03) compared to control trials (M = 1054.30 ms, SD = 327.53), $t(34) = 5.11$, $p < .001$. The overall sample

Stroop interference score was 108.77 ± 122.64, but there was no significant disease group difference (alcohol dependent: M = 83.73, SD = 124.51; ALD: M = 136.75, SD = 117.84), $t(34) = -1.31$, $p = .200$.

Markers of Liver Injury

Table 8 presents the liver injury markers. ALD patients demonstrated higher Maddrey's discriminant function scores than the alcohol dependent group, $U = 64.5$, $p = .048$. There was a trend toward a higher MELD score for ALD, but only 3 ALD (20%) patients scored above a MELD cut-off of 9; with scores below this associated with very high survivability at three months (Wiesner et al., 2003). ALD patients thus demonstrated evidence of liver injury compared to alcohol dependent participants, but relatively low ALD disease severity.

Drinking Profile Between Disease Groups

Table 7 shows the TLFB, ADS, and DrInC scores. ALD reported higher consumed TLFB units, $t(34) = -2.40$, $p = .022$. When applying an ADS cut-off score of 9, 17 alcohol dependent participants (94.7%) were classified with alcohol dependence, compared to 14 ALD patients (82.4%). However, there were no differences in dysregulated drinking measures between groups for ADS scores (p's > .05). This suggests while ALD had significantly greater alcohol intake they did not present a different profile to alcohol dependent participants regarding severity of alcohol problems and experienced a similarly wide range of negative drinking consequences.

Overall Subjective Craving Elicited During the Cue Reactivity Task

Table 10 presents the AUQ scores across the cue reactivity task. An LMM of all cue reactivity task stages (baseline, water exposure, recovery 1, alcohol exposure, recovery 2) showed no overall main effects of cue reactivity task stages, disease group for AUQ scores, and executive functioning performance was not related to overall AUQ scores (p's > .05).

Table 10

Subjective craving and psychophysiological measures during cue reactivity task stages for alcohol dependent and alcoholic liver disease groups

Measure	Group	Baseline	Water cue	Recovery 1	Alcohol cue	Recovery 2
AUQ	AD	13 (5.07)	13.37 (8.12)	13 (7.34)	22.47 (12.95)	15.05 (9.93)
	ALD	20.13 (12.25)	16.81 (9.74)	14.88 (8.78)	20.56 (15.43)	15.76 (10.51)
SCL	AD	24.9 (8.9)	31.77 (14.4)	31.84 (14.3)	33.28 (15.21)	32.16 (14.22)
	ALD	24.72 (7.88)	30.95 (10.88)	31.15 (11.01)	31.87 (11.63)	31.77 (11.4)
RMSSD	AD	3.01 (0.68)	3.12 (0.62)	3.02 (0.67)	3.15 (0.65)	3.03 (0.65)
	ALD	2.93 (0.85)	2.91 (0.8)	2.85 (0.88)	2.95 (0.71)	2.82 (0.87)
HF HRV	AD	3.46 (0.73)	3.11 (0.69)	3.24 (0.82)	2.86 (0.74)	3.21 (0.74)
	ALD	3.48 (0.77)	3.21 (0.67)	3.35 (0.71)	3.18 (0.61)	3.24 (0.58)

Note: Means presented with *SD*s in brackets. AUQ = Alcohol Urge Questionnaire; SCL = skin conductance level, in microsiemens; RMSSD = square root of mean squared differences between successive R-R intervals (natural log transformed); HF HRV = High-frequency heart rate variability, normalised units (natural log transformed); AD = alcohol dependent; ALD = alcoholic liver disease.

However, there was a disease group and cue reactivity task stage interaction, $F(1,132) = 5.75$, $p = .018$, with the alcohol dependent group demonstrating greater changes to AUQ scores across the cue reactivity task compared to ALD. There was no overall increase in AUQ scores from baseline to cue exposures, no disease group or executive functioning main effects, or significant interactions (p's > .05). The alcohol cue-elicited higher overall AUQ scores compared to water cues, $F(1,62) = 10.53$, $p = .002$, and there was a two-way contrast and Stroop interaction, $F(1,62) = 4.27$, $p = .043$, with participants with greater Stroop interference demonstrating increased craving from water to alcohol cue, while those with lower interference scores reported little craving across the cues. There was a weak trend toward a two-way contrast and disease group interaction, $F(162) = 2.99$, $p = .089$, with alcohol dependent group reporting increased craving from water to alcohol cue, while ALD reported uniformly elevated craving. A recovery effect was observed after cue offsets with a reduction in AUQ scores during recovery periods compared to cue exposures, $F(1,132) = 5.06$, $p = .026$. There was a reduction in AUQ scores during recovery 2 after alcohol cue offset, $F(1,62) = 6.54$, $p = .013$, indicating the task elicited a sufficiently specific alcohol recovery effect. No executive functioning main effects, executive functioning across cue reactivity task interactions, or three-way interactions with disease group for key contrast models were otherwise observed (p's > .05). In sum, the cue reactivity task sufficiently elicited an alcohol-specific craving response, and there was evidence of consequent reduction during recovery to test key study hypotheses.

Physiological Reactivity to Cues

Table 10 displays means of the physiological indices during cue reactivity task stages. An LMM of SCL assessing somatic arousal over the cue reactivity task demonstrated an overall change across the stages, $F(1,136) = 46.63$, $p < .001$. No other main effects were seen, or two-

way interactions between SCL and cue reactivity task, or disease groups. Planned contrast models showed that, overall, participants' SCL increased from baseline to cues, $F(1,64) = 84.7$, $p < .001$. There were no other significant contrasts for SCL when comparing cue exposures.

LMMs of RMSSD and high-frequency HRV assessed parasympathetic system response during the cue reactivity task. An LMM across all cue reactivity task stages indicated no overall RMSSD changes across the task for the whole sample ($p > .05$). Planned contrast models revealed no RMSSD differences from baseline to cues, or reactivity differences between water and alcohol exposures, and no differences between groups (p's > .05), signifying autonomic cue reactivity was not evidenced for RMSSD to cues overall.

An LMM For high-frequency HRV across all cue reactivity task stages demonstrated a significant overall difference in whole sample high-frequency HRV levels, $F(1,136) = 3.94$, $p = .049$. LMMs of key contrasts demonstrated that overall, whole sample high-frequency HRV decreased during cue exposures from baseline, $F(1,64) = 15.21$, $p < .001$, indicating a reduction in parasympathetic system response to cues overall, but no difference in high-frequency HRV levels between water and alcohol exposures (p's > .05), suggesting an overall reactivity to cues not specific to alcohol. No disease group differences or significant interactions between disease group and contrast were observed, indicating the parasympathetic activity elicited by cues did not differ between groups.

Reduced Recovery Effect in ALD Patients Following Cue Exposures, but no Alcohol-specific Recovery Effect

Autonomic response indices during the recovery periods following cue exposures should capture parasympathetic system regulation, as indices return to baseline levels after cue offset. Key contrast LMMs for SCL during recovery periods found no SCL changes during recovery periods following cue exposures, or specific alcohol recovery effect (p's

>.05), indicating that SCL was consistently elevated after initial baseline stage. Furthermore, there were no disease group differences or respective contrast interactions indicating arousal differences.

LMMs were similarly conducted for HRV indices. No changes were observed when comparing RMSSD levels between cue exposures and recovery periods, and no alcohol-specific recovery effect comparing alcohol cue and subsequent recovery period, or interactions with disease group were seen (*p*'s >.05). LMMs of high-frequency HRV demonstrated an overall increase in high-frequency HRV levels from cue exposures to recovery periods, $F(1,136) = 5.67$, $p = .019$, indicating an overall recovery effect after observed reductions in parasympathetic response during the cue exposures. There was a contrast and disease group interaction, $F(1,136) = 4.64$, $p = .033$, with the ALD group demonstrating a reduced overall recovery effect compared to the alcohol dependent group (see Figure 2).

For the alcohol-specific recovery effect, there was a weak trend for overall increased high-frequency HRV levels during recovery after alcohol cue offset, $F(1,64) = 3.08$, $p = .084$, but this did not reach significance, and there were no effects of disease group, suggesting a general, rather than alcohol specific, parasympathetic recovery effect.

Association between Executive Functioning and Cue Reactivity to Eliciting Cues

A central hypothesis involved the role of executive functioning in the regulation of appetitive cue-elicited responses, with a focus upon an alcohol-specific response. Regarding SCL, there was a trend for an interaction of Trails and disease group which was consistent across the task, $F(1,30.55) = 3.31$, $p = .079$. Alcohol dependent participants with lower Trails difference scores (indicating better performance) had lower SCL activation than ALD patients with similar performance, while alcohol dependent participants with higher scores had higher SCL activation compared to similarly performing ALD patients. The ALD group

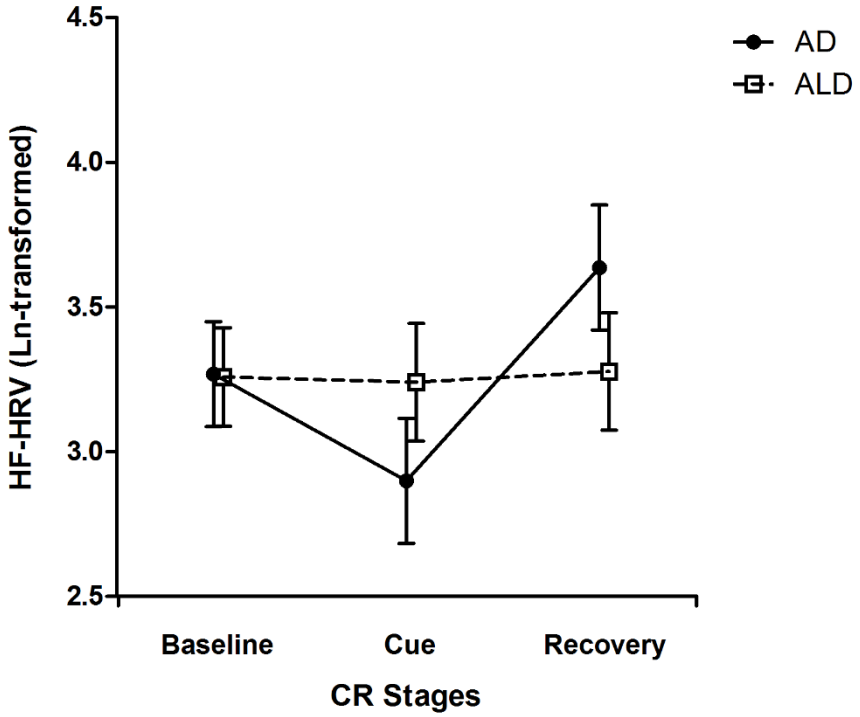

Figure 2. Estimated marginal means for high-frequency HRV (power in normalised units) comparing cue exposures (water, alcohol) versus recovery periods (recovery 1, recovery 2) between alcohol dependent (AD) and alcoholic liver disease (ALD) groups, controlling for main and interaction effects of treatment and executive functioning scores. Greater high-frequency HRV indicates more parasympathetic activity. The alcohol dependent group demonstrated a significant increase high-frequency HRV during recovery periods after cue offset, while alcoholic liver disease patients demonstrated little change between cue and recovery stages. Error bars represent ± 1 *SEM*. Points are offset horizontally, so that error bars are visible.

demonstrated similar overall activation levels regardless of Trails performance. No other main effects or interactions were found (*p*'s > .05).

For RMSSD, there was a two-way disease group and Stroop interaction during baseline versus cues, $F(1,28) = 5.08$, $p = .032$, whereby alcohol dependent participants with lower Stroop interference showed higher RMSSD from baseline to cues compared to the ALD group, indicating greater overall parasympathetic activity; while alcohol dependent participants with higher Stroop interference demonstrated little difference to the ALD group (see Figure 3). A similar pattern was seen comparing water and alcohol cues, with a significant two-way interaction of Stroop and disease group, $F(1,28) = 5.08$, $p = .032$. There

were trends for a Trails main effect for baseline versus cues, $F(1,28) = 3.17$, $p = .086$, and comparing water and alcohol exposures, $F(1,28) = 3.17$, $p = .086$, with participants with lower Trails difference scores demonstrating reduced RMSSD than those with higher Trails difference scores. No other main effects or interactions were observed (p's > .05).

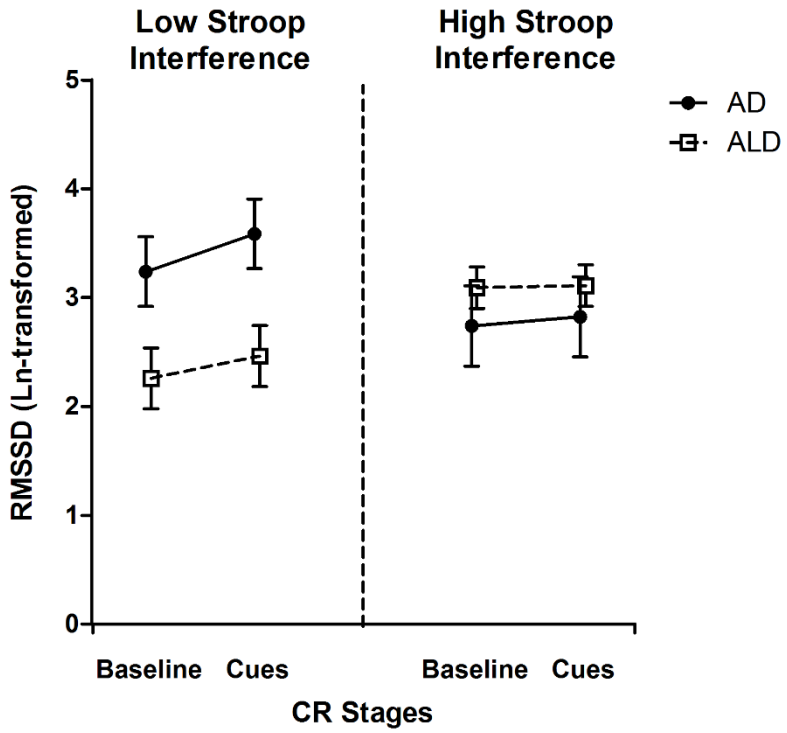

Figure 3. Estimated marginal means for square root of mean squared differences (RMSSD) between successive R-R intervals during planned contrast comparing baseline versus cue exposures (water, alcohol), according to poorer (left panel) and better (right panel) Stroop performance (Stroop interference score, better performance = low interference, -1 *SD*; worse performance = high interference, +1 *SD*) for alcohol dependent (AD) and alcoholic liver disease (ALD) disease groups, controlling for main and interaction effects of age, sex, DrInC, and Trails scores. Higher RMSSD indicates greater parasympathetic activity. Alcohol dependent participants with lower Stroop interference (better performance) demonstrated overall higher parasympathetic activity compared to ALD patients with similar performance, while participants with higher Stroop interference (worse performance) demonstrated little change between cue and recovery stages regardless of disease group. Error bars represent ± 1 *SEM*. Points are offset horizontally, so that error bars are visible.

High-frequency HRV results showed a two-way interaction for baseline versus cues contrast and Trails, $F(1,64) = 5.75$, $p = .019$, whereby participants with higher Trails scores (reflecting poorer performance) showing reductions in parasympathetic response from

baseline to cues, while those with lower scores demonstrated little change. A three-way interaction for baseline versus cues contrast, disease group, and Stroop score was seen, $F(1,64) = 4.19$, $p = .045$. To aid interpretation, Figure 4 presents estimated marginal means of high-frequency HRV during baseline compared to cue exposures across disease groups, according to better/poorer Stroop performance. For those with low Stroop interference, alcohol dependent participants demonstrated a significant high-frequency HRV reduction to the cues compared to baseline. ALD patients with low interference revealed little change from baseline to cue exposures, and this pattern was similar to participants with high Stroop interference, regardless of disease group. This suggests those with better executive functioning within the alcohol dependent group demonstrate the expected response to cues here (signified by a parasympathetic system reduction), while other groups demonstrated inflexibility in parasympathetic system response. No other executive functioning main effects or interactions between disease group and key contrasts were found.

Executive Functioning Ability Associated with Better Overall Parasympathetic Recovery Effect, But no Evidence of Alcohol-specific Recovery Effects

A primary hypothesis predicted an association between executive functioning performance and regulation following cue exposures. LMMs of RMSSD showed a two-way interaction during cue exposures versus recovery periods for disease group and Stroop, $F(1,28) = 4.48$, $p = .043$, with alcohol dependent participants with low Stroop interference demonstrating higher RMSSD than those with ALD with similar performance, while there were no differences in alcohol dependent and ALD groups with high Stroop interference. This pattern was also demonstrated during specific alcohol cue and consequent recovery contrast

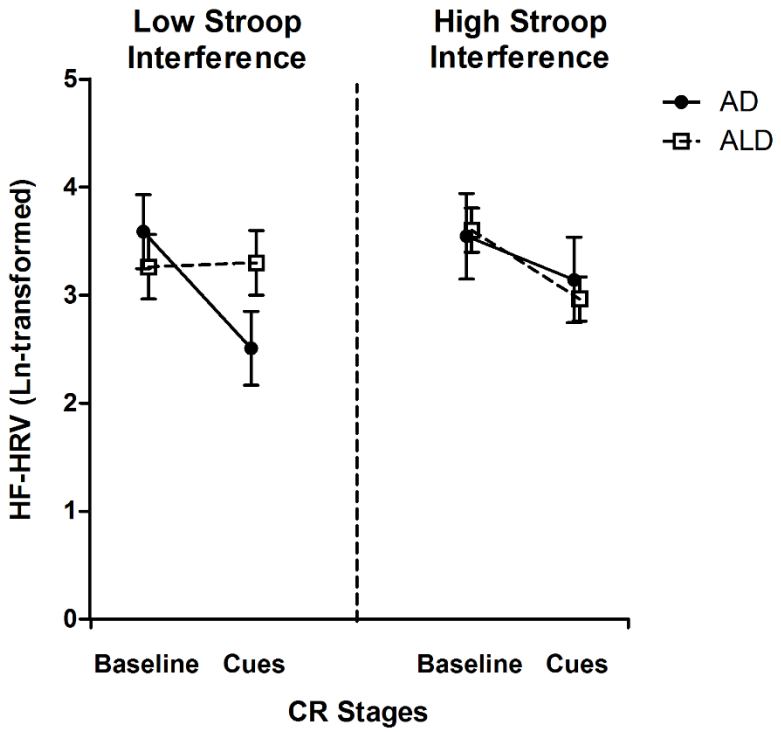

Figure 4. Estimated marginal means for high-frequency HRV (power in normalised units) during planned contrast comparing baseline versus cue exposures (water, alcohol), according to poorer (left panel) and better (right panel) Stroop performance (Stroop interference score: better performance = low interference,-1 *SD* ; worse performance = high interference, +1 *SD*) for alcohol dependent versus alcoholic liver disease groups, controlling for main and interaction effects of age, sex, and DrInC, and Trails scores. Greater high-frequency HRV indicates greater parasympathetic activity. Alcohol dependent participants with lower Stroop interference (better performance) demonstrated a reduction in parasympathetic activity from baseline to cue exposures compared to alcoholic liver disease patients with similar performance. Participants with higher Stroop interference (poorer performance) demonstrated little change, regardless of disease group. Error bars represent ± 1 *SEM*. Points are offset horizontally, so that error bars are visible.

LMM, indicating alcohol dependent participants with better Stroop performance demonstrated higher RMSSD during these periods. However, no main effects or interactions were found across the cue and recovery periods, for overall contrast or alcohol-specific (*p*'s > .05).

For high-frequency HRV recovery contrast LMMs, there was an interaction between trails difference score and cue exposures versus recovery periods $F(1,136) = 6.19$, $p = .014$: interestingly, participants with greater Trails difference scores (denoting poorer performance) demonstrated increased high-frequency HRV levels during recovery periods after cue offset, while there was little change observed for participants with lower difference scores. No other

significant three-way interactions of disease group, executive functioning, and recovery effect contrasts (*p*'s > .05) were seen, indicating that while better Stroop performance differentiated disease groups when observing an overall recovery effect, there were no associations with executive functioning performance specific to an alcohol recovery effect.

Discussion

We observed overall cue reactivity through physiological indices of parasympathetic responses to cues, with a reduction in high-frequency HRV levels to water and alcohol cues. However, there were no differences between alcohol dependent and alcohol liver disease groups. An overall recovery effect after cue offsets was also apparent with a return to high-frequency HRV baseline levels. Additionally, the ALD group exhibited reduced recovery effects after cues compared to the alcohol dependent group, suggestive of impaired parasympathetic system response in returning to baseline levels, but this was not specific to alcohol. A primary hypothesis implicated a role of executive functioning in the appropriate regulation of cue-elicited responses, indicating a functional reflective system postulated by the dual-process model (Bechara, 2005; Lubman et al., 2004; Wiers & Stacy, 2006b). Better Stroop performance was associated with more RMSSD parasympathetic activity and overall cue reactivity compared to baseline. Furthermore, differences in high-frequency HRV levels according to disease group and executive functioning ability were seen. Alcohol dependent participants with better Stroop performance (i.e., lower Stroop interference) demonstrated dynamic parasympathetic responses during cue exposures. However, those with worse performance (i.e., greater Stroop interference) and the ALD patients demonstrated minimal overall parasympathetic responses. This may suggest that better executive functioning may be associated with more appropriate responding to environmental cues, at least in alcohol dependent participants. Additionally, for ALD patients, they may no longer be able to respond

appropriately regardless of executive functioning ability, for we would expect some impulsive system motivational responses toward eliciting cues.

Overcoming Stroop interference requires successful response inhibition to suppress prepotent word colour-naming, and correctly name the text colour (MacLeod, 1991; Miyake et al., 2000), and involves "overall executive functioning" domain ability (subsuming inhibition; Miyake & Freidman, 2012). Several studies have demonstrated deficits in response inhibition tasks in alcohol use disorder samples (Kamarajan et al., 2005; Noël et al., 2005; Ratti et al., 2002) including worse Stroop performance (Noël et al., 2001). However, no significant overall or alcohol-specific recovery effects were observed according to executive functioning performance, or interactions with executive functioning and disease group, which did not support our hypothesis. Nevertheless, this is some of the first evidence associating potential executive functioning deficits and reduced parasympathetic responses to tangible eliciting cues in an alcohol dependent sample.

Differences in executive functioning performance between groups were seen, with ALD patients performing worse for Trails Part B. Sorrell et al. (2006) similarly found a relationship between Trails performance and liver disease in participants with previous alcohol abuse—the present study suggests there may be more severe executive functioning deficits specific to ALD. Considering that the ALD patients in this study were also consuming significantly more alcohol per drinking day than the alcohol dependent group, potential alcohol-related brain damage from excessive drinking may be a factor (Butterworth, 1995a), which has been shown to markedly effect executive functioning (Noël et al., 2001; Ratti et al., 2002; E. V. Sullivan et al., 2000), but we cannot clarify this with these results.

The study results showed the cue reactivity task sufficiently elicited subjective alcohol craving in these drinker samples, with alcohol cue exposure eliciting greater craving than water exposure. Importantly, there were overall craving recovery effects after cue offsets, and

an alcohol-specific recovery effect, indicating the task was sensitive in eliciting alcohol-specific responses to tangible cues. We observed significant changes in subjective alcohol craving across the cue reactivity task for the whole sample during cue exposures, with reductions in craving during recovery periods. Craving also increased respective to alcohol cue, along with reduction post-alcohol cue offset, indicating the cue reactivity task sufficiently elicited subjective alcohol-specific responses. However, groups did not differ in subjective craving across the cue reactivity task. Interestingly, an expected increase in craving from baseline to cues was not observed during the cue reactivity task for the sample. Closer inspection of cue reactivity task stages revealed that ALD self-reported craving decreased from baseline to water stage, while alcohol dependent demonstrated the expected pattern of increased craving to water cues and reduction to baseline levels during recovery. As ALD patients are treatment-seekers due to the severity of their disease, reported craving might have been lower across the cue reactivity task due to demand characteristics and social desirability bias (Tiffany & Carter, 1998). Abstinence was a desired outcome for these patients, such that reporting of craving may be considered detrimental among the ALD group.

We also measured several psychophysiological indices during the cue reactivity task to comprehensively assess any group differences in responses elicited by tangible cues. SCL did not significantly change according to different stages, with only increased overall arousal from water cue exposure onward, reflecting an overall increased arousal. Regarding HRV indices, time-domain RMSSD showed no discernible patterns across the task, either for the overall sample or between groups. However, high-frequency HRV demonstrated overall reactivity to the cues compared to baseline, reflecting a decreased parasympathetic response. Furthermore, a consequent return to baseline levels during the recovery periods was observed through increased parasympathetic response. This can be explained by Thayer and Lane's (2000) neurovisceral integration model, whereby reduction in parasympathetic activity leads

to the disinhibition of the sympathetic response, potentially controlled through prefrontal brain areas such as the ventromedial prefrontal cortex. As alcohol cues act as eliciting stimuli through Pavlovian conditioning (Pavlov, 1927) for chronic drinkers, this demonstrates the expected dynamic parasympathetic system response to cues. Increases in high-frequency HRV levels may relate to active regulation of motivational, impulsive cue-elicited responses (e.g., cravings), particularly when unable to consume the desired appetitive cue (Ingjaldsson, Laberg, et al., 2003; Segerstrom & Nes, 2007). However, the overall response to both water and alcohol cues we observed suggests a general appetitive response to cues. Considering water and alcohol share several characteristics (e.g., hydration), water may elicit similar cue responses to those elicited by alcohol, as these associated cues may sufficiently signal an alcohol drinking opportunity, established from chronic alcohol consumption (Cooney et al., 1997).

The ALD group displayed an overall reduced recovery effect after cues compared to the alcohol dependent group, although an alcohol-specific recovery effect was not seen. A dysfunctional parasympathetic system unable to effectively regulate responses to eliciting cues may lead to impaired drinking due to inability to disengage from cues (Pieper et al., 2010; Verkuil, Brosschot, Putman, & Thayer, 2009), or continued impulsive system responses to consume the substance even when the cue is removed (Garland, 2011). Considering our ALD sample are severely dysregulated drinkers that are unable to control their drinking even when faced with negative related consequences, reduced capacity to dynamically respond to environmental demands, particularly after exposure to eliciting cues, may precipitate poorer drinking outcomes such as relapse (Garland et al., 2012). This parasympathetic system inflexibility demonstrated by ALD patients, and alcohol dependent participants with executive functioning deficits may reflect an "allostatic state" of system function (Koob & Le Moal, 2001). That is, an individuals' normal functioning level has shifted to a new set point to adapt

to chronic alcohol consumption, and is evidenced through reduced response flexibility. It is important to note that autonomic activity can be affected in liver disease patients, with vagal dysfunction demonstrated in both alcohol- and non-alcohol-related well-compensated liver disease patients (Hendrickse, Thuluvath, & Triger, 1992), which may explain the dysfunction of these ALD patients. However, as this was a within-subjects repeated design and ALD patients demonstrated low liver disease severity with the MELD score, so are unlikely to suffer from significant disease-related cardiac problems at that stage.

While we observed overall recovery effects during the cue reactivity task across the whole sample, no associations with executive functioning and any overall or alcohol-specific recovery effects were seen. Additionally, there was no evidence of differences between the disease groups. Notably, the disease groups did not differ significantly either in their alcohol dependence severity, or history of dysregulated drinking represented by negative consequences of the DrInC. If we considered that the distinction between the groups was due to reflective system capability in appropriately regulating impulses when exposed to eliciting alcohol cues, then we would expect ALD patients to exhibit more profound dysregulation characteristics. Yet the groups demonstrated similar profiles of severity and negative consequences, although ALD patients had greater consumption levels. It was apparent through the ADS and DrInC scores there was heterogeneity within the groups, which is evident in alcohol use disorder per se (Litten et al., 2015). Interestingly, though ALD participants had expected worse CLDQ scores of liver disease symptoms, alcohol dependent participants also reported high levels of symptoms, suggesting these participants would represent a more severe sample. Relatedly, the ALD sample was primarily classed with a low severity of disease using the MELD score, indicating similarities between these two groups. Employing a more sensitive measure of negative consequences or capturing the frequency of experienced consequences may better delineate the disease groups: the DrInC employed in

this study only considered lifetime incidences of negative consequences, and many of these are experienced by heavy drinkers, whereas repeated negative consequences may indicate consistent difficulties in regulation of drinking.

We cannot ascertain from the results whether the relationship between worse executive functioning and reduced parasympathetic system activity observed in this study stem from pre-existing neuropsychological vulnerabilities that presage alcohol problems or are the result of alcohol consumption per se (e.g., alcohol-related brain damage). For instance, EFs have been shown to be particularly susceptible to alcohol-related damage and take longer to recover after abstinence (Bates, Bowden, & Barry, 2002), and chronic alcohol consumption has negative physical effects, including brain morphometry changes (Chanraud et al., 2007; Pfefferbaum et al., 2009; E. V. Sullivan et al., 2010) and neuronal loss (Butterworth, 1995a). Alternatively, there is some evidence of pre-existing vulnerabilities from reduced cognitive functioning during critical developmental periods (such as adolescence) predicting future alcohol problems (Khurana et al., 2013; Nigg et al., 2006). A future research direction could prospectively examine executive functioning and cue reactivity task responses in high-risk groups, such as adolescents with family history of alcoholism. This may determine whether executive functioning and cue-elicited responses predict future drinking outcomes, as increased parasympathetic responses during cue reactivity have been shown to predict relapse in alcohol dependent patients (Garland, 2012).

This study has some limitations. The modest sample size may have restricted our ability to detect between-group differences for executive functioning and regulation. We observed differences in craving and cue reactivity associations and executive functioning, and overall recovery effects, indicating the task was sensitive enough to detect differences in regulation. Secondly, we only sampled ALD patients that were seeking treatment for drinking problems, many drinking chronically at intake. Capturing a group of ALD participants that

exhibit successful regulation, such as post-operative transplant, long-term abstinent participants may reveal differences regarding alcohol-specific recovery effects. Relatedly, clinically evident withdrawal was not assessed on test day which may have impacted on performance, though most participants were still regularly drinking or had reduced consumption by this time.

In conclusion, this study identified some associations between neuropsychological measures of executive functioning and regulation during the cue reactivity task. However, we did not observe any reduced recovery effects according to disease severity that was specific to alcohol, which would have signified impaired regulation of responses after exposure to tangible alcohol cues. Considering the similarity of the dysregulated drinking profiles of our two subsamples (some who were still chronically drinking), this may explain our lack of group differences in recovery effects and associations with executive functioning. Future studies could incorporate more sensitive measures of negative physical consequences inherent to ALD and include participants that have exhibited successful regulation (such as abstinent post-transplant patients) which may better elucidate the role of executive functioning in the regulation of cue-elicited responses in this subsample of dysregulated drinkers.

Chapter Four

Impaired Decision-making and Reduced Somatic Responses Indicating Expectation of Risky Choices during the Iowa Gambling Task in Severe Alcohol Use Disorder

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WBL designed the study, developed the methodology, collected the data, performed the analysis, and wrote the manuscript. KCM and AJB provided feedback for the manuscript.

*This work is being prepared for publication submission.

Abstract

Individuals with alcoholic liver disease represent a subsample of chronic alcohol drinkers that have difficulty self-regulating alcohol consumption, despite significant adverse health consequences from drinking. This may be due to reduced ability to incorporate previous negative feedback, which leads to poor decision-making processes. We employed the Iowa gambling task to assess whether decision-making is impaired in a sample of alcoholic liver disease patients compared to a chronic drinking alcohol dependent sample, and measured skin conductance response during the task as an index of somatic autonomic arousal to task events that may indicate impaired expectancy of negative outcomes. Seventeen treatment-seeking alcoholic liver disease patients and 19 alcohol dependent treatment-seeking drinkers were assessed for dysregulated drinking history (alcohol use disorder severity, experienced negative consequences). They completed the Iowa gambling task, and skin conductance responses were recorded continuously during the task. Both the alcoholic liver disease patients and alcohol dependent group showed behavioural impairment during the Iowa gambling task, but no group differences for total or block net scores were evidenced. Groups did not differ on skin conductance response for reward outcomes, or anticipatory skin conductance response for advantageous deck choices. When assessing associations with disadvantageous deck anticipatory skin conductance response with measures of history of dysregulated drinking, there was a significant interaction of history of negative consequences and group: alcohol dependent participants with fewer experienced negative consequences had higher anticipatory skin conductance response compared to those with more experienced consequences, while alcoholic liver disease patients showed significantly lower anticipatory skin conductance response for disadvantageous deck choices overall regardless of experienced negative consequences; a trend toward a similar pattern was also seen for punishment outcome skin conductance responses. Impairment in expectancy of negative

outcomes from risky choices may result in poor decision-making processes and worse future outcomes, which was indexed through reduced skin conductance responses in alcohol dependent group individuals with more experienced negative consequences and alcoholic liver disease patients.

Impaired Decision-making and Reduced Somatic Responses Indicating Expectation of Risky Choices during the Iowa Gambling Task in Severe Alcohol Use Disorder

Some individuals with alcohol use disorder (AUD) continue to drink despite possible harmful consequences (Schuckit, 1998), potentially reflecting poor or dysfunctional decision-making regarding drinking choices. Research has identified that people dependent on substances demonstrate preference for immediate short-term gratification rather than avoid negative consequences in the long-term, suggesting deficits in decision-making (L. Clark & Robbins, 2002). People with alcoholic liver disease (ALD) represent a subsample of chronic drinkers that fail to regulate their drinking, even after experiencing salient biological and physiological consequences from their disease—potentially due to poor or impaired decision-making processes. This study examines whether people with ALD who still drink show impaired decision-making in the Iowa gambling task (IGT; Bechara et al., 1994), a computerised card game which models real-life decision-making processes for short-term and delayed reward, thus indicating deficits in decision-making related to difficulties learning from negative consequences.

The IGT (Bechara et al., 1994) is a sensitive neuropsychological measure simulating real-time decision-making that involves reward, punishment and learning processes. It was developed to investigate individuals with ventromedial prefrontal cortex (VMPFC) damage who exhibited decision-making deficits, but no impairments to other functions. Participants make choices between higher short-term rewards leading to larger punishments that long-term are disadvantageous, versus lower short-term rewards with smaller punishments that are more advantageous over time. This emulates real-world decision-making situations, and the IGT can be used to identify impaired decision-making (Buelow & Suhr, 2009). The IGT has revealed decision-making deficits in various substance use disorders, including cocaine (Bartzokis et al., 2000; Mintzer & Stitzer, 2002), marijuana (Bolla, Eldreth, Matochik, &

Cadet, 2005; Whitlow et al., 2004), opiates (Mintzer & Stitzer, 2002; Pirastu et al., 2006), and polysubstance users (Barry & Petry, 2008; Bechara & Damasio, 2002; Bechara et al., 2001; Verdejo-García, Vilar-López, Pérez-García, Podell, & Goldberg, 2006). Alcohol dependent patients in long-term treatment demonstrated poorer IGT performance than normal controls (Dom et al., 2006). Additionally, recently detoxified alcohol dependent patients who demonstrated preference for disadvantageous choices on the IGT were more likely to relapse than those choosing more advantageous outcomes (Bowden-Jones et al., 2005). This preference for short-term rewards over those that are more delayed appears to persist even in abstinence, with long-term abstinent alcoholics demonstrating deficits in IGT compared to healthy control participants (Fein et al., 2006).

Measurement of psychophysiological indices of autonomic nervous system activity such as skin conductance response (SCR) during the IGT, both before the onset, and after the reinforcers are presented allows for examination of participants' expectation of potential consequences. Bechara and Damasio (2002) examined the behavioural performance in IGT of participants with substance use disorder, patients with VMPFC-lesions, and healthy controls, while measuring SCRs for key IGT trial periods. These periods comprised SCRs after reward and punishment reinforcement outcomes, and anticipatory responses prior to receiving reinforcement. A subgroup of substance use disorder individuals who demonstrated behavioural impairment on the IGT also exhibited reduced anticipatory SCR for these risky choices compared to healthy controls, but were not as significantly impaired as VMPFC-lesioned patients (Bechara & Damasio, 2002). However, anticipatory SCR to advantageous choices, and reward and punishment outcome SCRs were comparable to both the substance use disorder group without impaired behavioural performance, and the healthy controls. This suggests an absence of arousal signalling expectancy of a negative reinforcer for "risky" decisions with potentially severe negative outcomes (Bechara & Damasio, 2002). Similar

results have also been demonstrated in healthy control samples, with skin conductance level discriminating between advantageous and disadvantageous decision-making choices, though this did not correlate with impaired behavioural performance when comparing impaired and non-impaired performers (Jenkinson, Baker, Edelstyn, & Ellis, 2008). Anticipatory SCRs are assumed to indicate affective evaluation processes involved in different choice options (Figner et al., 2012). This response can even occur prior to understanding of potential choice consequences (Bechara, Damasio, Tranel, & Damasio, 1997). Therefore, reduction in SCRs may reflect decision-making deficits in individuals with severe AUD in a real-world context, such as appropriate regulation of alcohol consumption.

Patients with ALD who continue to drink characterise a subsample of chronic drinkers with severe AUD that may demonstrate decision-making deficits through their inability to regulate their alcohol intake, even when consequences can be severe and fatal. The amount of alcohol consumption appears to be the primary risk factor for developing ALD (Savolainen, Liesto, Männikkö, Penttilä, & Karhunen, 1993), and the best intervention for treatment of ALD is abstinence (Miguet et al., 2004; Pessione et al., 2003). Furthermore, continued consumption significantly effects short-term and long-term ALD survival rates (Kelly et al., 1995), underscoring the need for ALD patients to regulate their intake. However, relapse is common in patients with ALD (Miller, Walters, & Bennett, 2001), and even occurs after liver transplant, with a significant proportion of those consuming at risky levels (Miguet et al., 2004). As abstinence is central to survival in ALD, patients that continue risky drinking despite the risk of deleterious outcomes may have potential decision-making deficits, that could facilitate poor drinking choices such as dysregulated consumption. Regulating intake appropriately and avoiding excessive of harmful consumption requires the capacity to assess available choices to make optimal decisions relevant to an individual's goals (Le Berre et al., 2017). For ALD patients, the strength of alcohol-related cues leads to difficulty in resisting

the temptation to drink and receive immediate gratification compared to regulating alcohol consumption and abstinence which may represent longer-term goals (e.g., better health outcomes), for which decision-making processes may be key. Patients with end stage liver disease and a history of alcohol dependence have demonstrated cognitive impairment in in standardised neuropsychological measures of executive functioning (Sorrell et al., 2006), and excessive alcohol consumption was associated with poorer performance during memory tasks in liver disease patients (Hart et al., 2012). However, to our knowledge, potential deficits in decision-making have not been investigated in an ALD patient sample.

This study aims to assess whether ALD patients demonstrate greater decision-making impairment compared to alcohol dependent participants in the IGT, and whether there are differences in SCR in anticipation of reinforcers, as a potential indicator of impaired expectation of negative outcomes. We hypothesise that ALD patients will demonstrate lower IGT net scores than alcohol dependent participants, indicating a deficit in decision-making processes. As ALD patients typify a subsample of chronic drinkers that fail to self-correct even after significant negative consequences from drinking, we also hypothesise that ALD patients will demonstrate reduced anticipatory SCRs to disadvantageous deck choices during the IGT compared to alcohol dependent participants, indicating impaired anticipation of reinforcers potentially due to dysfunctional learning from negative outcomes. However, we predict there will be no differences in anticipatory SCRs to advantageous deck choices, or SCRs to response outcomes of reward and punishment, reflecting Bechara and Damasio's (2002) findings. Lastly, we hypothesise that reduced anticipatory SCRs to disadvantageous deck choices will be associated with a greater previous history of dysregulated drinking, either in AUD severity or experienced negative consequences—reflecting an incapacity to appropriately learn from disadvantageous choices that result in detrimental outcomes.

Method

Participants

Participants were initially recruited for the BacALD study at Drug Health Services, Royal Prince Alfred Hospital, examining the efficacy and biobehavioural basis of baclofen in participants with ALD (Morley et al., 2013). They were recruited after alcohol-related admissions, and through online advertisements requesting participants with alcohol problems seeking treatment. Recruitment strategies and inclusion/exclusion criteria have been described in detail elsewhere (Morley et al., 2013) so only a summary of the central criteria for this study is provided here. Assessments were conducted by researchers to identify alcohol dependence and markers of ALD, with further formal assessment for ALD conducted by medical specialists where required.

The inclusion criteria for the trial were: 1. ALD, defined as the presence of symptoms and/or signs related to liver disease or its complications, with or without cirrhosis, in which alcohol use was judged to have a major aetiological role. Markers of liver injury including the Child Pugh score (Pugh et al., 1973), Mayo Clinic End of Stage Liver Disease (MELD) score (Forman & Lucey, 2001), and the Maddrey's discriminant function score (Maddrey et al., 1978) were used as standardised measures of liver condition. Alcohol use must have exceeded an average of 60 g/day in women and 80 g/day in men for $N = 10$ years. If other co-factors such as chronic hepatitis C were present, a significant contribution of alcohol to liver disease was considered present if a period of supervised abstinence (e.g., in hospital) led to a ≥50% improvement in liver enzymes. 2. Alcohol dependence according to the ICD-10 criteria (World Health Organization, 1990). 3. Aged 18–75. 4. Adequate cognition and English language skills to give valid consent and complete research interviews and perform cognitive tasks. 5. Willingness to give written informed consent. 6. Abstinence from alcohol for between 48 hrs and 28 days. 7. Resolution of any clinically evident alcohol withdrawal (score

of < 10) using the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar; J. T. Sullivan et al., 1989)

Exclusion criteria included: 1. Any active major mental disorder associated with psychosis or significant suicide risk. 2. Pregnancy or lactation. 3. Concurrent use of any psychotropic medication (other alcohol pharmacotherapy to cease within 3 months of trial commencement) apart from antidepressants (provided that these are taken at stable doses for at least two months). 4. Unstable substance use other than nicotine. 5. Clinical evidence of persisting hepatic encephalopathy (drowsiness, sleep inversion or asterixis). Alcohol dependent participants were matched based on the average age and gender of the ALD participants, and were subject to the same inclusion/exclusion criteria, with the caveat of absence of liver disease.

Forty-two participants were initially tested but some were excluded from following analyses: one alcohol dependent participant reported previous frontal lobe damage and was excluded due to the decision-making component of the IGT, while one ALD patient demonstrated significant performance anxiety and IGT was ended prematurely; one ALD patient was marginally above .05 blood alcohol concentration (BAC) at test and also excluded; SCR recording issues produced significant variance due to poor electrode contact, resulting in insufficient data for three alcohol dependent participants. The final sample (N = 36) thus comprised 19 alcohol dependent participants (5 females; Age M = 47.47, SD = 10.75) and 17 ALD (4 females; Age M = 52.12, SD = 7.8) patients (see for Table 11 for sample characteristics). All participants gave informed consent, and participants were reimbursed $40 AUD for their participation. The study was approved by the Human Ethic Review Committee of the Sydney Local Health District (Ref: X11-0154; HREC/11/RPAH/223)

Table 11

Sample demographics, clinical characteristics, neuropsychological and Iowa gambling task performance

	AD (*n* = 19)	ALD (*n* = 17)	Test-value	*P*-value
Age (years)	47.47 ± 10.75	52.12 ± 7.81	-1.47	.152
Sex, *n* (%) Male	14 (73.7)	13 (76.5)	.037	.847
TLFB mean units per drinking day [a]	11.69 ± 4.04	16.73 ± 7.71	-2.44	.020
TLFB mean units per week [a]	2.92 ± 1.01	4.18 ± 1.93	-2.44	.020
Alcohol Dependence Scale (ADS)	19.9 ± 9.26	20 ± 12.81	-0.03	.977
Drinkers Inventory of Negative Consequences (DrInC)	29.74 ± 7.5	32.35 ± 12.57	-0.77	.448
Penn Alcohol Craving Scale (PACS)	17.42 ± 7.76	16.236 ± 7.38	0.47	.643
BIS	22.05 ± 3.85	19.589± 2.92	2.14	.039
BAS	36.16 ± 7.61	32.94 ± 15.92	0.79	.437
Trails Difference Score	32.39 ± 10.46	47.93 ± 25.61	-2.43	.020
Stroop Interference Score [b]	73.49 ± 115.64	152.79 ± 114.31	-1.86	.074
IGT Net score	1.05 ± 45	-4.82 ± 35.37	0.43	.669

Note. Means with *SD*s shown in brackets unless specified otherwise. Pearson chi-square tests and *t*-tests conducted comparing groups, where appropriate. AD = alcohol dependent, ALD = alcoholic liver disease; TLFB = Timeline followback; BIS = Behavioural Inhibition Scale; BAS = Behavioural Activation Scale; IGT = Iowa gambling task.

[a] AD: *n* = 18.

[b] AD: *n* = 17, ALD: *n* = 14.

Measures

Measures of dysregulated alcohol consumption.

Timeline follow-back interview (TLFB; Sobell & Sobell, 1992) was used to measure the number of standard drinks per drinking day in the preceding 30 days of drinking. Participants were actively prompted to recall number of drinks. The TLFB has demonstrated reliability and validity (Sobell, Brown, Leo, & Sobell, 1996)**.**

Alcohol dependence scale (ADS; Skinner & Allen, 1982) is a 25-item self-report measure of alcohol dependence which has demonstrated high levels of consistency and reliability (Ross, Gavin, & Skinner 1990). The total score was used as an index of the severity of alcohol dependence.

Drinkers Inventory of Consequences *(DrInC)* Lifetime (Miller et al., 1995) is a 50-item questionnaire measuring physical, emotional and social consequences related to alcohol use have ever been experienced, and is a reliable and valid measure of experienced adverse consequences (Forcehimes, Tonigan, Miller, Kenna, & Baer, 2007). The internal reliability of the subscales for this study were acceptable or higher (Impulse control $\alpha = .74$; Interpersonal $\alpha = .82$; Intrapersonal $\alpha = .86$; Physical $\alpha = .70$; Social $\alpha = .72$). The total score was used as an index of lifetime negative consequences related to drinking.

Penn Alcohol Craving Scale (PACS; Flannery et al., 1999) is a five-item self-report measure regarding the frequency, intensity and duration of craving for alcohol over the last week. It has a high degree of internal consistency ($\alpha = .92$) and good convergent and divergent validity (Flannery et al., 1999).

Behavioural Inhibition/Behavioural Activation Scales (BIS/BAS; Carver & White, 1994) contains 20 items assessing reward drive and responsiveness. The internal consistency for the scales for this study were acceptable or higher (BIS: $\alpha = .70$; BAS: $\alpha = .90$), but BAS

subscales demonstrated reduced reliability (Drive: α = .67; Funseeking α = .81; Reward Responsiveness α = .66).

Neuropsychological measures of executive function.

Trail making test (Trails): A and B (Reitan & Wolfson, 1993) required participants to connect a series of circles in order as quickly as possible. Part A involves joining circles with consecutive numbers only. Part B requires connecting circles of numbers and letters alternately in the correct order, and is further regarded as a measure of executive function, specifically set-shifting flexibility, alternating attention, and inhibition (Strauss et al., 2006). A difference score calculated by the difference in completion time between Part B and Part A (Trails B – Trails A) is considered to reflect executive functioning-specific deficits.

Stroop task (Stroop, 1935) was an automated original colour version similar to that used by Houben and Wiers (2009), measuring the common executive functioning domain of Miyake and et al.'s (2000) unitary/diversity model of executive functioning. Participants were required to indicate the colour of the printed text using keys, with 3 trial types: a control trial type, with symbols '####' '%%%%,' '&&&&' '****' presented in the colours red, green, blue or yellow; congruent trials, where the words 'red', 'green', 'blue' or 'yellow' were presented in the corresponding text colour (e.g., the word 'red' coloured in red text); and incongruent trials, where the word text meaning and text colour were incompatible (e.g., the word 'red' coloured in blue text), with 84 trials in total (n = 7 trials per trial type, per colour). A Stroop interference score was calculated by subtracting the mean response latencies of the control trials from the mean response latencies of the incongruent trials, where a higher score indicated poorer performance due to greater Stroop interference.

Iowa Gambling Task

A computerised version of the IGT (Bechara et al., 1994) was used in this study—previous research has demonstrated no differences in performance between the original and

computerised versions (Bechara, Tranel, & Damasio, 2000; Bowden-Jones et al., 2005). Participants are presented with four decks of cards on screen (decks A', B', C' and D'); they are provided with a hypothetical balance of $2000 and instructed to win as much money as possible. However, two decks (decks C' and D') are considered disadvantageous, as choosing these decks will reward participants with high money gain ($100), but will also be followed unpredictably with higher penalties, so that the difference between rewards and losses in these decks will be negative over the long-term (i.e. -$250 net loss per block of 10 cards). Inversely, the decks A' and B' are advantageous over the long-term—while there is a smaller immediate $50 gain per selection, future losses are also smaller over the long run, so that overall the long-term difference between reward and losses in these decks will be positive (i.e. $250 net gain per block of 10 cards). Participants were instructed that some decks are more advantageous than others, and they were free to switch between decks as they chose, using the mouse to select cards from any of the decks. This was followed by a discrete audio sound (akin to a gambling machine) and information was presented below the chosen deck, indicating how much money was won and lost per selection. Information was also presented at the bottom of the screen indicating current balance, as well as the balance resulting prior to previous trial outcome.

There were in total 100 trials, which participants were instructed of, but the program automatically exited the task after completion and participants had no indication of trial number during the task. Deck positions were counterbalanced across participants; punishment trials were randomised within each deck per 10 selections according to specific rules, for disadvantageous (A' five penalty cards, range $150-$350; B' one $1250 penalty card) and advantageous (C' five small penalty cards, range $25-$75; D' one $250 penalty card) decks. A net score was calculated by subtracting the total trial selections from advantageous the disadvantageous decks for all trials ([A' + B'] – [C' + D']); total net score), and per block of

20 trials (block net score), with scores above 0 reflecting better overall decision-making performance.

As a primary objective of this study was examination of SCR during the IGT, trial components were implemented, with inter-component-intervals where participants were unable to respond: *trial start*, the beginning of a new trial signalled by participants clicking a continue button; *trial selection*, when participants clicked on a deck, and followed by a 5-sec inter-component-interval; and *trial outcome*, the moment when information was presented of wins and losses associated with the selected card, also followed by 5-sec inter-component-interval (see Figure 5). The trial components were scored online by the experimenter to demarcate quantification of SCR periods of interest using Labchart Pro 7.3.7 software (ADInstruments, 2012); scoring synchronisation was further confirmed post-task using recordings of the task presentation.

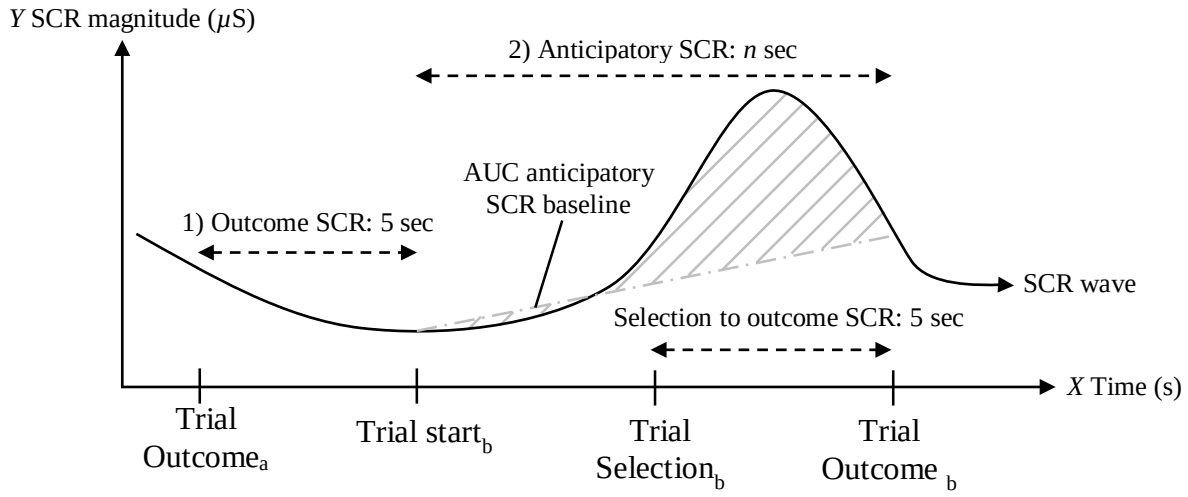

Figure 5. Schematic of an example skin conductance response (SCR) wave (μS) over time (s), illustrating relevant trial components (start, selection, and outcome), time periods of interest, and area under the curve (AUC) for anticipatory SCR (depicted by shaded area) with baseline.

SCR Acquisition

Skin conductance data was acquired using MLT117F GSR Electrodes (ADInstruments; Sydney, Australia) fixed to the second and third middle phalanges of the participants' non-dominant hand, with the signal amplified via the FE116 GSR Amplifier (ADInstruments; Sydney, Australia) via the PowerLab 8/25 System (ADInstruments; Sydney, Australia) to a PC operating Labchart Pro software. Samples were captured at a rate of 1000/sec. Skin conductance was manually inspected for movement artefacts and automatically processed using Labchart Pro software.

There were two main time periods of interest for SCR per trial (see Figure 5 for schematic representation): outcome SCR, the 5-sec period immediately following trial outcome to examine responses to both reward and punishment cards; anticipatory SCR, which measures the period from trial start where a participant is free to choose which deck to select, up to beginning of trial outcome presentation. This anticipatory SCR period differs slightly from the time window applied in Bechara et al.'s (1999) study (which accounted for the period directly after the outcome SCR outlined above [e.g., trial $outcome_a$], until the presentation of the following trial $outcome_b$). We aimed to provide a clear separation of outcome SCR from the previous trial, and the period of deck selection (i.e. $trial_b$ start to $trial_b$ selection) coupled with an enforced period whereby participants could not respond and contemplated the impending outcome ($trial_b$ selection to $trial_b$ outcome). Therefore, the anticipatory SCR period varied according to the time taken by participants to select a deck after the beginning of a trial.

Procedure

Participants underwent a structured interview and medical consultation on day 0 of the BacALD trial to assess eligibility for the trial and for medical markers of liver disease. Medical markers of liver function were obtained at this stage, and confirmed through

laboratory evaluation, including bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose, urinalysis, urine toxicology and human chorionic gonadotropin (β-HCG) (see Table 12). Markers of liver injury including the Mayo Clinic End of Stage Liver Disease score (Forman & Lucey, 2001), and the Maddrey discriminant function (Maddrey et al., 1978) were used as standardised measures assessing liver condition (see Table 12). Based on the medical assessment participants were allocated to the ALD or alcohol dependent groups. Baseline questionnaires ADS, DrInC, TLFB were also administered on day 0. Testing was conducted 7 (± 4) days after enrolment with IGT completed at a consistent time of day (10:30 am-3 pm). Participants were instructed to avoid drinking alcohol the night preceding test session and session day, and to avoid caffeine and nicotine for 4 hrs prior to the test session. Participants were breathalysed prior to session, with a BAC above .05 excluding them from testing. Throughout the session participants were seated in an armchair in front of a 58cm monitor used for Stroop and IGT presentation. All questionnaires were completed with pen and paper. A face-to-face interview was first conducted to obtain drinking over the past week with a TLFB, and exposure to alcohol in the previous week. Table 11 reports patient demographic and clinical characteristics. Participants then completed the executive functioning task Trails A and B using pen and paper. The Stroop was then completed on a PC using Inquisit 3.0.5.0 software (Millisecond Software LLC, 2009), followed by the BIS/BAS and unrelated current study questionnaires to reduce cognitive load effects of the executive functioning tasks on consequent baseline recordings. The IGT was then completed within Inquisit, and participants were then debriefed.

Data Transformations and Statistical Analysis

Standardised scores for measures were used for all model analyses, including: executive functioning tasks (Trails difference score; Stroop interference score); consumption

measured by TLFB drinks per drinking day (henceforth TLFB units), dysregulated alcohol consumption including alcohol severity (ADS), and history of dysregulated drinking experiences (DrInC); subjective alcohol craving (PACS); and reward and punishment sensitivity (BIS/BAS). Participants did not differ in age or sex between groups, so these covariates were not included in the consequent analyses to increase parsimony of the models. Independent *t*-tests and chi-square tests were conducted for group differences for demographics, dysregulated drinking measures, and neuropsychological task performance for Stroop and Trails, and IGT total net score. Correlational analyses were also conducted using Pearson's correlation coefficient tests examining relationships between the above variables, which were false-discovery rate (FDR) corrected for multiple comparisons (Benjamini & Hochberg, 1995) which informed subsequent model covariate addition.

Table 12

Baseline markers of liver function for alcohol dependent and alcoholic liver disease groups

Measure	AD (*n*=16) [a]	ALD (*n*=14) [a]	*p*-value [b]
Creatinine (µmol/L)	75.07 ± 9.12 (57–87)	65.71 ± 14.64 (44–86)	–
Bilirubin (µmol/L)	8.36 ± 3.75 (4–14)	18.5 ± 20.55 (4–81)	–
Albumin (g/L)	47.79 ± 2.19 (44–51)	42.79 ± 5.77 (31–49)	–
Alkaline Phosphatase (U/L)	65.36 ± 21.5 (39–109)	118.07 ± 64.79 (59–294)	–
γ glutamyltransferase (U/L)	81.21 ± 81.39 (15–311)	426.36 ± 649.43 (26–2083)	–
Alanine aminotransferase (U/L)	32.57 ± 15.08 (15–61)	63.21 ± 34 (23–115)	–
Aspartate aminotransferase (U/L)	29.64 ± 16.78 (17–78)	86.64 ± 63.17 (24–229)	–
International normalised ratio (INR)	0.99 ± 0.06 (0.9–1.1)	1.11 ± 0.24 (1–1.9)	–
Maddrey's Discriminant Function [b]	6.54 ± 3.10 (2.59–12.31)	12.22 ± 11.87 (4.72–50.28)	.047
MELD score [b]	3.32 ± 1.86 (.94–6.16)	6.27 ± 4.92(.94–19.5)	.058

Note: Means and *SD*s presented with range (minimum – maximum) shown in brackets unless specified otherwise. AD = alcohol dependent; ALD = alcoholic liver disease; MELD = Model End-Stage Liver Disease.

[a] Measures not obtained for AD: n = 3, ALD: *n* = 3.

[b] Mann-Whitney *U* tests conducted comparing groups, where appropriate.

SCR data analysis was conducted using Labchart Pro, which allows for post-acquisition transformation of the raw SCR data, adapting previously employed techniques (Bechara et al., 1999; Naqvi & Bechara, 2006). First, a low pass filter using a triangular window (window width = 1 second) was applied to the raw SCR data to smooth out high-frequency noise. A difference function was then used remove slow drift of the SCR signal, whereby a moving difference function was applied subtracting a value a set distance prior to the processed sample value—a difference interval of 50 msec (50 sample points for 1000 samples/sec) was employed—which was then divided by the time period, thus retaining information of tonic skin conductance level (Naqvi & Bechara, 2006). Next, to measure the magnitude of the SCR during the two outlined periods of interest, the "area under the curve" was measured for the smoothed and differenced function within respective time periods of interest using the "integral to baseline" function within Labchart Pro, calculated with the rectangular rule. This applies the mathematical calculation of the "integral", except that rather than applying a baseline of zero for integration, a trial-specific baseline was employed involving a straight line drawn between the endpoints from the values of the selected time period (see Figure 5). The resulting area is divided by the relevant time period in seconds and is reported in amplitude units of squared microsiemens per time period (μS/sec).

SCR data were analysed using marginal models, as this allows participants' data to remain in the model if a data point from a level of the repeated measure (i.e. ≥ 1 card blocks) is missing. This is relevant for both anticipatory responses of deck choice outcomes (advantageous, disadvantageous decks) and outcome responses (reward, punishment) as participants performing well at the IGT should select more cards from the advantageous decks as the task progresses, resulting in fewer (and potentially zero) disadvantageous deck choices within blocks. Correspondingly, the marginal model still incorporates these values with no loss of participants from the overall analysis. Four SCR blocks were calculated,

comprising the first two blocks of 10 selections (i.e. trials 1-10, 11-20), and last two blocks of 40 selections (trials 21-60, 61-100); this accounted for the expected reduced number of disadvantageous deck choices as participants progressed through the IGT (Bechara & Damasio, 2002). A marginal model was fitted to compare the outlined SCRs across repeated within-subjects fixed factor of the four SCR blocks. Fixed factor group (alcohol dependent, ALD), and an interaction between anticipatory blocks and group were also added. Covariance structures were tested for potential covariance of anticipatory responses between blocks, with best model fits assessed using likelihood ratio tests. To assess whether participants' previous history of dysregulated drinking behaviour was associated with impaired anticipatory responses, ADS and DrInC scores were further added as covariates, and two-way interactions for anticipatory blocks and group variables. As initial group analyses revealed a significant negative relationship of BIS scores for the ALD group and IGT scores (see Table 11 and Table 13), it was also added as a covariate-of-interest main effect and two-way interaction with group to examine whether reduced sensitivity to punishment was associated with SCR responses during the IGT.

Behavioural performance in the IGT was assessed using marginal models for parsimony, assessing block net score applying a within-subjects repeated factor IGT block (five levels of blocks = 20 deck selections). The models were similarly fitted with fixed factor group and an IGT block and group interaction, and suitable covariance structures were tested for potential covariance that resulted in best model fit.

Table 13

Correlations between demographic characteristics, neuropsychological task performance, and Iowa gambling task performance

	1	2	3	4	5	6	7	8	9	10
1. Group (0 = AD; 1 = ALD)	-									
2. Gender (0 = Male, 1 = Female)	.244	-								
3. Age	-.032*	.007*	-							
4. ADS Score	.005*	-.369*	.009*	-						
5. DrInC Total Score	.131	-.233*	-.024*	.602	-					
6. TLFB units per drinking day [a]	.391	-.22*	.117	.628	.452	-				
7. BIS	-.345*	-.003*	.18	.13	.17	.084	-			
8. BAS	-.134*	-.155*	-.015*	-.318*	-.051*	-.167*	.191	-		
9. Trails Difference score (B-A)	.385	.186	.23	.16	.018*	.312	-.058*	-.373*	-	
10. Stroop Interference score [b]	.335	.173	-.038*	.312	.486	.344	.161	-.067*	.148	-
11. IGT total net score	-.074*	.054	-.288*	-.045*	-.192*	.109	-.027*	.071	.072	.026

Note: Correlations FDR-corrected with $P_{(FDR)} = .05$. $N = 36$, except for: [a] $N = 35$; [b] $N = 31$. AD = alcohol dependent; ALD = alcoholic liver disease; ADS = Alcohol Dependence Scale; DrInC = Drinkers Inventory of Consequences; TLFB = Timeline followback; BIS = Behavioural Inhibition Scale; BAS = Behavioural Activation Scale.

* $P_{(FDR)} < 0.05$ (2-tailed).

Results

Sample Demographics and Clinical Characteristics

Table 11 presents the data for the groups. There were no group differences for age or sex. ALD participants consumed significantly more TLFB units per drinking day, and per week compared to the alcohol dependent group. However, there were no significant differences in history of dysregulated drinking, for either ADS or DrInC scores, or craving as measured with PACS. Sixteen ALD patients and 17 alcohol dependent participants were categorised as alcohol dependent participants using the ADS when applying a cut-off score of 9 (Ross et al., 1990). ALD patients had significantly lower BIS scores compared to alcohol dependent participants, indicating decreased sensitivity to punishment, but no group differences in reward sensitivity as reflected in the BAS. ALD participants demonstrated worse executive functioning performance with greater Trails difference scores and a trend for greater Stroop interference.

Relationships with IGT Performance

Table 13 displays correlations among demographic and clinical characteristics, executive functioning tasks, and IGT net score. There were medium to strong correlations for dysregulated drinking measures ADS and DrInC scores, and TLFB consumption, which was expected. Because of this, ADS and DrInC only were entered in following analyses. Furthermore, there was a significant negative relationship with age and ADS score, with reported severity scores decreasing with increasing age. TLFB consumption was positively associated with group, whereby consumption increased for ALD. There was no correlation between executive functioning tasks, or with IGT total net score, for which previous research has illustrated modest or no relationships between IGT and performance in various neuropsychological executive functioning tasks (Toplak, Sorge, Benoit, West, & Stanovich,

2010). BIS was positively correlated with IGT score , and negative correlations with BAS scores and ADS and DrInC scores, with lower reward sensitivity with increasing severity and dysregulated drinking scores. IGT total net score was negatively correlated with Age, ADS score, and DrInC, with lower scores as the other variables increased. ALD participants demonstrated worse executive functioning performance with greater Trails difference scores, but no differences in Stroop interference..

IGT Behavioural Performance

Figure 6 presents the net block scores for 5 blocks of 20 cards by group. A marginal model was conducted with a compound symmetry covariance structure, as it provided the best model fit. Results showed that block net scores differed across the task overall, $F(1,136)$ =

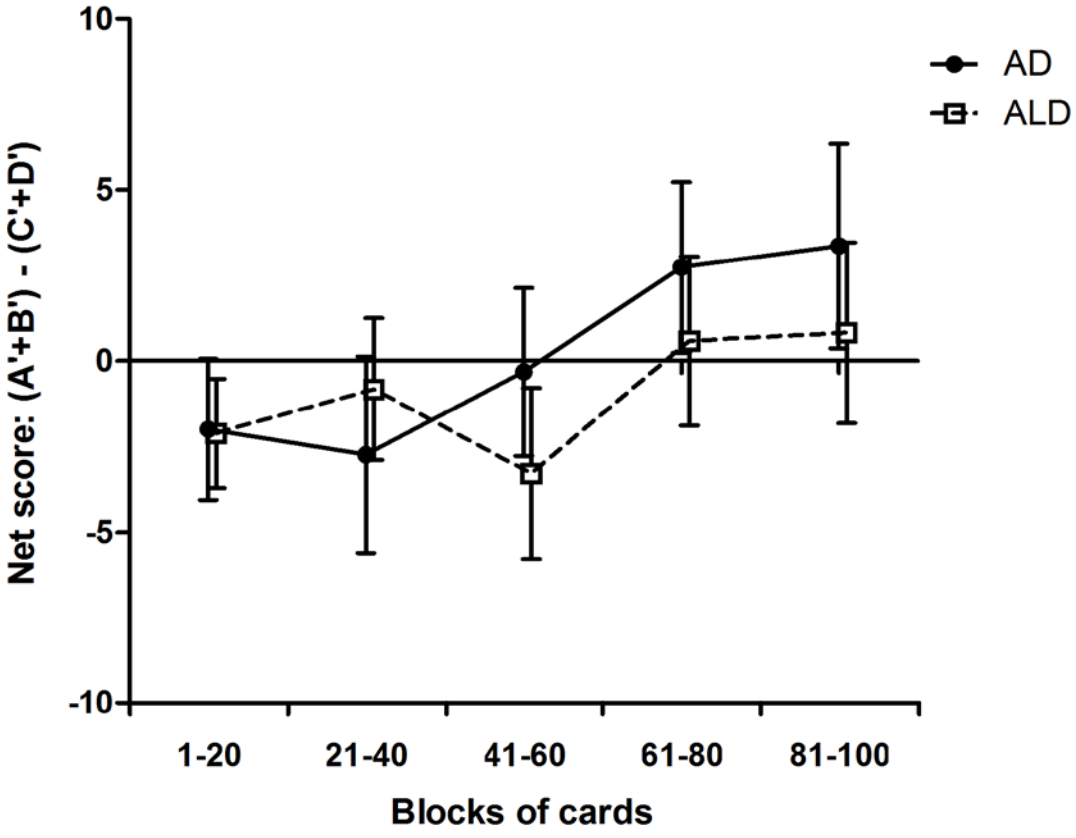

Figure 6. Net scores across blocks for IGT task performance between alcohol dependent (AD) and alcoholic liver disease (ALD) groups. A higher score indicates better task performance through more advantageous deck choices. Error bars represent ±1 *SEM*. Points are offset horizontally so that error bars are visible.

2.85, p =.026. Sidak-adjusted pairwise-comparisons conducted using the first card block as a reference category demonstrated a trend towards a more positive net block score for the last block comparatively (mean difference = 4.16, *SEM* = 1.73, p = .07), but this was the only indication of better performance from task start. However, there was no main effect of group, $F(1,34) = .19$, $p = .669$, or interaction of group and block, $F(1,136) = .70$, $p = .596$, (p's > .05) indicating groups did not differ in their behavioural performance of the IGT. Figure 6 demonstrates that mean performance of both groups across blocks shifted to a positive score for alcohol dependent participants within the last two blocks, but ALD failed to clearly do so, demonstrating an overall impairment in the task. When applying total net score cut-off of 10—the highest score observed in VMPFC-impaired patients in Bechara and Damasio's (2002) study and used to delineate impaired (≤ 10 total net score) versus non-impaired (> 10 total net score) performance—only 6 alcohol dependent participants (31.15%) and 4 ALD (23.53%) participants were considered non-impaired within respective groups in this study. However, there was insufficient power to run analyses within these subgroups to identify potential differences in performance-related impairment in further analyses.

Mean SCR for Deck Outcomes

Figure 7 presents the overall group means for outcome SCRs (reward, punishment) and anticipatory SCRs for deck choices (advantageous, disadvantageous). Alcohol dependent participants showed slightly higher SCR for both outcome SCRs than ALD patients, but independent samples *t*-tests demonstrated no significant difference between groups either reward or punishment outcome mean SCRs (p's > .05).

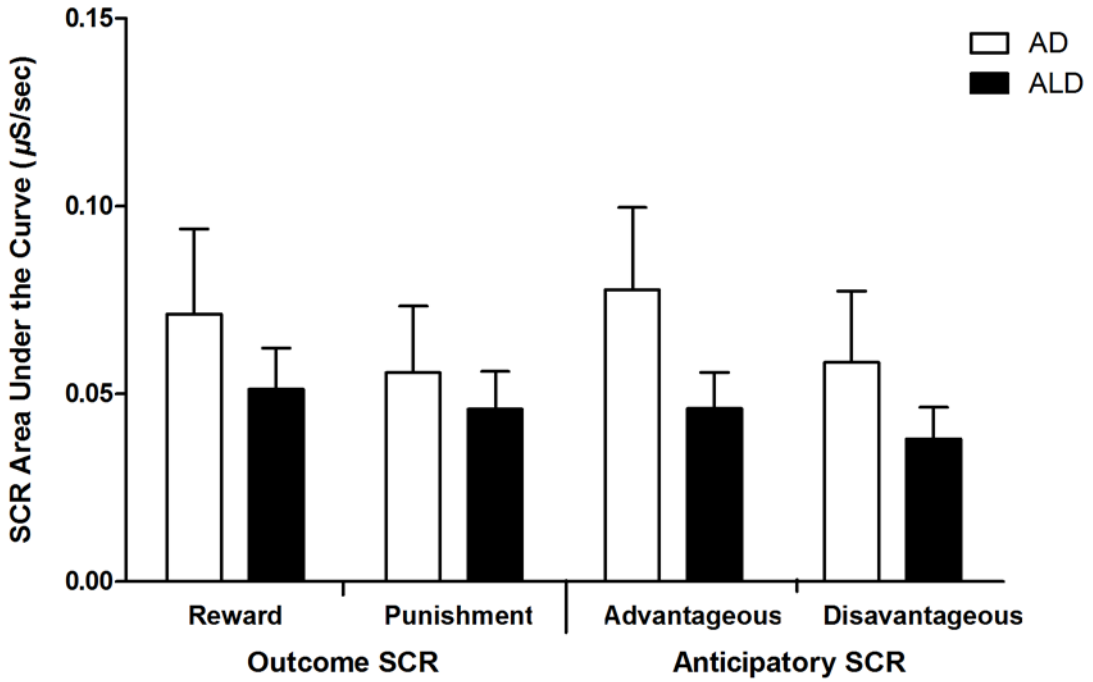

Figure 7. Mean SCRs for key trial outcomes and anticipatory periods for alcohol dependent (AD) and alcoholic liver disease (ALD) groups. Error bars represent ±1 *SEM*.

Figure 8 shows the average SCR for reward and punishment outcomes by SCR blocks and group. Both respective marginal models were conducted employing heterogeneous compound symmetry covariance structure, which provided the best fit accounting for the covariance between adjacent SCR blocks. The marginal model for reward outcome SCR demonstrated no main effects for SCR block or group. Regarding dysregulated drinking measures there was a main effect of DrInC, $F(2,29.98) = 4.62$, $p = .040$, with participants with higher DrInC scores exhibiting lower reward outcome SCR than those with lower reported scores; no effects of ADS or BIS scores were evidenced.

For punishment outcome SCR, the marginal model demonstrated no main effects found for SCR block or group, but there was a trend toward significance for DrInC, $F(2,28.5) = 3.94$, $p = .057$, with higher DrInC scores associated with lower punishment outcome SCR;

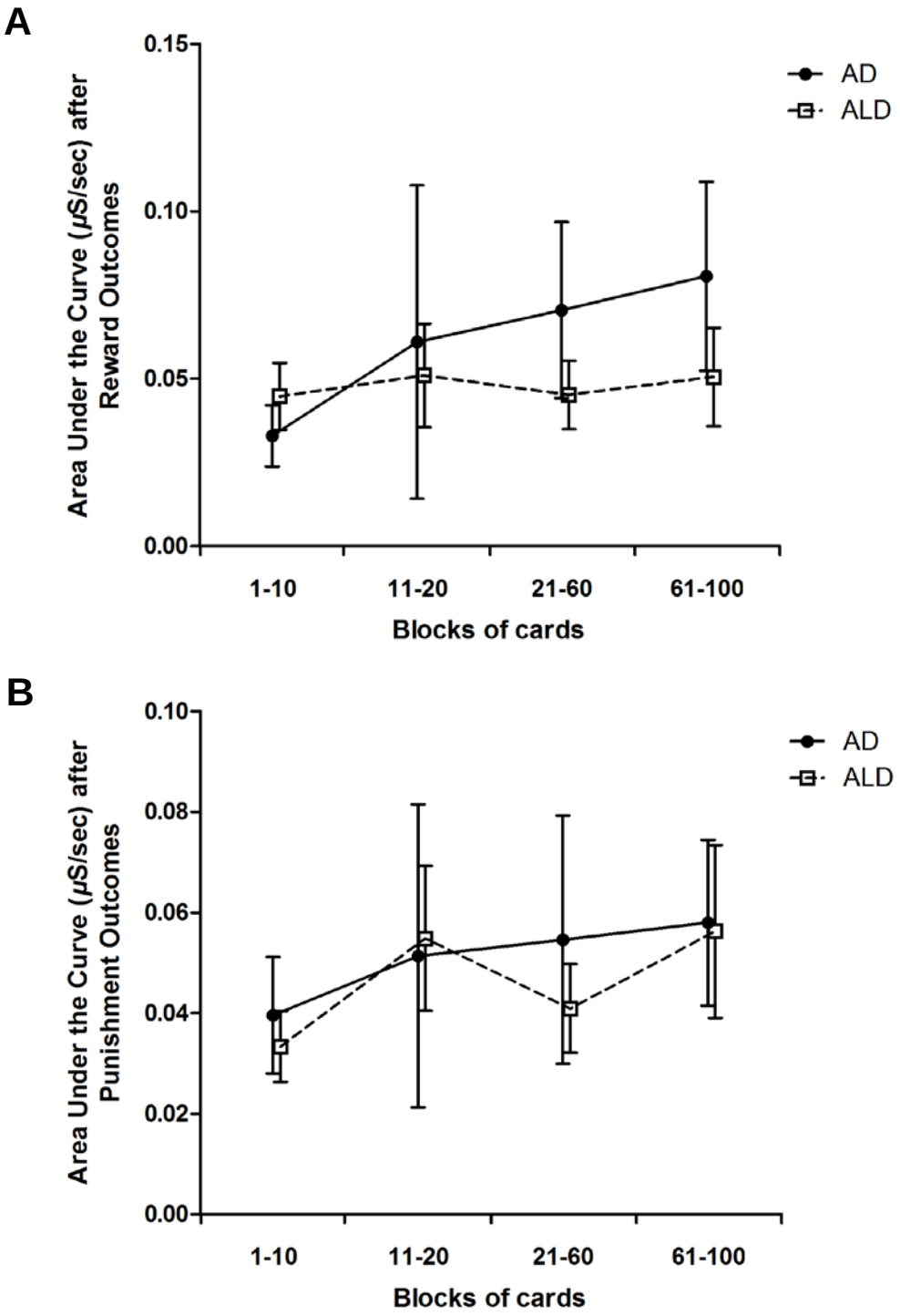

Figure 8. Outcome SCRs during IGT for a) Reward and b) Punishment, presented as mean area under the curve of responses across SCR blocks for alcohol dependent (AD) and alcoholic liver disease (ALD) groups. Error bars represent ± 1 *SEM*. Points are offset horizontally so that error bars are visible.

and a weaker trend for ADS, $F(2,28.65) = 3.41$, $p = .075$, with higher ADS scores related to lower punishment SCRs. There was also a trend for an interaction of group and DrInC,

$F(2,28.5) = 3.20$, $p = .084$, whereby alcohol dependent participants with higher DrInC scores exhibited reduced punishment SCRs compared to those with lower reported scores, while ALD groups did not differ according to DrInC scores. This indicates that a greater history of negatively experienced consequences was related to lower punishment SCR, but this did not reach significance. No BIS main effect or other covariate interactions were seen (p's > .05).

Reduced Anticipatory SCR in Alcohol Dependent Group, with Reduced Overall SCR in ALD Group

Anticipatory responses to decks should provide information of participants' capacity to distinguish between advantageous versus disadvantageous and potentially risky deck choices (Figner et al., 2012). Mean anticipatory SCRs are presented in Figure 7. Alcohol dependent participants again showed higher SCR for both outcome SCRs than ALD, but independent samples *t*-tests demonstrated no significant group differences for either anticipatory mean SCRs for advantageous or disadvantageous deck choices (p's > .05).

Both respective marginal models for anticipatory SCRs to advantageous and disadvantageous decks were conducted employing heterogeneous compound symmetry covariance structure, as it provided the best fit accounting for the covariance of SCRs between adjacent SCR blocks. Figure 9 displays mean advantageous deck choices SCRs across anticipatory blocks. The marginal model assessing advantageous anticipatory SCR deck choices showed no main effect of SCR block, group, or SCR block by group interaction (p's > .05), indicating no significant differences in anticipatory SCR for advantageous deck choices across the IGT overall, or between groups. Furthermore, there were no main effects of ADS, DrInC, or BIS scores (p's > .05), suggesting history of dysregulated drinking or punishment sensitivity were not related to anticipatory SCR for advantageous selections.

Anticipatory SCR of disadvantageous deck choices across the IGT are presented in Figure 9. As initial model testing demonstrated significant two-way associations with group

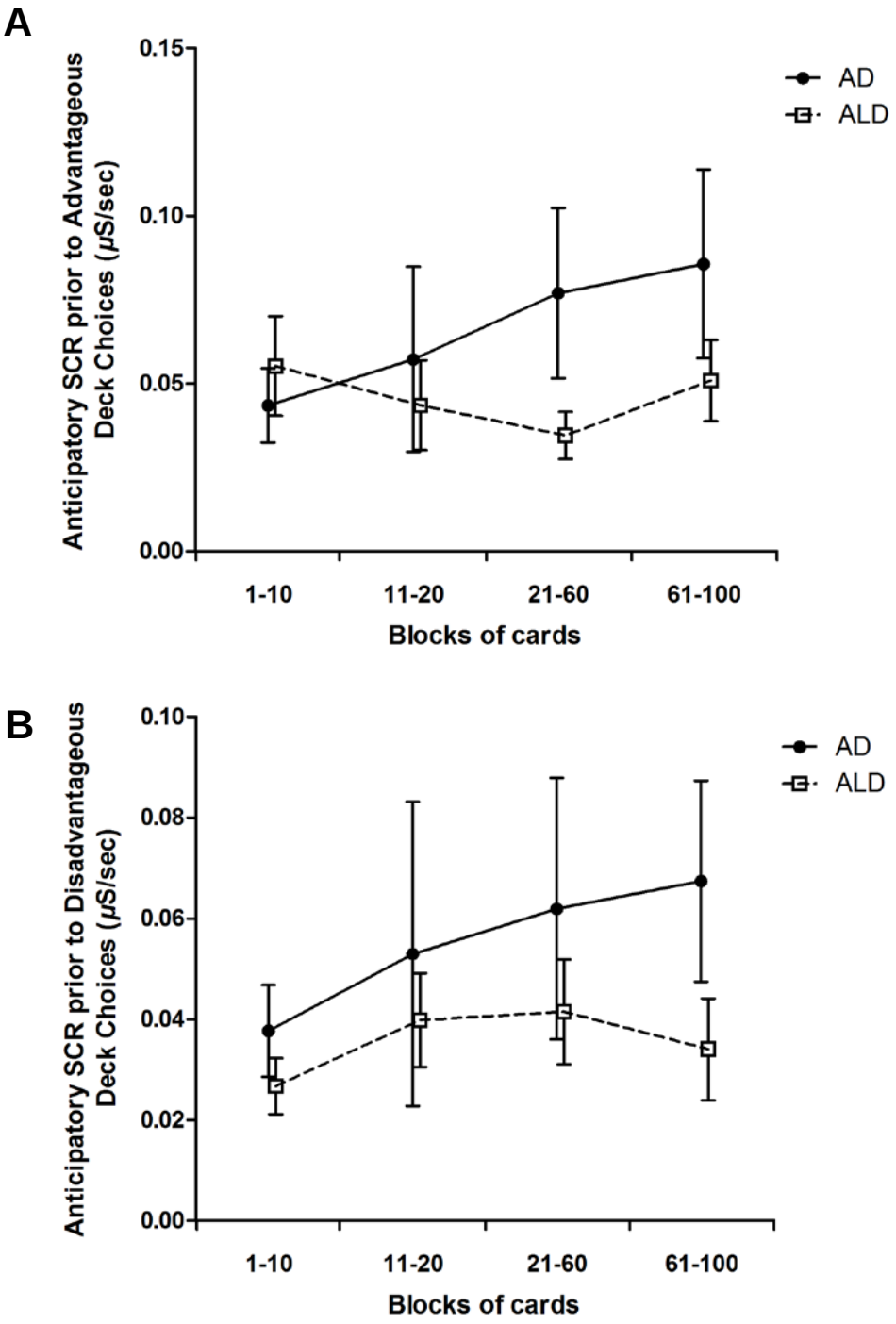

Figure 9. Anticipatory SCR for a) advantageous decks (C' and D') and b) disadvantageous decks (A' and B') displayed as mean area under the curve of responses from trial start to trial outcome for alcohol dependent (AD) and alcoholic liver disease (ALD) groups. Error bars represent ± 1 *SEM*. Points are offset horizontally so that error bars are visible.

and covariates-of-interest DrInC and BIS, a three-way interaction was added to the marginal model of group, DrInC, and BIS scores which led to best model fit (likelihood ratio test: $\chi^2(4)$

= 25.77, $p < .001$). The final marginal model revealed no main effect of SCR block or group for disadvantageous anticipatory SCR, but a significant DrInC main effect, whereby participants with higher DrInC scores demonstrated reduced anticipatory SCR for risky deck choices compared to those with lower scores, $F(1,26.16) = 5.85$, $p = .023$, and an ADS main effect, with participants with higher ADS scores demonstrating greater anticipatory SCR for risky choices than those with lower scores, $F(1,25.63) = 5.94$, $p = .022$. A trend for BIS was observed with participants reporting higher BIS scores exhibiting higher SCR, $F(1,25.8) = 3.3$, $p = .081$.

There was a significant interaction of group and DrInC score, $F(1,25.8) = 5.23$, $p = .031$; to aid interpretation, Figure 10 presents the estimated mean anticipatory SCRs for disadvantageous deck choices for -1 *SD* / +1 *SD* of the mean DrInC score, relating to lower/higher number of experienced consequences respectively, across the two groups.

Within the alcohol dependent group, participants with lower DrInC scores (indicating fewer drinking consequences) showed the highest anticipatory SCR to disadvantageous deck choices, while those with higher DrInC scores displayed significantly reduced anticipatory SCR. Contrastingly, the ALD patients demonstrated relatively reduced anticipatory SCR regardless of DrInC score, indicating that, at least for the alcohol dependent group, there is an association between a greater history of dysregulated drinking and reduced anticipatory response to risky outcomes with potentially negative outcomes, while ALD patients demonstrate an overall reduction in SCR independent of previous drinking consequences. No significant interactions for ADS score or BIS with group were seen (p's > .05).

Within the alcohol dependent group, participants with lower DrInC scores (indicating fewer drinking consequences) showed the highest anticipatory SCR to disadvantageous deck choices, while those with higher DrInC scores displayed significantly reduced anticipatory

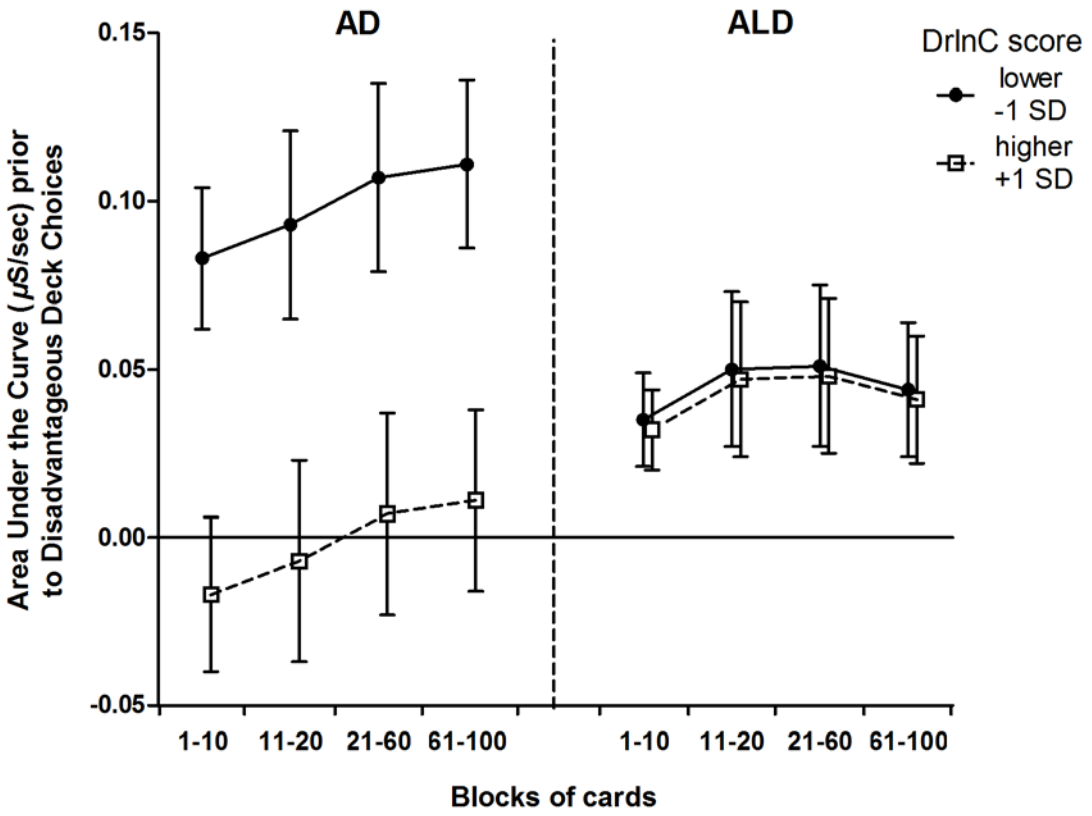

Figure 10. Estimated marginal means for anticipatory responses for disadvantageous deck choices for alcohol dependent participants (AD) and alcoholic liver disease (ALD) groups across SCR blocks. Alcohol dependent participants with higher reported DrInC scores showed reduced SCRs compared to those participants with lower DrInC scores; while ALD patients demonstrate overall reduced anticipatory responses, regardless of DrInC score. Error bars represent ± 1 *SEM*. Points are offset horizontally so that error bars are visible.

SCR. Contrastingly, the ALD patients demonstrated relatively reduced anticipatory SCR regardless of DrInC score, indicating that, at least for the alcohol dependent group, there is an association between a greater history of dysregulated drinking and reduced anticipatory response to risky outcomes with potentially negative outcomes, while ALD patients demonstrate an overall reduction in SCR independent of previous drinking consequences. No significant interactions for ADS score or BIS with group were seen (*p*'s > .05).

Discussion

This study assessed differences in physiological responses between severe AUD samples during the IGT decision-making task. We hypothesised ALD patients would exhibit reduced anticipatory SCR to disadvantageous decks. This was not observed overall. However,

when previously experienced drinking consequences were considered, alcohol dependent participants with a greater lifetime history of negative consequences from alcohol consumption demonstrated reduced anticipatory SCR to risky choices than alcohol dependent participants with fewer reported consequences. Additionally, the ALD group showed a reduced SCR responses overall, regardless of negative consequences. There were no differences in SCR to advantageous deck choices or to reward outcomes, suggesting specific impairment in somatic signalling for risky choices with possible negative outcomes. However, there were some trends for reduced SCR to punishment outcomes related to greater lifetime history of consequences according to DrInC, including a trend for similar discrepancy within the alcohol dependent group of reduced punishment SCR for those who experienced more drinking consequences, with no differences in ALD group. Nevertheless, to our knowledge, this is the first study to demonstrate differences in psychophysiological responses during the IGT in an ALD patient sample compared to otherwise healthy chronic drinker alcohol dependent participants.

The study results revealed no differences in IGT performance between alcohol dependent participants and ALD patients. The ALD group mean total net score was negative, indicating an overall tendency to choose risky deck choices, while alcohol dependent participants had a marginally positive total net score, but this difference was not significant. However, the ALD group would be considered within a impaired performance range of less than 50 cards (<50%) from advantageous decks using cut-offs from normative data (Bechara, 2007; Bechara, Damasio, Tranel, & Anderson, 1998). Furthermore, a significant proportion of participants within both groups were categorised as impaired on the task, scoring below a total net score cut-off of 10, as defined using VMPFC-impaired performance from Bechara et al.'s (1997) study. This reflects previous study findings of poorer performance in IGT for participants with substance use disorders (Barry & Petry, 2008; Bechara & Damasio, 2002;

Bechara et al., 2001; Verdejo-García et al., 2006) and AUD specifically (Bowden-Jones et al., 2005; Dom et al., 2006). However, it is suggestive that both groups were similarly significantly impaired on the task, but there was not enough sensitivity to delineate them according to behavioural performance alone.

This study also captured somatic arousal index SCR across the IGT to ascertain whether ALD patients differ from alcohol dependent participants in their responses to deck outcomes, and whether they developed anticipatory responses according to their deck choices. There were no observed differences between groups in SCR to reward outcomes, and no group differences in anticipatory SCRs for advantageous deck choices. Furthermore, ALD patients did not demonstrate significantly lower anticipatory SCRs for disadvantageous deck choices across the task overall. However, we observed a relationship between previous lifetime history of drinking-related consequences measured by the DrInC and anticipatory SCRs to disadvantageous deck choices according to group. Results showed that alcohol dependent participants with fewer experienced negative drinking-related consequences exhibited higher anticipatory SCRs, while those with more reported negative consequences demonstrated significantly lower responses—similar to ALD patients, who did not differ according to DrInC scores and showed reduced overall anticipatory SCR, indicating a potential impairment in expectancy of negative reinforcement for risky deck choices across the IGT task. These results reflect the pattern of SCR activations observed in substance use disorder individuals compared to healthy control participants in Bechara and Demasio's (2002) study, with a reduced magnitude of disadvantageous deck anticipatory SCRs, while other SCRs were comparable to the performance of the healthy control group. A potential explanation can be provided by the somatic marker hypothesis (Bechara & Damasio, 2005; Damasio, 1994), which posits decision-making is largely effected by emotional signals that inform decision-making processes, shifting choices toward advantageous outcomes. This is

demonstrated in the IGT through the development of anticipatory SCRs to disadvantageous decks across the task in this study, which act as emotional indicators signalling risky choices that may have a negative consequence (Bechara & Damasio, 2005). It is likely the reduced anticipatory SCR to disadvantageous deck choices in the ALD group in this study suggest these individuals do not develop these responses which help guide decision-making, and this may lead to erroneous decision-making involving drinking choices that may result in deleterious negative consequences. Moreover, the impairment in emotional signalling may lead to a greater number of negative consequences in these alcohol dependent participants (Bechara, 2005), ostensibly as they do not learn from previous consequences or develop somatic emotional responses signalling risky drinking choices.

Interestingly, the pattern that was observed with DrInC and anticipatory responses across groups was similarly reflected in trends for relationships between SCRs for punishment outcomes and the DrInC, an association that was not identified in other research employing SCR, such as Bechara and Damasio (2002). The association within the alcohol dependent participants of reduced SCR to punishment responses seen in those with more reported negative drinking consequences suggests an incapacity for these individuals to appropriately react to negative outcomes. It is not clear whether this is due to: a lack of comprehension of negative outcomes; a dysregulated somatic response, that does not adequately reinforce the outcome with an appropriate emotional response; or a potentially a combination. However, considering there were no associations with BIS scores, which should indicate punishment sensitivity as a feature of the Behavioural Inhibition System (Gray, 1981), suggests that insufficient somatic signalling may have a role in this lack of appropriate responses to punishment stimuli. Relatedly, while the Behavioural Activation System (Fowles, 1980; Gray, 1987) which encapsulates impulsivity and reward sensitivity has demonstrated links in AUD samples (Franken, 2002), there were no initial correlations with reported BAS scores in this

study. Moreover, post-hoc models assessing the role of BAS in reward and punishment responses (data not shown) did not reveal any meaningful relationships. However, reward sensitivity has been shown to increase after exposure to alcohol cues in heavy social drinking samples, evidenced through performance on a reward incentive card-sorting task (Kambouropoulos & Staiger, 2004). Implementing the IGT after alcohol exposure using an alcohol cue reactivity procedure in future research may therefore reveal decision-making deficits in these subsamples that are influenced by alcohol-relevant cues, and have a subsequent negative role in drinking choices.

This study showed ALD patients had reduced overall anticipatory SCR to potentially risky negative choices, but we did not observe the correlation between reduced anticipatory SCR on the IGT and poorer behavioural performance when compared to alcohol dependent participants across the task—a pattern exhibited by substance use disorder patients in Bechara and Demasio's (2002) study when compared to the healthy control group. There are potential explanations for this. Firstly, the current study did not implement a healthy control group, as the primary goal examined whether ALD patients demonstrated greater impairment than alcohol dependent participants in decision-making through behavioural and psychophysiological outcomes in the IGT. However, when comparing the behavioural performance of this sample with other studies measuring IGT in substance- and alcohol- use disorder, we have already outlined that both groups largely exhibit poor performance similar or below those observed in studies implementing similar clinical samples (Barry & Petry, 2008; Bechara & Damasio, 2002; Bechara et al., 2001; Bowden-Jones et al., 2005; Verdejo-García et al., 2006).

Secondly, the groups did not differ in their history of dysregulated drinking through either AUD severity with the ADS or negative consequences with the DrInC. Therefore, behavioural performance on the IGT may not significantly differ between these groups due to

the similarity of their drinking-related problems, and suggests they equally exhibit decision-making deficits that may be reflected in real-world situations through deleterious drinking choices. This is particularly relevant as both are treatment-seeking subsamples that fail to regulate alcohol consumption—yet the ALD patients evidently experience more specific biological and physiological feedback of negative consequences related to their drinking (Madhotra & Gilmore, 2003), from which they still fail to self-correct, as demonstrated by high relapse rates among ALD patients (Miller et al., 2001). This is apparent in their significantly greater consumption evidenced by more TLFB units per drinking day compared to the alcohol dependent group, representative of a considerably dysregulated chronic drinking subsample. Considering this, and the observed reduced anticipatory SCR to disadvantageous deck choices, ALD patients may not adequately identify or learn from negative consequences that may be used to inform future choices toward advantageous options regarding drinking, resulting in poorer drinking choices and thus considerable negative outcomes. Decision-making is a complex cognitive process that involves individuals appropriately assessing and evaluating choices while accounting for the wider context, in order to select the optimal response (L. Clark & Robbins, 2002). For ALD patients, inability to retain information of previous deleterious outcomes from drinking may lead to suboptimal decision-making choices when faced with future drinking situations. Additionally, the strength of the alcohol cues inherent in the choice of drinking increases the temptation toward immediate gratification and dysregulated drinking (Camchong, Endres, & Fein, 2014; Le Berre et al., 2017), rather than the option of restricting intake which would be more advantageous in the long-term, lead to better health outcomes and avoidance of negative drinking consequences.

ALD patients may therefore represent the end-stage of a trajectory that individuals with alcohol dependence may transition toward, considering the similarity in their

dysregulated drinking profile. Thus, if we consider that ALD is the severe end of a "spectrum" of chronic drinkers with AUD, this subsample of alcohol dependent participants with reduced anticipatory SCR and significant experienced negative consequences may represent a prodromal stage of ALD, and this reduced anticipatory somatic signalling may be potentially predictive of chronic drinkers at high-risk of developing ALD in the future due to their incapacity to make appropriate decisions to regulate their drinking. Bowden-Jones et al.'s (2005) pilot study demonstrated that worse behavioural IGT performance of alcohol dependent patients was predictive of earlier relapse, indicating the IGT may be a useful screening tool in drinking outcomes in AUD. Future studies implementing case-control design may be useful in establishing whether this association is apparent in heavy drinker individuals with significantly dysregulated history of drinking behaviours, particularly regarding negative drinking consequences.

The study results cannot summarily conclude on the aetiology or potential mechanisms involved in the observed overall poor behavioural performance, or reduced anticipatory responses in ALD and subset of alcohol dependent participants during the IGT. One explanation may be impacts related to alcohol-related brain damage in chronic drinkers. It is well documented that chronic alcohol consumption impacts upon brain morphometry, with marked effects to grey matter in prefrontal areas in abstinent treatment-seeking alcohol dependent patients (Fein et al., 2002; Jernigan et al., 1991; O'Neill et al., 2001), and in active drinkers with greater alcohol use severity (Cardenas et al., 2005), including decreased white matter in chronic drinking alcoholics, particularly in anterior brain networks connecting the prefrontal cortex and limbic systems (Pfefferbaum et al., 2009). The VMPFC is considered crucial in reversal-learning and contingency based decision-making using emotional information (L. Clark, Cools, & Robbins, 2004). As IGT performance activates prefrontal regions including the VMPFC, dorsolateral prefrontal cortex and OFC in healthy participants

(X. Li, Lu, D'Argembeau, Ng, & Bechara, 2010), and hyperactivity is demonstrated in these areas in binge-drinking adolescents (Xiao et al., 2013), alcohol-related brain damage may explain the poor IGT behavioural performance observed by both groups in the current study. It should be noted the IGT manual (Bechara, 2007) suggests that poor performance on the IGT in substance use disorder samples indicates decision-making deficits, rather than frontal lobe damage per se, but as the current study contains drinkers with a significant history of chronic consumption, there is a viable link with subsequent alcohol-related brain damage and the poor performance in both alcohol dependent and ALD groups.

Relatedly, SCR has been demonstrated to be functionally linked to the above regions, with activity observed in medial prefrontal cortex related to generation of SCR (Critchley, Elliott, Mathias, & Dolan, 2000). When measuring SCR during IGT for bilateral amygdala- and VMPFC-lesioned patients, Bechara et al. (1999) demonstrated that amygdala-lesioned patients demonstrated global impairment in SCR during outcome and anticipatory time periods. However, VMPFC-lesioned patients exhibited reduced anticipatory responses, but comparable outcome responses to reward and punishment to those of normal participants (Bechara et al., 1999). In the current study, the reduction in anticipatory SCR is demonstrated by the disadvantageous deck choices in both alcohol dependent participants who experience a wide variety of negative drinking consequences and the ALD group, suggestive that they do not react to potentially risky choices, and may potentially reflect VMPFC dysfunction. Considering our findings of reduced anticipatory SCR, VMPFC damage due to alcohol-related brain damage may impair generation of anticipatory SCR that signal risky choices in the IGT, which may be reflected in real-world outcomes. Furthermore, as ALD patients often display significantly compromised liver function—including hepatic encephalopathy and cirrhosis—they may have more significant cognitive deficits related to neuronal dysfunction

and/or direct structural damage (Butterworth, 1995b, 2007) which would affect normal function in these outlined brain structures, though our ALD sample had low ALD severity.

There were some limitations to this study. The DrInC version (-2L) employed in this study was limited as it does not capture the frequency of consequences, only whether experienced during a participants' lifetime. Thus, we cannot determine whether participants experience the same negative consequences several times, which would indicate an inability to learn from previous negative outcomes to inform future decisions. Future research could implement a frequency measure, such as the DrInC-2R (Miller et al., 1995) which assesses occurrences of negative consequences within the previous three months of drinking to elucidate whether impaired anticipatory responses are reflective of impaired decision-making in drinking. Moreover, as ALD patients experience a variety of salient and deleterious biological negative feedback (O'Shea et al., 2010), this may further reveal differences within the ALD participants. The physical subscale of the DrInC demonstrated only acceptable reliability ($\alpha = .70$) within this sample, suggestive it may not comprehensively capture these range of chronic drinking negative outcomes in the ALD sample. Development and implementation of a measure that captures the frequency of physical negative consequences, such as the Chronic Liver Disease Questionnaire (but assessing a longer time period than two weeks in its original form; Younossi et al., 1999) may improve the sensitivity for accurately representing negative outcomes in ALD. Secondly, as outlined above, the frontal regions are vulnerable to alcohol-related brain damage through chronic alcohol consumption (Cardenas et al., 2005; Fein et al., 2002; Jernigan et al., 1991; O'Neill et al., 2001). Considering the heavy reported consumption observed in this study, particularly in ALD patients, there remains the possibility that participants in this study may be severely dysfunctional overall. The association with dysregulated drinking history and SCR signalling within the alcohol dependent participants suggests heterogeneity within these subsamples with different drinking

experiences, but the study is limited as participants in this study are largely still consuming alcohol regularly, and therefore demonstrate a failure to regulate their drinking. Implementing a sample of ALD patients that have successfully regulated and reduced alcohol consumption, or similarly a group of abstinent alcohol dependent participants, would help reveal whether these study results are a specific SCR impairment, or an overall effect due to chronic alcohol consumption.

In conclusion, this study identified reduced physiological responses during key periods of the IGT in severe AUD individuals, potentially reflecting impairment in learning and anticipation of negative events. ALD patients and individuals with alcohol dependence with significant history of previous drinking problems demonstrated reduced anticipatory responses for risky choices punishment outcomes, but no differences in SCR to advantageous deck choices or to reward, suggesting specific impairment in somatic signalling for risky choices with possible negative outcomes. These reductions in SCR may manifest in poorer future outcomes inherent in these samples with severe AUD, particularly the ALD patients who demonstrated reduced overall SCR regardless of experienced consequences. Examination of psychophysiological responses during the IGT may reveal appropriate decision-making that was not apparent through behavioural performance, as both groups were significantly impaired on the task. This suggests that physiological responses to key periods of IGT may be a potential method to identify high-risk chronic drinkers who have difficulties in learning from negative outcomes and understanding potentially risky choices, which may also reflect real-life impaired decision-making regarding drinking choices in these individuals.

Chapter Five

Neural Correlates of Alcohol Cue-Induced Brain Activation and Neuropsychological Executive Functioning Measures in Individuals with Alcohol Dependence

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WBL and KCM designed the study. WBL and RWM developed the methodology. WBL collected the data, performed the analysis, and wrote the manuscript. KCM and RWM provided feedback for the manuscript.

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Abstract

Individuals with alcohol use disorder fail to regulate alcohol consumption, which may be due to dysfunctional regulation of motivational responses when exposed to alcohol cues. Cognitive processes such as executive functioning are potentially involved in this regulation. We tested whether there was a convergence of brain areas related to regulation of responses to alcohol cues and worse executive functioning, and areas associated with a greater history of dysregulated drinking. Twenty-eight drinking alcohol dependent participants and 11 healthy controls completed a visual fMRI alcohol cue reactivity task, measuring blood oxygen level dependent responses as an index of alcohol cue reactivity. Within the alcohol dependent participants, we examined whether alcohol cue reactivity in prefrontal regions was negatively correlated with participants' previous history of dysregulated drinking (alcohol use disorder severity, experienced negative drinking consequences) and poorer executive functioning performance (Stroop; Trail making test), indicating worse regulation of alcohol cue-elicited responses . Conjunction analyses were conducted to examine if overlapping neural activity in these prefrontal areas was associated with greater history of dysregulated drinking and poorer executive functioning performance. Alcohol dependent participants demonstrated more cue-induced activation to alcohol cues than control cues compared to healthy controls in reward and motivational pathways. Within alcohol dependent participants, conjunction analyses showed overlapping activation for the negative correlation with Stroop Interference score (higher score = poorer performance) and alcohol cue-activation, and negative correlation with alcohol use severity score and alcohol cue-activation in the right dorsolateral prefrontal cortex. Executive functioning performance and history of dysregulated drinking were thus associated with differences in alcohol cue reactivity within alcohol dependent participants. The convergence of prefrontal activation suggests reduced brain activation may indicate

dysfunctional regulation of responses to alcohol cues for alcohol dependent participants with worse executive functioning ability and greater alcohol use problems.

Neural Correlates of Alcohol Cue-Induced Brain Activation and Neuropsychological Executive Functioning Measures in Individuals with Alcohol Dependence

Individuals with alcohol dependence who continue to chronically drink demonstrate an difficulty in controlling their consumption, even when faced with negative consequences associated with their drinking (Schuckit et al., 1993). This may be due to dysfunctional regulation of responses to motivational cues. A key factor in models of addiction involve enhanced responses elicited by alcohol-related cues. For example, repeated exposure to environmental cues predicting the availability of alcohol can lead to those (once neutral) cues eliciting motivational urges toward alcohol (Carter & Tiffany, 1999; Goldstein & Volkow, 2002; Koob et al., 2008; Koob & Volkow, 2009; Tiffany, 1990). These urges include craving, defined as the conscious experience of a desire to take a drug (Drummond, 2000). Cravings elicited by these cues can lead to negative drinking outcomes such as dysregulated consumption and relapse, even after extended periods of abstinence (Anton, 1999). Insufficient regulation of these motivational urges may therefore be a key factor in alcohol dependence.

Dual-process models of addiction posit two systems that regulate behaviour: a motivational “impulsive system”, which induces motivational drive and urges toward substances of addiction, and include craving; and the “reflective” system, which regulates these impulses (Bechara, 2005; Lubman et al., 2004; Wiers & Stacy, 2006b). The reflective system is postulated to include executive functions, an umbrella term for several cognitive processes involved in planning, directing, and monitoring adaptive goal-directed behaviour and responding to novel situations (Alvarez & Emory, 2006; Le Berre et al., 2017). These underlying processes include response inhibition, mental flexibility, attentional processes, and working memory (Crews & Boettiger, 2009; Miyake et al., 2000). In this view, executive functioning deficits may reflect impairments in the reflective system, which manifest as an

incapacity to appropriately regulate alcohol cue-induced impulsive responses and lead to adverse drinking outcomes. There has been increasing evidence documenting the links between alcohol use disorder (AUD) and executive functioning. Executive functions are most vulnerable to impairment in chronic drinking samples (Nixon, 2006; Parsons, 1998), and take longer to recover from (Bates et al., 2006; Zinn et al., 2004), and impairment from chronic consumption can persevere even through abstinence (Stavro et al., 2013). Thus, a failure to regulate appropriately may be due to executive functioning deficits or impairment and subsequently result in dysregulated consumption, and/or poor drinking outcomes (such as relapse) in AUD individuals.

The implementation of imaging techniques such as functional magnetic resonance imaging (fMRI) has established key regions in the prefrontal cortex are more active (indicated by blood-oxygen level dependent [BOLD] response) when exposed to alcohol-related cues (visual, olfactory, gustatory) during imaging cue reactivity tasks (Grüsser et al., 2004; Heinz et al., 2009; Wrase et al., 2002) These functional regions include the dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex (VMPFC), the orbitofrontal cortex (OFC), and the anterior cingulate cortex (ACC) (for a review, see Schacht, Anton, & Myrick, 2013); regions also associated in the neurocircuitry implicated in regulation of emotional and motivational cues. Moreover, these brain regions are also implicated in intact executive functioning, with appropriate performance in well-established neuropsychological executive functioning tasks involving these areas identified by BOLD activation in fMRI studies (Yuan & Raz, 2014). Taken together, this indicates a possible role of executive functioning in alcohol dependence in the appropriate regulation of motivational responses signalled by the impulsive system. This study assesses the relationship between executive functioning and alcohol cue-elicited responses during a visual fMRI cue reactivity task in alcohol dependent

participants, in order to bridge the current gap between impulsive system responses and dysregulated drinking behaviours.

We employ established standard neuropsychological tests in this study to assess executive functioning in alcohol dependent participants. This includes: the colour-naming Stroop task (Stroop, 1935), which requires inhibitory and cognitive control to identify and suppress automatic responding to task-irrelevant stimuli; and the Trail making test (Trails; Reitan & Wolfson, 1993) which involves set-shifting and cognitive flexibility. Associations with an executive function network in each of these tasks has been demonstrated previously. Functional regions involved in task components of the Stroop include increased activation during the task in the ACC related to appropriate conflict resolution (Bench et al., 1993; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; Kerns et al., 2004) and in the DLPFC in cognitive control (Kerns et al., 2004; Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000; MacDonald, Cohen, Stenger, & Carter, 2000; Milham, Banich, Claus, & Cohen, 2003; Zysset, Müller, Lohmann, & von Cramon, 2001). Regarding Trails, better performance during fMRI versions of executive functioning-related component (i.e., Part B; Lezak, Howieson, Bigler, & Tranel, 2012) correlated with prefrontal activation primarily in DLPFC and associated non-prefrontal regions such as supplementary motor areas and cingulate sulcus (Allen, Owens, Fong, & Richards, 2011; Moll, Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002; Zakzanis, Mraz, & Graham, 2005). These prefrontal regions identified in these neuropsychological executive functioning tasks are therefore among those targeted in our investigation of regulation of alcohol cue-elicited responses.

This study investigated whether BOLD responses uniquely elicited by alcohol cues is associated with executive functioning task performance and drinking outcomes (history of dysregulated drinking) in alcohol dependent participants relative to a healthy control group.

We expected the alcohol dependent group to show greater overall regional brain activation in reward and motivational circuitry to alcohol-related cues compared to the healthy control group during the cue reactivity task. Alcohol dependent participants were measured on executive functioning tasks before completing an fMRI cue reactivity task; it was hypothesised that participants with worse executive functioning performance will show greater cue-induced activation in reward-based circuitry, and less activation in areas involved in monitoring and regulation of responses (such as the DLPFC, VMPFC, OFC, and ACC). The study also examined participants' previous history of dysregulated drinking and relationship with executive functioning and alcohol cue-elicited brain activation. We hypothesised that alcohol dependent participants reporting greater dysregulated drinking problems (AUD severity and/or experienced negative drinking consequences) will demonstrate differences in alcohol cue-induced activation compared to those with lower scores. Lastly, we also assessed whether there is a convergence of areas related to alcohol cue reactivity brain activation, and correlations with executive functioning tasks and dysregulated drinking measures. We hypothesised that alcohol dependent participants demonstrating better executive functioning performance and less history of dysregulated drinking will show greater activation of areas related to better performance in executive functioning tasks (e.g., prefrontal cortical areas), whereas poorer executive functioning performance and greater previous dysregulated history of alcohol problems will exhibit reduced brain activation in these areas related to poorer regulation of responses to alcohol cues.

Method

Participants

Thirty-two alcohol dependent participants and 11 healthy control adults were screened for the study. Alcohol dependent participants were initially recruited for a multi-site double-blinded randomised controlled trial (Morley et al., 2013) examining the efficacy of baclofen

treatment in alcohol dependence. Recruitment strategies and inclusion/exclusion screening criteria have been described in detail elsewhere (Morley et al., 2014); a summary of the central criteria for this study is provided here. Structured clinical and medical interviews were conducted for alcohol dependent participants at baseline of clinical trial (day 0), with alcohol dependence confirmed according to ICD-10 criteria. Participants were required to be alcohol abstinent for at least three days prior to baseline consultation; mean abstinence for the alcohol dependent group was four days (*SD* = 4.42). Clinically evident withdrawal required resolution per the withdrawal symptom checklist (CIWA-Ar: score of <10; J. T. Sullivan et al., 1989). Any participants with active major mental disorder associated with psychosis or significant suicide risk were excluded, as were those with neurological or MRI-related contraindications. Duration of alcohol dependence in years was calculated by subtracting self-reported years of problem use from age at baseline. Severity of alcohol dependence was measured using the Alcohol Dependence Scale (ADS; Skinner & Allen, 1982), and drinkers inventory of consequences (DrInC; Miller et al., 1995) assessed history of dysregulated drinking outcomes. Problematic drinking history for alcohol dependent participants was measured using the Timeline followback (TLFB; Sobell & Sobell, 1992), measuring the last four weeks of drinking. All clinical diagnoses were confirmed independently using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). The healthy control group were screened for the above criteria with the exception that they were not considered alcohol dependent with the MINI and the ICD-10 (World Health Organization, 1990), or categorised as dependent with the ADS using a cut-off score of 9 (Ross et al., 1990); there were no reported alcohol-related problems in the healthy control group.

Participants were informed to abstain from caffeine for four hours prior to scan session, and alcohol for the preceding 24 hrs confirmed by blood alcohol level (BAC) of 0.00 by breathalyser on arrival; three alcohol dependent participants had a BAC exceeding 0.00,

and their test session was concluded. Gross cognitive impairment was assessed using the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975); one alcohol dependent participant scored below the cut-off score of 25 and was also excluded. One alcohol dependent participant failed all incongruent trials of the Stroop task (n = 1), and their results were also excluded. Recording issues during scanning session occurred for 2 healthy controls and results were also excluded, while subjective pre- and post-scan craving was incomplete for 3 alcohol dependent participants. The final sample thus comprised 27 alcohol dependent (age: M = 49.08, SD = 2.1) participants and 9 healthy controls (age: M = 35.56, SD = 10.36) participants (N = 36; see Table 14 for sample descriptives). All participants granted informed consent and were reimbursed $40 AUD for session participation. The study was approved by the Human Ethic Review Committee of the Sydney Local Health District (X11-0154; HREC/11/RPAH/223; See Appendix A).

Measures

Neuropsychological tasks of executive function.

Stroop task (Stroop, 1935) was selected due to its consistent interference effect. An automated original colour version was employed similar to that used by Houben and Wiers (2009). Participants indicated the colour (red green, blue or yellow) of the text on a screen using the corresponding coloured keys. There were three trial conditions: a control condition, with symbols '####' '%%%%,' '&&&&' '****' presented in the colours four colours; a congruent condition, with words 'red', 'green', 'blue' or 'yellow' presented in the corresponding text colour (e.g., the word 'red' coloured in red text); and an incongruent condition, where the word text meaning and text colour were incompatible (e.g., the word 'red' coloured in blue text). A practice block (20 trials, indicating colour of a rectangle) was first completed for key familiarisation. The test block (84 trials) followed, with each trial condition presented seven times per colour. Stimuli were presented in random order during

the blocks, and stimuli were not consecutively presented in the same colour. A Stroop interference score was calculated by subtracting the mean response latencies of the control trials from the mean response latencies of the incongruent trials, where a higher score indicated worse performance due to greater Stroop interference.

Table 14

Clinical characteristics and neuropsychological executive functioning task performance

Measure	HC (*n* = 9)	AD	
		Whole sample (*n* = 27)	Reduced sample (*n* = 17)
Demographics			
Age (years)	35.56 ± 10.36	49.08 ± 2.09	51.06 ± 10.49
Right-handed, *n* (%)	9 (100.0)	26 (96.3)	16 (94.11)
Sex, *n* (%) Male	4 (44.44)	19 (96.2)	11 (64.71)
Clinical characteristics			
TLFB units per drinking day			
4 weeks prior to baseline	-	10.48 ± 3.82	10.75 ± 4.94
1 week prior to scan session	1.098 ± 1.36	5.22 ± .93	5.32 ± 4.94
Alcohol Dependence Scale (ADS)	.33 ± .71	16.42 ± 1.67	17.29 ± 8.21
Years of problem use	-	14.41 ± 11.11	17.29 ± 12.72
Penn Alcohol Craving Scale (PACS)	-	16.96 ± 5.17	16.06 ± 6.06
AUQ pre-scan	10.44 ± 4.85	15.29 ± 2.26	12.13 ± 6.15
AUQ post-scan	11.44 ± 4.33	19.08 ± 2.54	15.93 ± 8.40
EF measures			
Trail making test			
Part A: (s)	-	-	26.68 ± 9.16
Part B: (s)	-	-	63.17 ± 20.30
Trails difference Score (s)	-	-	36.47 ± 3.84
Stroop difference Score (ms)	-		86.82 ± 87.87

Note. Means, with *SD*s reported, unless otherwise stated. HC = healthy controls; AD = alcohol dependent; TLFB = Timeline followback; AUQ = Alcohol Urge Questionnaire; EF = executive functioning.

Trail making test (Trails): A and B (Reitan & Wolfson, 1993) requires participants to connect a series of circles in order as quickly as possible. Part A involves joining circles with

consecutive numbers only. Part B requires connecting circles of numbers and letters alternately in the correct order. Both parts involve motor speed and dexterity, and visual scanning ability. Part B is regarded as a measure of executive function; specifically set-shifting flexibility, alternating attention and inhibition (Strauss et al., 2006). The Trails task is considered a reliable and valid task assessing brain damage and neurological impairment (Lezak et al., 2012), with reaction times increasing with cognitive impairment. A difference score calculated by the difference in completion time between Part B and Part A (Trails B – Trails A) indicates specific executive functioning impairment.

Cue reactivity task.

A well-established visual cue reactivity task (Grüsser et al., 2004) was used to measure alcohol cue-elicited brain activity. Stimuli comprised three types: 15 alcohol-related pictures (Grüsser et al., 2004; Wrase et al., 2002); a first control type comprising 15 neutral pictures (affective neutral) from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1995) matched for colour and complexity (for image numbers, see Grüsser et al., 2004); and 15 scrambled versions of the alcohol pictures (scramble alcohol), controlling for potential activity related to novelty of neutral images (Wrase et al., 2002). Images were presented for 6.6 s in blocks of three images of the same type, totalling five blocks per type (alcohol, scramble alcohol, affective neutral). Stimuli and block order was randomised across subjects, and blocks of the same image type did not follow consecutively. Each condition block was preceded by a fixation cross presented for 10 s, which was modelled as a regressor of no interest. Following each block, a 11 point visual analogue scale was presented asking participants to rate their "severity of their craving for alcohol now" from 'no craving (0)' to 'very severe craving (10)'; participants selected their level on the scale using a Lumina MRI-compatible two-button response pad (Cedrus Corporation; San Pedro, U.S.A) within a 10 s

window. The cue reactivity task was triggered by MRI scanner pulse to ensure precise temporal equivalence of stimulus presentation and fMRI data acquisition.

Procedure

Testing was performed over two sessions for alcohol dependent participants: the first session for executive functioning task administration occurred seven days (+/- 4 days) after medical consultation and screening, and the imaging session at 14 (+/- 5) days. The healthy controls only completed the imaging session, with screening questionnaires obtained immediately prior to session. For the first session, participants completed executive functioning tasks as part of a related study protocol (Chapter Three).

Scan imaging sessions were conducted between 9:30 am and 4 pm. A 7-day TLFB was completed assessing participants' previous weeks drinking history. Participants were then escorted to the imaging location and given instructions on using the two-button response pad in the scanner to indicate their craving during the cue reactivity task. Participants completed an Alcohol Urge Questionnaire (AUQ; Bohn et al., 1995), an eight-item questionnaire measuring current craving and urges to drink prior and after scanning. Participants were debriefed directly following test session to address potential continued craving elicited during the scanning.

MRI Data Acquisition

MRI data were acquired on a 3-Tesla GE Discovery using a 32-channel head coil. A T1-weighted high-resolution (1-mm^3 voxel resolution) structural scan was acquired for each subject for screening and registration (TR: 7200 ms, TE 2.7 ms, 176 sagittal slices, 1 mm thick, no gap, 256 × 256 × 256 matrix). For BOLD acquisition, we acquired 203 echoplanar image (EPI) volumes comprising 39 axial slices in an ascending interleaved fashion with a voxel resolution of 1.88 × 1.88 × 2 mm (TR: 3000 ms, TE 30 ms, FA 90 degrees, FOV 240

mm, matrix 128 × 128, acceleration factor 2, slice gap: 1 mm). Participants' heads were fixated with foam pads to minimise head movement.

Image Processing

Preprocessing and statistical analyses of brain imaging data were conducted using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK, www.fil.ion.ucl.ac.uk/spm). Functional images were slice time corrected to the middle slice and realigned with the first volume. The structural image was co-registered to the mean functional image, segmented and warped to Montreal Neurological Institute (MNI) space. The warp parameters were then used to normalise the resampled functional images (2 mm^3). Images were then smoothed with a Gaussian kernel of 8-mm full-width half maximum (FWHM) to improve sensitivity for group analysis.

Statistical Analyses

Sample characteristics and neuropsychological scores were analysed using IBM SPSS Statistics 20.0 (IBM, New York, NY, USA). Student *t*-tests, non-parametric Mann-Whittney *U* tests, or Chi-squared tests were conducted between groups for demographic and drinking variables, where appropriate. AUQ craving scores prior and after scanning were analysed using a repeated measures ANOVA of within-subjects factor of time (pre-scan, post-scan) and between-subjects factor group (alcohol dependent group versus healthy controls).

The reaction time (RT) distributions for neuropsychological measure Stroop were skewed and/or kurtotic, and consequently transformed to achieve normality (Miyake et al., 2000). A two-stage trimming procedure for outliers was employed: firstly, cut-off criterion values were first established whereby RTs outside the values were omitted, with the lower and upper criterion 200ms and 3000ms respectively (4.12 % of total RTs). The Median Absolute Deviation method (Leys et al., 2013) was applied in the second stage, a within-subjects

procedure that identified and excluded outliers outside 3 Median Absolute Deviation units (3.7% of remaining RTs).

Statistical analysis of imaging data was conducted in SPM12 at two levels. In the first level (subject-specific), two conditions were modelled: alcohol-related (Alcohol) cues; and both control cues combined in a single condition (Control; Grüsser et al., 2004), modelled as a box-car function convolved with the canonical haemodynamic response. We combined affectively neutral and scramble alcohol images in the same condition to control for both novelty and visual complexity of the stimuli. Motion correction parameters (six regressors) and VAS blocks were also modelled as regressors of no interest within the first-level model. The fixation cross was left as an implicit baseline.

Alcohol cue reactivity between alcohol dependent and healthy control groups.

Individual contrast images comparing conditions Alcohol > Control were entered into a second-level random-effects analysis using two-sample *t*-tests to assess group differences between alcohol dependent and healthy control participants. Executive functioning performance (Stroop Interference, Trails difference score) and behavioural measures of dysregulated drinking with (ADS, DrInC scores) scores were included as covariates in separate analyses. Days since last drink to test day can potentially affect performance on these executive functioning tasks, and GLMs were conducted with this as a covariate; as there were no marked activation changes this was not included in further analyses to prevent model saturation. Whole-brain effects were examined within a reduced sample of the alcohol dependent group who completed the executive functioning tasks (reduced alcohol dependent group, $n = 17$) to determine associations between cue-induced alcohol stimuli brain activation and both executive functioning and dysregulated drinking measures, respectively. However, there was no evidence for correlation of DrInC scores and cue-activated frontal brain activation, so only the two analyses with ADS entered are fully reported here. For each

analysis, we report clusters which survived a threshold of $p < .005$ uncorrected with voxel extent $k > 15$, as a proxy for multiple comparison correction (Lieberman & Cunningham, 2009), in order to keep parsimony with the conjunction analyses which require an otherwise more liberal threshold due to the restrictive nature in combining the outcomes of two or more thresholded maps using the minimum statistic of the conjunction null (Friston, Penny, & Glaser, 2005) which may provide false negatives that mask the potential convergence of effects.

Regions of interest analyses of functional prefrontal regions.

To examine specific activation of prefrontal areas during cue reactivity and the relationship with executive functioning tasks, a priori region of interest (ROI) analyses were performed. Bilateral masks were created using the automatic anatomical labelling atlas (AAL; Tzourio-Mazoyer et al., 2002) within the WFU-PickAtlas Tool (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) to anatomically define functional prefrontal brain areas implicated in higher order executive functioning that implicated in addiction outlined by (Goldstein & Volkow, 2011), and furthermore, have been identified in functional imaging of the executive functioning tasks, including: activation of the DLPFC (superior and middle frontal gyri; BA 9, 46) for the executive functioning - component (Part-B) of Trails (Moll et al., 2002; Zakzanis et al., 2005) and the interference during Stroop (Egner & Hirsch, 2005; Zysset et al., 2001), the VMPFC (BA 10, 11, 25) the DLPFC (BA 8, 44, 46, 47), and ACC (BA rostral and caudal-dorsal BAs 24, 32) (Goldstein et al., 2011; Goldstein & Volkow, 2011). Significant brain activations that survived family-wise error (FWE) correction for multiple comparisons using small volume correction ($P_{SVC\text{-}FWE} < 0.05$) are reported here.

Convergence of executive functioning and ADS effects with alcohol cue reactivity within alcohol dependent group.

To assess alcohol reactivity and convergence of activity related to executive functioning and ADS measures, we conducted separate whole-brain conjunction analyses within the reduced alcohol dependent group using the minimum statistic for the conjunction null method (Friston et al., 2005), with an overall alpha of p <.005 and cluster threshold of k > 15 voxels, (Lieberman & Cunningham, 2009) to ascertain any shared brain regions related to alcohol cue reactivity and associations with ADS scores and executive functioning performance. Therefore, the T-contrasts within the separate regression models for executive functioning task (Stroop, Trails) were simultaneously entered with the negative ADS T-contrast. There was no evidence of a positive correlation with ADS score and significant frontal region cue-elicited activity, so this was not carried through to the conjunction analyses.

Results

Sample Characteristics

Table 14 summarises the demographic and clinical characteristics of the healthy controls, all alcohol dependent participants (whole alcohol dependent sample), and the reduced alcohol dependent group. When comparing whole alcohol dependent sample and healthy controls, alcohol dependent participants were significantly older than healthy control participants, U = 45, p = .004. The whole alcohol dependent sample reported significantly higher ADS scores, U = .000, p < .001; and 24 alcohol dependent participants (88.4%) were categorised as alcohol dependent using a cut-off score of 9 (Ross et al., 1990), whereas no healthy controls were. The whole alcohol dependent sample demonstrated a wide range of problematic drinking levels during the four weeks prior to baseline reflected by high TLFB units per drinking day. The whole alcohol dependent sample demonstrated significantly greater levels of consumption with TLFB units per drinking day one week prior to scan

session compared to healthy controls, $U = .025$, $p = .036$. The mean years of problem use for drinking experienced by the whole alcohol dependent sample was 14.41, with a significant variation ($SD = 11.11$). No significant differences between the whole alcohol dependent sample and the reduced alcohol dependent sample were seen, (p's > .05).

No Differences in Subjective Craving between Alcohol Dependent and Healthy Control Groups

Table 14 presents pre- and post-scan AUQ craving scores. A repeated measures ANOVA of AUQ scores of within-subjects factor time (pre-scan, post-scan) and between-subjects factor group (Whole alcohol dependent sample versus healthy controls) showed a trend for increased craving scores post-scan, $F(1,31) = 3.24$, $p = .082$, but groups did not differ overall, and there was no interaction of time and group (p's > .05) indicating no group differences in their craving responses pre- and post-scan.

Figure 11 shows the VAS craving ratings during the cue reactivity task. A mixed ANOVA examining VAS ratings after image blocks during the task was conducted using within-subjects factor image condition (alcohol, scramble alcohol, affectively neutral) and between-subjects factor group (Whole alcohol dependent sample, healthy controls). There was a main effect of condition, $F(2,66) = 5.04$, $p = .009$, with simple contrasts demonstrating that, overall, higher VAS ratings were reported for alcohol images than both scramble alcohol images, $F(1,33) = 5.07$, $p = .031$, and affectively neutral images $F(1,33) = 5.20$, $p = .029$. There was a main effect of group, with alcohol dependent participants reporting greater overall VAS ratings across conditions compared to healthy controls, $F(1,33) = 5.77$, $p = .022$, and a significant interaction of image condition and group, $F(2,66) = 3.42$ $p = .039$. A simple slopes analysis showed trends for alcohol dependent participants reporting greater VAS ratings after alcohol blocks compared to scramble alcohol, $F(1,33) = 3.41$, $p = .074$, or affectively neutral images $F(1,33) = 3.56$, $p = .037$, but these did not reach significance.

Healthy controls demonstrated little change across conditions. There were no significant differences between whole alcohol dependent sample and reduced alcohol dependent sample for VAS scores across image types (*p*'s >.05).

Neuropsychological Executive Functioning Task Performance

Mean scores for executive functioning tasks completed by reduced alcohol dependent sample are reported in Table 14. The reduced alcohol dependent sample completed the Trails: Part A (*M* = 26.68 s, *SD* = 9.16) significantly faster than executive functioning -related Part B (*M* = 63.17 s, *SD* = 20.30); a paired-sample *t*-test indicated a significant Trails difference

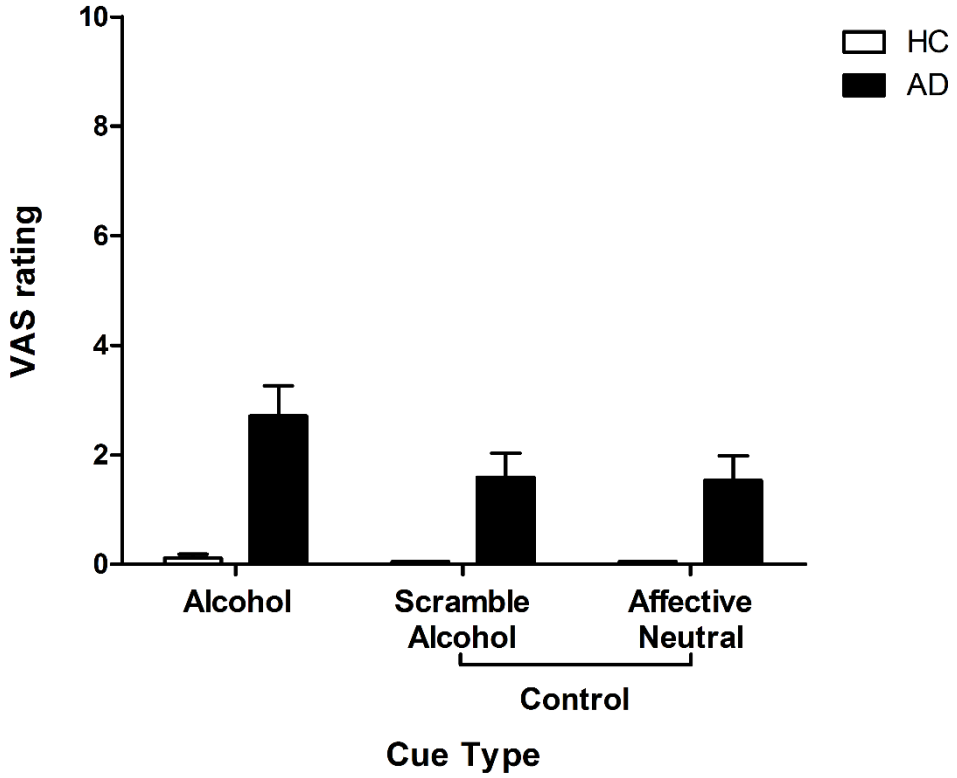

Figure 11. Mean subjective craving VAS ratings for alcohol dependent group (AD; *n* = 27) versus healthy controls (HC; *n* = 9) for alcohol condition and control conditions (scramble alcohol, affective neutral). Error bars represent + 1 *SEM.*

score, $t(16) = 9.57$, $p < .001$. Colour-naming during the Stroop was significantly slower for incongruent trials (*M* = 1171.91 ms, *SD* = 286.33) than control trials (*M* = 1064.88 ms, *SD* = 232.36), with a paired *t*-test demonstrating a significant Stroop effect, $t(16) = 5.38$, $p < .001$.

The two executive functioning scores were moderately correlated, $r(17) = .52$, $p = .031$, indicating that while they measuring a common underlying executive functioning construct they involve the separate subdomains, in accordance with influential theoretical frameworks (Miyake et al., 2000). However, there were no significant associations of either executive functioning task with severity of AUD with ADS score, ($p > .05$).

Greater Alcohol Cue-induced Activation in Alcohol Dependent Participants Compared to Healthy Controls

The main effects for the Alcohol > Control whole-brain analyses across the whole sample and per group are reported in Supplementary Table 1 in Appendix C. A broad network of brain areas was activated during the cue reactivity task, including reward and motivational pathways, and visual object recognition and attentional networks, and motor areas, as demonstrated in other alcohol cue activation studies (Grüsser et al., 2004; Sjoerds et al., 2014; Vollstädt-Klein et al., 2012).

Table 15 shows Alcohol > Control alcohol cue-induced activation for whole alcohol dependent sample compared to healthy controls. Two-sample *t*-tests showed higher alcohol cue-induced activation for the alcohol dependent group in areas of the middle temporal gyrus, occipital cortex, ACC, and dorsomedial prefrontal cortex and DLPFC (inferior frontal gyrus, BA 9), replicating findings from previous studies implementing cue reactivity tasks (Grüsser et al., 2004; Sjoerds et al., 2014; Vollstädt-Klein et al., 2012) and indicating alcohol dependent participants demonstrated cue reactivity elicited by visual alcohol cues (see Figure 12).

Associations with Alcohol Cue-Induced Activation, Executive Functioning Performance and AUD Severity, Within the Alcohol Dependent Group

Correlations with Stroop performance and AUD severity.

Whole-brain correlation analyses were conducted examining associations of alcohol cue reactivity with Stroop interference score and ADS score regressors. A significant negative correlation between alcohol cue-induced brain activation and Stroop interference score (higher score = worse executive functioning) was seen, whereby alcohol dependent participants with worse executive functioning demonstrated lower brain activation in several regions including prefrontal areas, the supplementary motor area, and insula (see Supplementary Table 2 in Appendix C). A priori ROI analyses of prefrontal regions revealed a significant negative correlation between Stroop interference score and alcohol cue-reactivity in the right DLPFC after small-volume FWE-correction, Z = 4.47, $P_{SVC\text{-}FWE}$ <.030, but no other regions of interest survived small-volume FWE-correction.

Table 15

*Clusters of Significant Cue-induced Brain Activation for Contrast Alcohol>Control comparing Whole Alcohol Dependent Sample (*n *= 27) and Healthy Controls (*n *= 9).*

Area	Side	BA	cluster size	Z	x	y	z
Whole AD Sample > HC							
Fusiform Gyrus	L	30	31	3.78	-18	-42	-12
Parahippocampal Gyrus	R	36,37	175	3.69	30	-38	-10
Middle Temporal Gyrus	R	21	86	3.48	56	-30	-6
	L	21	51	3.25	-62	-36	-4
Middle Frontal Gyrus	L	9	52	3.37	-36	6	40
Inferior Frontal Gyrus	R	47	25	3.22	52	38	-8
Inferior Frontal Gyrus_	R	47	38	3.09	40	32	-12
Middle Occupital Gyrus	R		77	3.21	42	-70	26
Superior Temporal Gyrus	L	39	100	3.12	-46	-54	12
Superior Frontal Gyrus	L		18	2.84	-16	64	16
HC > Whole AD Sample							
No significant clusters of activation							

Note. Corrected at $p < .005$, voxel threshold $k > 15$; AD = Alcohol dependent; HC = Healthy controls; BA = Brodmann's Area; Z = Z-value; x, y, z = MNI coordinates; L = left; R = right.

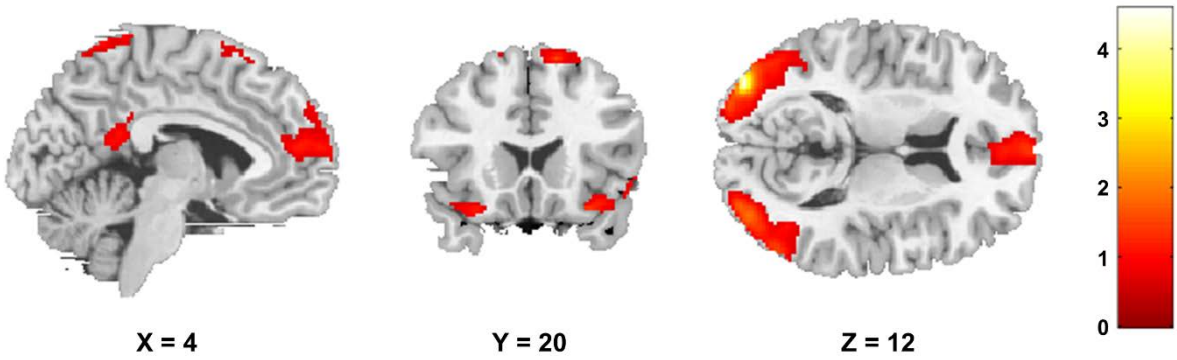

Figure 12. Main effects of Alcohol > Control contrast cue activation in alcohol dependent participants compared to healthy controls. Clusters of activation are visible in the occipital cortex, fusiform area, ACC, dorsomedial prefrontal cortex and DLPFC, and orbitofrontal cortex. Coloured bar represents Z-scores from 0 to 5, $p < .005$, cluster size threshold $k > 15$.

Positive correlations between alcohol cue-induced brain activation and Stroop interference score was also seen, whereby higher Stroop Interference scores (indicating worse EF) corresponded with higher cue reactivity. However, this pattern was evident in fewer regions than seen in the negative correlation, with markedly less activation in prefrontal areas (see Supplementary Table 2 in Appendix C).

Whole-brain negative correlations for ADS score and alcohol cue-activation with several regions were evidenced, indicating those with greater AUD severity (higher ADS score) demonstrated reduced brain activity in regions including: prefrontal areas, temporal and parietal lobes, and the precuneus (see Supplementary Table 2 in Appendix C). No positive correlations of ADS score and alcohol cue reactivity for whole brain analyses, or for a priori regions of interest.

Correlations with Trails performance and AUD severity.

Whole brain analyses for the regression assessing Trails difference score and ADS score and alcohol cue reactivity demonstrated a negative correlation between Trails difference

score (higher score = worse EF) and alcohol cue-induced activation. Worse executive functioning was thus associated with reduced alcohol cue-induced activity in several prefrontal regions related to Trails performance, such as the DLPFC and supplementary motor areas (Moll et al., 2002; Zakzanis et al., 2005). There were also positive correlations for Trails and alcohol-related cue activation in a smaller number of regions, with activity related chiefly to motor areas and occipital lobes, and less overall activation in prefrontal areas (see Supplementary Table 3 in Appendix C).

There were negative correlations with ADS score and alcohol cue reactivity in the DLPFC, supplementary motor area, bilateral insula, and temporal visual processing areas, but no positive correlation with ADS and alcohol cue reactivity was evidenced (see Supplementary Table 3 in Appendix C).

Convergence of Reduced Brain Activation in Prefrontal Region DLPFC According With Worse Executive Functioning Task Performance and Greater AUD Severity

Whole-brain conjunction analyses comparing contrasts of executive functioning correlates and alcohol dependent participants' scores (conjunction null: $p < .005$, cluster-threshold $k > 15$) found a convergence of neural activation in the right inferior frontal gyrus/DLPFC (MNI: $x = 32$ $y = 38$ $z = 36$; $Z = 3.11$; see Figure 13) for contrasts of the negative correlation Stroop performance and alcohol cue-reactivity, $r(17) = -.76$, $p < .001$, and negative correlation with ADS score and alcohol cue-reactivity, $r(17) = -.73$, $p < .001$. That is, higher right DLPFC activity was seen in those with less Stroop interference (better EF), and with lower ADS scores. This activity pattern was also seen in the right inferior parietal lobule (MNI: $x = 46$ $y = -60$ $z = 38$; $Z = 3.55$). No evidence for activation was found other conjunction analyses of Stroop and ADS. Similarly, no Trails and ADS correlation contrasts showed evidence of overlapping activation using conjunction analyses.

Lastly, we conducted a post-hoc analysis to examine whether this observed overlapping increased right DLPFC activity related to reduced activation throughout the rest of the brain, particularly in subcortical areas involved in impulsive motivational responses to alcohol cues. Using the identified cluster in the right DLPFC (MNI: $x = 32$ $y = 38$ $z = 36$) we created a functional region of interest (ROI) mask image using the SPM toolbox MarsBar (http://marsbar.sourceforge.net; Brett, Anton, Valabregue, & Poline, 2002) . Mean beta values of masked ROI were then extracted for each participant of the reduced alcohol dependent sample using SPM toolbox REX (http://web.mit.edu/swg/software.htm; Whitfield-Gabrieli, 2009). These beta values were then entered as ROI covariate values in the same regression of Alcohol > Control brain activation using a negative T-contrast, to examine whether reduced activity in the right DLPFC related to increased activity in subcortical areas involved in motivational responses to cues. There were no significant clusters at the $p = .005$

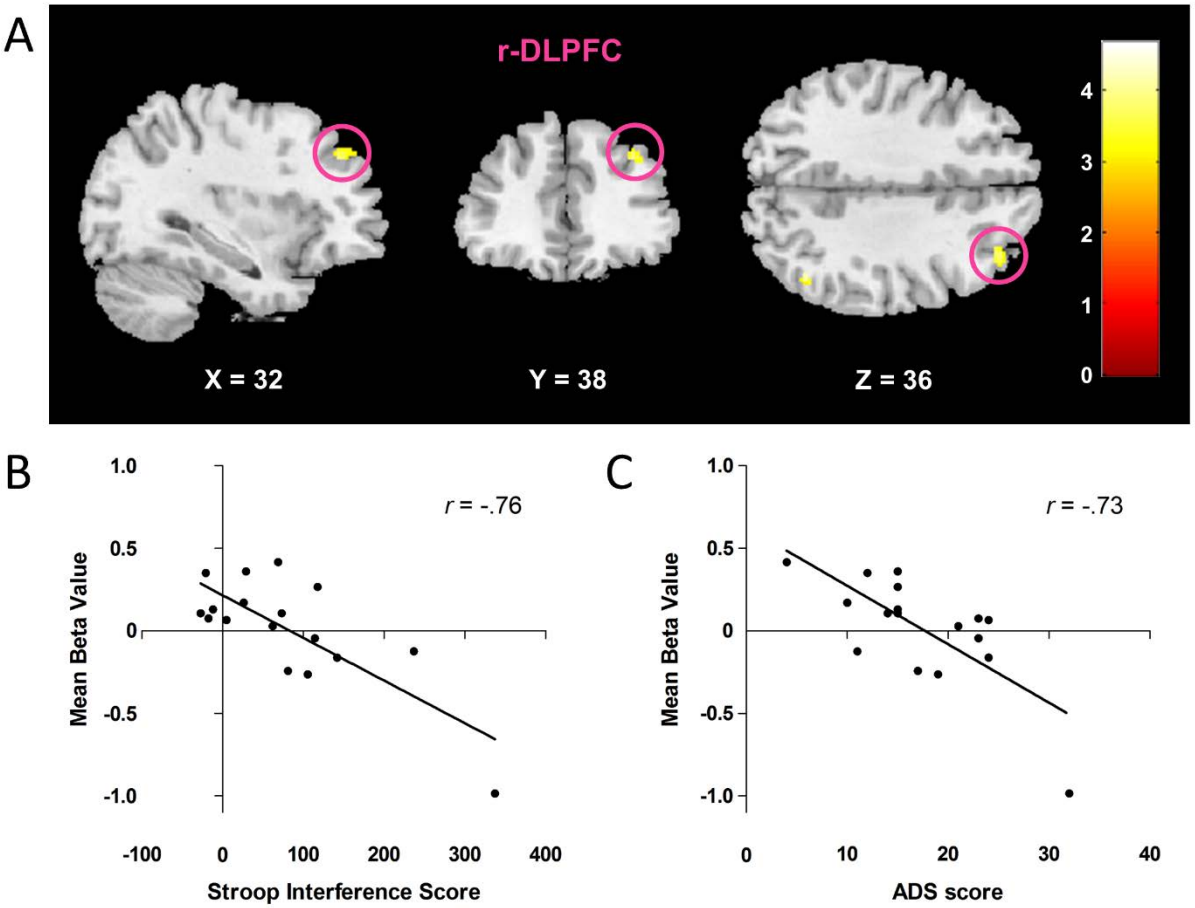

Figure 13. Overlap of alcohol cue-elicited brain activation and correlations with Stroop Interference score and Alcohol Dependence Scale (ADS) score. A) Conjunction analysis overlap of Reduced alcohol dependent sample (n = 17) with Alcohol > Control brain activation for negative Stroop correlation and negative ADS correlation (conjunction null, p < .005, cluster-threshold k > 15), with two visible clusters of activation in the right DLFPC and right inferior parietal lobule; Coloured bar represents Z-scores from 0 to 5. B) Scatterplot showing the correlation between mean contrast Alcohol > Control beta values for brain activation in the right DLPFC with Stroop Interference scores. C) Scatterplot showing the correlation between mean contrast Alcohol > Control beta values for brain activation in the right DLPFC with ADS scores.

(uncorrected), k > 15 threshold, but when applying a more liberal threshold (p < .01 [uncorrected], cluster size k > 5) lower right DLPFC ROI activity was associated with greater alcohol cue-elicited activity in subcortical areas, including the bilateral caudate nucleus and thalamus (see Figure 14, and Supplementary Table 4 in Appendix C).

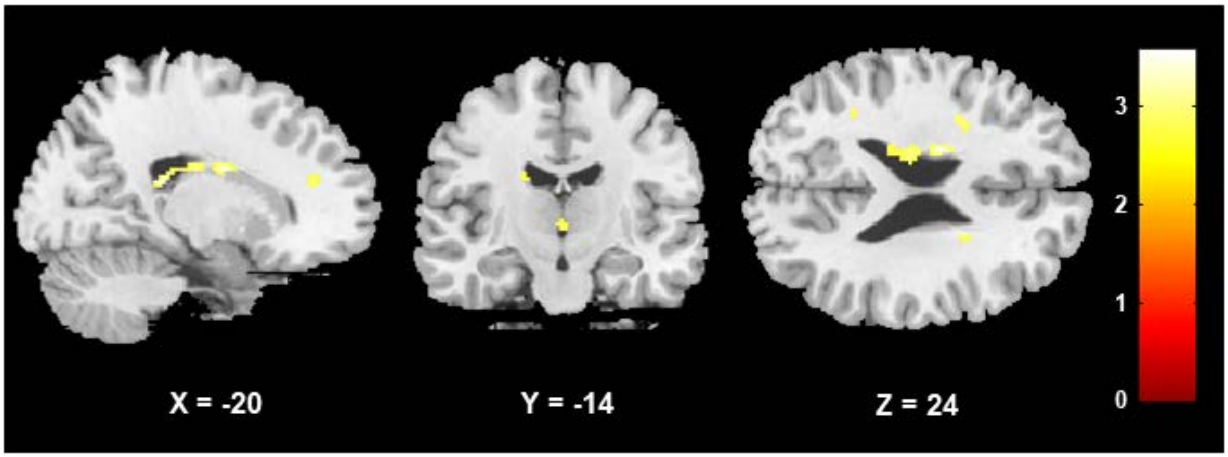

Figure 14. Whole brain regression analysis showing clusters of brain activity associated with the negative correlation between increasing activation during Contrast Alcohol>Control associated and lower functional ROI right DLPFC activity in the reduced alcohol dependent sample (n = 17). Greater activation can be seen in several clusters including the left and right caudate nucleus, the thalamus, and medial frontal gyrus. Coloured bar represents Z-scores from 0 to 4, $p < .01$, cluster size threshold $k > 5$.

Discussion

This study demonstrated greater alcohol cue-induced brain activation in motivational and visual networks, as well as prefrontal regions in alcohol dependent participants compared to healthy control participants. These prefrontal regions included the OFC, ACC and medial and lateral prefrontal areas, according with activation seen in other fMRI cue reactivity studies using AUD samples (Filbey et al., 2007; Filbey et al., 2011; Grüsser et al., 2004; Sjoerds et al., 2014; Vollstädt-Klein et al., 2012), and in heavy users of other drugs of abuse (Goldstein et al., 2011; Heinz et al., 2009; Jasinska et al., 2014). Healthy control participants did not demonstrate any greater alcohol cue-induced activity, even in areas potentially involved in regulation. As healthy controls are not sensitised to alcohol cues, they do not require regulation of impulsive, motivational cue-elicited responses experienced by alcohol dependent participants (Robinson & Berridge, 2008). However, aside from the amygdala in alcohol dependent participants, we found no evidence of cue-elicited whole-brain activation in other subcortical areas that have been previously implicated in motivational networks

related to habit formation for heavy alcohol users, such as the nucleus accumbens (NAcc), ventral tegmental area (VTA), or subregions of the striatum (Braus et al., 2001; Grüsser et al., 2004; Sjoerds et al., 2014).

Activation of these areas has primarily been demonstrated in recently abstinent participants (Sjoerds et al., 2014) and has been associated with CR task-elicited subjective craving (Grüsser et al., 2004; Wrase et al., 2002). Moreover, this effect may be transient, with activity in the dorsal striatum only demonstrated in early abstinence, and not apparent after three weeks (Braus et al., 2001). As several alcohol dependent participants in our sample were still regular drinkers (.00 BAC required prior to imaging only) this may explain the lack of activation evidenced in these areas. Interestingly, recently detoxified alcohol dependent participants (1–3 weeks) demonstrated no subcortical activation of these motivational areas during a fast-event related version of the cue reactivity task (Heinz et al., 2007), potentially as it interfered with automatic processing of salient cues by areas associated with habit formation. Yet prefrontal areas implicated in cue reactivity such as the OFC still exhibited cue-induced activation in our alcohol dependent sample, indicating duration of stimulus onset may play a role in eliciting heightened subjective craving responses. As the CR task employed here is well-established and previously shown subcortical activation in motivational regions, the consumption profile of these alcohol dependent participants may explain our lack of mesocortical region activation here.

We hypothesised that executive functioning task performance would be primarily associated with alcohol cue-activation in prefrontal regions within the alcohol dependent participants. Increasing Stroop interference scores (whereby higher scores indicate worse EF) were negatively correlated with alcohol cue-induced activation across prefrontal regions, signifying reduced brain activation associated with worse executive functioning performance in areas including the DLPFC, medial prefrontal cortex, and ACC. Increased activation in

these prefrontal cortical areas during neuroimaging Stroop tasks is associated with better task performance: increased DLPFC activity correlated with better cognitive control in a Stroop task (Kerns et al., 2004; Leung et al., 2000; MacDonald et al., 2000; Milham et al., 2003; Zysset et al., 2001); and greater ACC activity related to better conflict resolution during incongruent components of the Stroop (Bench et al., 1993; Botvinick et al., 1999; Fan et al., 2003; Kerns et al., 2004). As alcohol cues elicit an impulsive motivational response in chronic drinkers that can signal a drinking situation and induce craving, alcohol dependent participants with increased activity in these prefrontal areas may have better regulation of these impulsive responses of subcortical regions involved in motivation due to better cognitive control (Goldstein & Volkow, 2002). Considering mediofrontal hypometabolism using PET related to poor Stroop performance in abstinent alcohol dependent participants (Dao-Castellana et al., 1998), it is possible that less activation in prefrontal areas implicated in regulation in alcohol dependent participants may be related to impaired cognitive control, reducing the capacity to inhibit motivational cue-elicited responses. Positive correlations were also seen, whereby greater Stroop interference scores regions related to more alcohol cue-elicited activity, but this was limited and chiefly observed in parietal and temporal regions, such as primary and supplementary sensorimotor areas, and secondary visual processing areas.

A similar pattern was also seen with Trails results. Alcohol cue-induced activation across various brain regions negatively correlated with Trails difference score (higher scores indicates worse EF), with decreased activity in similar prefrontal cortical areas shown with Stroop. Interestingly, though better Trails performance is primarily correlated with greater activation in the left prefrontal cortex (Moll et al., 2002; Zakzanis et al., 2005), in our alcohol dependent sample we observed increased activity related to better Trails performance in the right DLPFC. The Trails Part B is considered to measure cognitive flexibility associated with

switching between different task sets of numbers and letters (Strauss et al., 2006), but this would also involve appropriate inhibition of consecutive responding to switch between rules, a cognitive function largely associated with the right DLPFC (Aron et al., 2003; Garavan, Ross, & Stein, 1999).

However, the pattern of positive correlations of higher Trails difference scores and increased activation revealed a wide range of brain regions with elevated alcohol cue-elicited activity. These were observed primarily in the visual, parietal primary motor and somatosensory cortices, and temporal areas; but significant prefrontal activation was also seen in prefrontal areas (e.g., cingulate cortex, the middle frontal gyrus, inferior frontal gyrus). Trails has been shown to activate several diffuse regions not restricted to the prefrontal cortex, and the few studies employing fMRI versions have shown a wide distribution of brain activation for executive function in executive functioning-related Part B (Moll et al., 2002; Zakzanis et al., 2005). Increased activation of areas that have been attributed with motor control for Trails task completion, including the precentral gyrus, midcingulate cortex, and premotor cortex (Zakzanis et al., 2005) are also identified using cue reactivity tasks in drug use samples, but are associated with automatised behaviour and motor planning related to drug taking action (Jasinska et al., 2014). Investigating brain activation using fMRI Trails versions in AUD samples would help to isolate key regions affected within this broad network as compared to those identified in healthy individuals.

There were significant associations with severity of AUD within alcohol dependent participants and alcohol cue-induced activation. ADS score was negatively correlated with alcohol cue activation, with increasing AUD severity related to reduced activity in several brain regions across the parietal, temporal, and frontal cortices. However, no alcohol cue-elicited activity was seen in mescorticolimbic areas. This is generally the opposite of findings from the few other studies assessing links with severity of AUD, with two studies of gustatory

cues showing positive relationships with severity of alcohol problems and increased activation in subcortical motivational areas such as the VTA, NAcc, and striatum (Claus et al., 2011; Filbey et al., 2007). However, activation of these areas was mainly revealed through a priori pre-defined ROI analyses within these studies focusing on mesocorticolimbic areas rather than whole brain activity, with prefrontal areas similarly identified. Additionally, prefrontal cortex activity was bi-directionally correlated with AUD severity in a visual CR task (Sjoerds et al., 2014), suggesting an effect of cue modality; gustatory cues may simultaneously act as both conditioned cues and unconditioned drug responses with reinforcement, whereas visual cues primarily elicit a conditioned cue response. No positive correlations with AUD severity and alcohol cue-elicited activity within our reduced alcohol dependent sample were seen, suggesting the observed negative correlations may relate to processing and underlying regulation of responses to eliciting cues, rather than a motivational response.

A primary study hypothesis involved the convergence of alcohol cue-induced brain activation in key prefrontal regions related to severity of alcohol problems and worse executive functioning performance, indicating a role of executive functioning in the regulation of cue responses. An overlap in the right DLPFC (Brodmann's area 9) was seen for both the negative correlation of alcohol cue-elicited activation with greater Stroop interference scores, and the negative correlation of alcohol cue-elicited activation with increasing AUD severity, respectively. That is, alcohol dependent participants with worse executive functioning performance and greater severity of alcohol problems exhibited less right DLPFC alcohol cue-elicited activity. The right prefrontal cortex is considered central to response inhibition (Aron et al., 2003; Garavan et al., 1999), and increased activity in the MFG (i.e. DLPFC) brain activation correlated with better performance (lower Stroop Interference scores) during incongruent trials of an fMRI Stroop (Adleman et al., 2002; Leung

et al., 2000). PET medial frontal metabolism was also negatively correlated with worse Stroop performance (e.g., greater Stroop interference, more task errors) in alcohol dependent participants (Dao-Castellana et al., 1998), indicating prefrontal cortex activity is influential in Stroop executive functioning performance in AUD individuals. Moreover, DLPFC hypoactivity observed in alcohol dependent participants compared to healthy controls during an fMRI stop-signal task (C. R. Li, Luo, Yan, Bergquist, & Sinha, 2009) related to increased desire of the alcohol dependent participants to consume alcohol, suggestive of impaired impulse control. This further corroborates the negative correlation observed in this study, with increasing AUD severity negatively correlating with DLPFC/MFG brain activation.

In our study, post-hoc analyses applying a functional ROI of the identified right DLPFC suggests a role for cognitive control of alcohol cue-elicited responses, as lower DLPFC activity within the alcohol dependent participants correlated with more alcohol cue-induced activation in motivational networks. This has been seen in other drug use samples; for example, active regulation during cue presentation in cocaine-dependent individuals reduced metabolism in motivational areas (right OFC, NAcc), and was associated with increased activation of the lateral prefrontal cortex (Volkow et al., 2010). Additionally, smokers implementing active cognitive regulation strategies during an fMRI task reported reduced craving, coupled with increased DLPFC activity and reciprocal reduced activity in the ventral striatum (Kober et al., 2010). This suggests a potential prefrontal cortex role postulated in dual-process models of addiction in downstream regulatory mechanisms, which may be integral to appropriate regulation of alcohol cue responses such as craving. Employing functional connectivity analyses to demonstrate downstream influences between these regions would help elucidate the link identified in our exploratory analyses in this AUD sample.

While significant converging evidence related to the Stroop and AUD severity was seen, no evidence of overlapping areas were identified with the Trails. This may be as Trails

activates a wide network of other cortical areas aside from the prefrontal cortex, and is considerably more diffuse than the Stroop task, which relies on crucial prefrontal areas for functional performance (Strauss et al., 2006). Alternatively, while the Trails difference score is demonstrated to be sensitive for cognitive impairment between drinker samples and healthy controls (Davies et al., 2005; Noël et al., 2001), it may not have the measurement sensitivity to substantially delineate within our reduced alcohol dependent sample of dysregulated drinkers. Though we observed significant associations with Trails and cue-induced brain activity, the differences may not have been considerable enough to be observable when applying the stringent conjunction null threshold. Investigation of the functional version of Trails in AUD samples may elucidate whether it suitably exhibits evidence of brain activity differences within these participants.

Self-reported craving, both with AUQ pre- and post-scan scores, and VAS ratings during the cue reactivity task were weakly or unaffected by the task, with low scores reported for both measures. Relationships between subjective craving and drinking outcomes such as consumption or relapse are relatively modest (Tiffany & Carter, 1998), and results of fMRI studies are inconsistent (Heinz et al., 2009). Positive correlations of alcohol cue reactivity and self-reported craving or desire for alcohol have been demonstrated in AUD samples across several regions chiefly comprising motivational areas (Kühn & Gallinat, 2011; Myrick et al., 2003; Seo et al., 2011; Wrase et al., 2002), and some studies have indicated this relationship in prefrontal areas (Filbey et al., 2007; Fryer et al., 2013; Myrick et al., 2003) including the DLPFC (M. Park et al., 2007). However, some studies employing similar task versions also show no clear associations with subjective craving and cue-elicited brain activation (Grüsser et al., 2004; Sjoerds et al., 2014; Vollstädt-Klein et al., 2012), particularly in prefrontal areas, and cue-induced activation better predicted relapse than subjective craving (Grüsser et al., 2004). Furthermore, as these were treatment-seeking alcohol dependent participants,

subjective craving may have been influenced by situational demand characteristics affecting the reliability of self-report measures (Tiffany & Carter, 1998).

There are notable study limitations. Behavioural outcome measures such as subsequent consumption or relapse within the alcohol dependent participants were not assessed, which may elucidate whether increased activity of identified prefrontal areas related to better drinking outcomes, and thus may represent better regulation of alcohol cues in these areas. Clinically evident withdrawal was not assessed on prior to scan which may have impacted on cue reactivity, though most participants were largely still regularly drinking or had maintained abstinence by this stage. The reduced sample of alcohol dependent participants that completed executive functioning tasks may have restricted our power to adequately identify the unique associations of executive functioning in regulatory regions, such as differences in Trails performance. Additionally, our control sample was not well-matched to our drinker sample and was moderately small, though there was still power to demonstrate main effects of alcohol cue reactivity in the alcohol dependent sample which was the primary reason for the control group's inclusion. It is also unclear from this study whether poorer regulation from executive functioning deficits are related to alcohol use, or whether they are individual differences that predispose individuals to alcohol use problems. Future prospective studies employing at-risk samples, such as those with family history of alcohol problems (e.g., Silveri, Rogowska, McCaffrey, & Yurgelun-Todd, 2011; Tapert et al., 2004) may clarify the link between executive functioning and regulation of motivational cue responses in alcohol use. Finally, while we were interested in regulatory processes during cue presentation, we did not assess whether potential regulation occurs after cue offset. Additionally, implementing an explicit regulation manipulation may further identify whether prefrontal areas are involved in active regulation of alcohol cue responses, such as those

demonstrated for smoking (Kober et al., 2010) and cocaine-use (Volkow et al., 2010) samples.

In conclusion, this study demonstrated that executive functioning performance and a history of dysregulated drinking were associated with differences in alcohol cue-induced brain activation within alcohol dependent participants using a visual fMRI task. Furthermore, we identified a convergence of poorer executive functioning and greater severity of alcohol problems related to reduced activity in prefrontal brain areas such as the DLPFC, potentially involved in regulation of motivational cue responses. Future studies assessing drinking outcomes such as relapse and subsequent consumption may elucidate whether this is related to dysfunctional regulation, evidenced by alcohol cue reactivity in these areas.

Chapter Six

General Discussion

General Discussion

This thesis examines regulation of responses to alcohol cues and influencing factors in alcohol use disorder (AUD). The literature to date has been characterised as fragmented and inconsistent in identifying these processes within AUD. In particular, studies relying on self-report methods to distinguish responses to eliciting cues show inconsistent evidence of associations (e.g., Bottlender & Soyka, 2004; Cooney et al., 1997; Grüsser et al., 2004; Heinz et al., 2005; Litt et al., 2000; Reich et al., 2010; Rohsenow et al., 1992), whereas experimental research utilising various physiological markers of regulation have demonstrated more consistent relationships between drinking behaviour and cue-elicited responses (e.g., Braus et al., 2001; Drummond & Glautier, 1994; Filbey et al., 2011; Garland et al., 2012; Grüsser et al., 2004; Ingjaldsson, Laberg, et al., 2003; Ingjaldsson, Thayer, et al., 2003; Rohsenow et al., 1992; Vollstädt-Klein et al., 2012). This thesis attempted to consolidate disparate approaches, implementing a wide range of laboratory methods to comprehensively assess self-regulatory processes in AUDs in samples with clear and profound behavioural indices of dysregulation, to better identify mechanisms involved in the appropriate regulation of cue-elicited responses and identify whether there were overlapping components between these approaches. Additionally, strong theoretical frameworks were applied to examine executive functioning as a key factor implicated in appropriate regulation (i.e., the unitary/diversity model; Miyake & Friedman, 2012), and a model of maladaptive regulation (i.e., the neurovisceral integration model; Thayer & Lane, 2000) assessing indices of autonomic nervous system activity, such as heart rate variability (HRV). The findings from four studies demonstrate regulation occurs across several stages before, during, and after cue presentation, and highlights how factors such as executive functioning influence aspects of underlying regulatory processes. This thesis explored: 1. If the reduced capacity of the reflective system to regulate alcohol cue-elicited responses is a primary factor underpinning AUD. 2. Whether executive functioning

has a significant role in the appropriate regulation of the reflective system. 3. The timescale of regulation across different stages of cue presentation. 4. Whether there was a convergence of the neurocircuitry involved in regulation of these cue-elicited responses, identified by comprehensive measurement using various psychophysiological, physiological, neuropsychological and imaging techniques.

The implications and limitations of the four empirical studies have been addressed in preceding chapters. This final chapter places the results of the previous chapters together in the context of common themes and begins with an overview of the results. The overall themes arising from the research findings are interpreted and discussed within the context of different stages of regulation, neurobiological components, conceptual models of addiction, the basis of cognitive dysfunction, and the timescale of regulation are addressed. Lastly, clinical and treatment implications and limitations are discussed, and directions for future research outlined.

Overview of the Four Empirical Studies

Several models of self-regulation implicate executive functioning as a key factor in appropriate regulation of behaviour. However, minimal research has comprehensively evaluated this role of executive functioning in AUD within the context of regulation of responses to salient alcohol cues. Chapter Two aimed to address this gap, employing Miyake and Friedman's (2012) influential unitary/diversity model of executive functioning as a comprehensive framework for investigating whether executive functioning domains were uniquely associated with the regulation of responses to alcohol cues. Overall cue reactivity was observed through increased psychophysiological responses and subjective craving to water and alcohol cues, and subsequent recovery effects were also demonstrated during the cue reactivity task, but this was not specific to alcohol. Furthermore, better inhibitory/common executive functioning domain task performance (Stroop task) was

associated with better recovery effects after cues offset for drinkers with greater AUD severity. This finding suggests greater executive functioning ability may have a protective role in regulation of responses to appetitive cues for those with more severe alcohol-related problems.

Chapter Three employed similar methods in severely dysregulated drinker samples to ascertain whether differences in regulation of cue-elicited responses were associated with executive functioning deficits. The cue reactivity task was completed by individuals with alcoholic liver disease (ALD), who represent a subsample of severely dysregulated drinkers who experience significant negative biological feedback from drinking, and a drinking control sample of participants with alcohol dependence. Individuals with ALD demonstrated executive functioning deficits compared to the alcohol dependent drinkers with a similar history of dysregulated drinking, and common-executive functioning domain Stroop task performance was again associated with differences in regulation during cue reactivity indexed by psychophysiological responses. However, no observed differences between the groups were demonstrated for regulation recovery effects related to executive functioning, although the similarity of ALD and alcohol dependent drinking profiles suggested groups were comparably severely dysregulated. Moreover, the increased reactivity to cues shown by alcohol dependent participants compared to the ALD patients showed some differences in responses to cues, indicating regulation could be occurring at multiple stages across cue presentation which merited further examination within these subsamples.

In Chapter Four, we employed a delayed-discounting card game the Iowa Gambling task to examine whether dysregulated drinking was associated with behavioural decision-making impairment. As an earlier study by Bechara and Damasio (2002) found that participants with substance dependence exhibited impaired anticipatory responses to risky decisions with potentially negative outcomes during the task, we employed similar measures

in our dysregulated samples. As individuals with ALD who continue to drink despite negative feedback from their health situation may do so because of failure to learn from negative consequences, we examined these anticipatory responses in the ALD and alcohol dependent subgroups as an index of reduced expectancy of potentially negative outcomes from poor choices that may explain dysregulated drinking. Both ALD and alcohol dependent groups demonstrated behavioural impairment during the task, showing a preference for risky choices with negative outcomes. Furthermore, alcohol dependent participants who experienced more negative drinking consequences demonstrated reduced anticipatory responses for risky choices with potentially negative outcomes, as did ALD patients overall to these outcomes. Additionally, similar patterns of reduced psychophysiological responses were seen after reinforcement with negative outcomes for these two subgroups. This suggests that impaired learning of choices with negative consequences, and/or the expectation that risky choices may have negative outcomes may impede appropriate decision-making, which may reflect deficits that affect poor real-world choices related to dysregulated drinking.

Chapter Five used functional neuroimaging techniques to assess whether there were overlapping neural correlates related to executive functioning performance and dysregulated drinking measures within alcohol dependent participants in regions implicated in regulation of cue responses. This was indicated by increased brain activity (shown through blood oxygen level dependent [BOLD] response) to visual alcohol cues during an alcohol cue reactivity task. Alcohol dependent drinkers demonstrated greater alcohol cue-elicited brain activation than healthy controls in prefrontal areas. Importantly, there was a convergence of reduced brain activity observed in the dorsolateral prefrontal cortex (DLPFC) for alcohol dependent participants with worse Stroop performance and greater AUD severity, indicating a potential role in this region involved in regulation of motivational responses to eliciting cues.

Thus, this thesis shows the convergence of factors that may influence regulatory processes self-regulation of cue-elicited responses in AUD, through comprehensive measurement of regulation across several stages of cue presentation and the integration of several techniques to triangulate these overlapping constructs. The next section will explain these research findings, identifying the factors involved in regulation within the context of conceptual models of self-regulation.

Interpretation of the Studies

Identification of regulation occurring across the stages of cue presentation.

Impulsive system responses to cues – physiological responses.

Several theoretical models of addiction (Bechara & Damasio, 2005; Goldstein & Volkow, 2002; Koob & Le Moal, 2008; Wiers & Stacy, 2006b) indicate a role of motivational responses to cues (such as craving) that elicit urges and drives to consume alcohol (Tiffany, 1990). However, empirical evidence linking self-reported craving during cue reactivity paradigms and behavioural drinking outcomes of dysregulated drinking behaviour in AUD samples is mixed (Carter & Tiffany, 1999; Heinz et al., 2009), a pattern also observed across the cue reactivity tasks implemented in our program of research. For example, self-reported craving during the cue reactivity task reflected the expected pattern of increased alcohol craving in the non-treatment-seeking community sample during water and alcohol cue presentations (Chapter Two), with an observed alcohol-specific craving effect, and craving reductions during subsequent recovery periods. However, our treatment-seeking clinical samples (alcohol dependent and ALD) in Chapter Three demonstrated overall increases in self-reported craving during both water and alcohol cues, but there was no evidence of significant alcohol-specific effects. Furthermore, treatment-seeking alcohol dependent participants reported weak or no experienced alcohol craving during the fMRI cue reactivity task (Chapter Five), either post-scan session or during the task with the VAS. This reflects

varied results of studies observing subjective craving and associations with behavioural outcomes within AUD samples (Carter & Tiffany, 1999; Heinz et al., 2005), with self-report measures potentially affected by the severity of AUD (Heinz et al., 2009; Jasinska et al., 2014), whether participants are still consuming alcohol and substance availability (Wertz & Sayette, 2001), and whether participants are treatment-seekers which may influence their reporting due to demand characteristics related to treatment outcome (Flannery et al., 1999; Hesselbrock, Babor, Hesselbrock, Meyer, & Workman, 1983). Additionally, factors related to the cues employed in our cue reactivity task that may impact these responses, such as the eliciting strength of the specificity of responses the cues, and suitability of control cues may all have affected the subjective craving response; these will be addressed in further detail below.

However, measurement of psychophysiological responses has demonstrated utility in capturing underlying indices of motivational impulsive system responses, particularly during exposure to eliciting cues. A strength of this thesis was the implementation of several modalities of psychophysiological response measurement, which allowed for observation of cue reactivity and regulation of elicited cue responses during cue reactivity tasks across a range of AUD samples. In our psychophysiological cue reactivity task, water and alcohol cue presentation effectively modulated parasympathetic autonomic nervous system activity reflected by changes in HRV, as an index of reactivity to salient eliciting cues within the environment (Thayer & Lane, 2000). This was observed in both the nonclinical, non-treatment-seeking drinker sample in Chapter Two, with similar patterns of activity observed in the dysregulated treatment-seeking ALD patients and alcohol dependent participants in Chapter Three. Moreover, alcohol cue-elicited fMRI brain activation was evidenced through increased BOLD activity during the visual imaging cue reactivity task in alcohol dependent patients compared to healthy controls (Chapter Five).

Rapid phasic changes in HRV (i.e. high-frequency HRV) due to parasympathetic nervous system activity is a learned response to environmental cues or stressors that prepare an organism for action or reinforcement (Porges, 2009; Thayer & Lane, 2000), and an indicator of adaptive response to dynamic environmental demands (Thayer & Lane, 2009). In the psychophysiological cue reactivity task we employed (Chapter Two and Chapter Three), multimodal (i.e., visual, tactile, olfactory) water and alcohol beverage cues sufficiently elicited reductions in parasympathetic activity, indicated by lower high-frequency HRV levels compared to baseline, suggesting a disinhibition of the sympathetic autonomic nervous system (Malliani et al., 1998). Considering regular drinkers become sensitised to alcohol with continued consumption through several neurobiological processes and pathways previously outlined (Everitt & Robbins, 2005; Koob & Le Moal, 2008; Koob & Volkow, 2009; Robinson & Berridge, 1993), this subsequently increases both the salience and range of alcohol-related stimuli, and an elevated motivational, impulsive response to appetitive cues is established. Interestingly, while there was some indication of alcohol-specific cue reactivity in the non-treatment-seeking regular drinkers, a considerable magnitude of parasympathetic cue reactivity was observed for both water and alcohol cues across the samples, with clinical alcohol dependent and ALD participants exhibiting the same levels of parasympathetic responses to both cue types.

There are some potential reasons for this. Firstly, water as a neutral stimulus may still elicit a motivational response due to generalising of cues. As water and alcohol share similar characteristics that may develop into triggering cues through classical conditioning (such as hydrating and thirst-quenching qualities, and visual properties), this may explain the cue reactivity observed during neutral beverage cue (water) presentation during our psychophysiological cue reactivity task (Chapter Two and Chapter Three); particularly for the severely dysregulated alcohol dependent and ALD samples in Chapter Three. While water

beverage stimuli have been used previously in cue reactivity studies (Monti et al., 1987; Monti et al., 1999), physiological arousal to alcohol cues have been attributed to general appetitive characteristics (Reid et al., 2006), and examination of appetitive response also identified general arousal to appetitive stimuli (such as high-caloric food cues) alongside alcohol cues in alcohol dependent drinkers (Naqvi et al., 2015). Relatedly, alcohol dependent patients rated "neutral" beverage image stimuli (e.g., water, soft drinks) used in an a cue activation task as more arousing, but less pleasant than alcohol cues (Wrase et al., 2002), indicating that appetitive stimuli do not have to be appealing to elicit arousal. Accordingly, control beverage image cues were not employed in the fMRI alcohol cue reactivity task (Chapter Five), instead using affectively neutral and abstract control cues to avoid eliciting an overall appetitive response, as also addressed in related studies implementing the same stimuli (Beck et al., 2012; Grüsser et al., 2004; Wrase et al., 2002), to avoid a potential confounding response to supposedly neutral beverage image stimuli.

As the cues used in the psychophysiological cue reactivity tasks in Chapter Two and Chapter Three were tangible beverage cues that present several cue modalities to the participant, such as visual, olfactory, and tactile stimuli, the ecological validity of these cues should sufficiently signal a potential drinking situation and potential reinforcement (participants only instructed "not to drink") and elicit overall arousal. Employing a further control stimulus during the cue reactivity task that elicits arousal, such as high-caloric food (Naqvi et al., 2015), or sexual or aversive stimuli (Childress et al., 2008), could further confirm whether the observed appetitive responses to water were due to associated, generalised cues related to alcohol, or a general dysregulated appetitive response driven by an overactive impulsive system.

Thus, a second explanation for the observed overall cue reactivity is that it is associated with a maladaptive impulsive system response, rather than one that is alcohol-

specific. Dual-process models of addiction posit overactive motivational and reward pathways that elicit impulsive/motivational drives signalled by salient cues, coupled with dysfunctional reflective system processes inadequately regulating these responses appropriately (Bechara, 2005; Lubman et al., 2004; Wiers & Stacy, 2006b). However, chronic alcohol consumption can disrupt this mesocorticolimbic neurocircuitry, at cellular, neuronal, and structural levels (Goldstein & Volkow, 2011; Koob & Volkow, 2009), with evidence of a specific vulnerability of the prefrontal cortex which may be a key area for regions involved in regulation within the reflective system. Some of these implications and supporting evidence from the program of research will be discussed in detail later in this chapter.

Evidence of regulation in our alcohol use disorder samples.

A key methodological strength of this body of research expanded the traditional cue reactivity procedure by incorporating recovery periods after cue offset to further capture regulatory processes of impulsive system responses. While several cue reactivity studies focus upon the eliciting strength of cues when presented and associated physiological responses such as HRV (Garland et al., 2012; Ingjaldsson, Laberg, et al., 2003; Witteman et al., 2015), the focus relies upon baseline differences cue reactivity for those with AUD. However, measuring the physiological responses after cues are removed (cue offset) and no reinforcement is forthcoming should provide superior information of regulation of responses, as elicited cue responses are dampened by underlying regulatory processes to return to a baseline level (i.e., a "recovery effect"). The addition of a recovery period was thus a critical implementation to effectively measure regulatory processes using indices such as HRV within different samples of dysregulated drinkers in Chapter Two and Chapter Three, and to assess the influence of factors that may be involved in regulation, such as executive functioning. While results have been addressed in some detail within respective studies, the overall findings are addressed and integrated here.

A recovery effect after cue offset should be evidenced by the return of psychophysiological indices to baseline levels (also known as "resting state") prior to presentation of the cues (Garland, 2011; Weber et al., 2010). Therefore, reduced or delayed recovery effects after observing elevated cue-elicited responses would suggest impaired regulation of cue reactivity responses (Segerstrom & Nes, 2007). Furthermore, if executive functioning is a significant component in the regulation of responses to cues in AUD, associations between executive functioning deficits (i.e., worse performance in neuropsychological tasks) and reduced recovery effects would elucidate this link. There was evidence of recovery effects exhibited by a return to baseline levels in HRV during the recovery periods following elevated responses to cue presentations. This was demonstrated in the non-treatment-seeking nonclinical drinkers (Chapter Two) and the clinical dysregulated alcohol dependent drinker sample (Chapter Three). Specifically, recovery effects were seen in changes in high-frequency HRV toward baseline levels, indicating increased parasympathetic activity during recovery periods, which can be attributed to the regulation of elevated physiological responses after the cue offset (Ingjaldsson, Laberg, et al., 2003; Segerstrom & Nes, 2007).

Notably, the ALD drinkers did not exhibit changes in parasympathetic system responses across the cue reactivity task compared to the alcohol dependent group (Chapter Three), displaying an overall pattern of limited parasympathetic activity across the task instead. This may indicate maladaptive autonomic nervous system inflexibility as per the neurovisceral integration model (Thayer & Lane, 2000; Thayer & Lane, 2009), and may reflect incapacity to appropriately react to eliciting environmental cues. Moreover, this may be evidence of an "allostatic state" of functioning (Koob & Le Moal, 2001), whereby chronic alcohol consumption has shifted ALD patients' physiological functioning to a new set point—resulting in overall inflexibility of autonomic nervous system activity. Considering this ALD

sample were severely dysregulated drinkers that fail to regulate consumption despite significant negative drinking consequences, these results suggest that individuals may continue to drink as an outcome of the incapacity of a dysfunctional reflective system response to effectively counter a consistently dysregulated, impulsive system allostatic state.

Few studies have evaluated psychophysiological regulation after cue offset in clinical samples, instead focussing primarily on the motivational correlates during presentation (Carter & Tiffany, 1999), or employing psychophysiological measures that only capture gross arousal or stress response (Monti et al., 1999). Two studies that have examined dynamic parasympathetic recovery post cue-offset indexed by HRV observed some recovery effects, but the magnitude of cue reactivity and subsequent recovery was not clearly distinguishable in one study (Garland, 2011), and an alcohol-specific recovery could not be determined due to the absence of a recovery period between stress and alcohol cue exposures in the other study (Garland et al., 2010). The cue reactivity task implemented in this body of research addresses these issues, with subsequent recovery periods after each cue type allowing for delineation of whether motivational responses and consequent regulation are specific to cue type or more generalised. However, as addressed earlier, these discrete recovery periods demonstrated overall cue reactivity to both water and alcohol cues in the psychophysiological cue reactivity task applied in Chapter Two and Chapter Three, likely due to the shared characteristics intrinsic to water and alcohol. Implementing discrete recovery periods thus provides greater specificity to isolate the alcohol-specific response from overall general appetitive arousal to stimuli that arises from the the conditioning of otherwise neutral cues.

Evidence for relationship between executive functioning and impaired regulation in alcohol use disorder.

Several models of addiction posit a significant role of executive functioning in appropriate regulation of substance use (Bechara, 2005; Goldstein & Volkow, 2002;

Goldstein & Volkow, 2011; Heatherton & Wagner, 2011; Koob & Volkow, 2009). There was evidence to suggest a role of executive functioning in regulation of motivational impulsive system responses. Importantly, a relationship between executive functioning ability and underlying regulatory processes during cue reactivity tasks was identified, with better neuropsychological executive functioning task performance associated with greater overall recovery effects within the nonclinical non-treatment-seeking drinker sample for those with more severe alcohol use problems (Chapter Two). The application of domain-specific tasks based upon the unitary/diversity theoretical framework of executive functioning (Miyake & Friedman, 2012; Miyake et al., 2000) distinguished that only greater common-executive functioning domain ability (indicated by better Stroop task performance) was associated with better recovery effects during the cue reactivity task. This indicates a potential protective role of executive functioning ability in the appropriate regulation of cue-elicited responses in non-clinical non-treatment-seeking drinkers (Chapter Two), and suggesting a specificity in executive functioning deficits related to appropriate regulation of motivational responses to cues.

Empirical research has previously identified executive functioning deficits using a range of neuropsychological tasks in clinical AUD samples (Noël et al., 2001; Ratti et al., 2002; E. V. Sullivan et al., 2000). One study has also applied the unitary/diversity model as a conceptual framework to identify discrete executive functioning deficits in heavy social drinkers compared to light drinkers (Montgomery et al., 2012). Chapter Two further extends this finding and examines whether executive functioning ability is associated with regulation of salient responses to cues, identifying a unique association of common-executive functioning domain capacity and appropriate regulation during exposure to salient alcohol cues. This draws together observations of executive functioning in these dysregulated drinker samples and models (i.e., a dual-process models) that posit a role of executive functioning in

regulatory processes, and attempted to directly assess these relationships. Furthermore, while cue reactivity has been linked with automatic cognitive processes involved in AUD—such as attentional bias to alcohol cues (Garland et al., 2012)—these results suggest that deficits in basic executive functioning components may underlie maladaptive regulation.

If executive functioning is significantly implicated in the appropriate regulation of responses to cues in AUD, then this should be evident in severely dysregulated samples through deficits in executive functioning coupled with reduced capacity to regulate cue-elicited responses effectively, particularly during recovery periods after cue offset. As such, we employed chronic drinkers with ALD, who typify a significantly dysregulated subset of drinkers as they have difficulties regulating their intake, even with evidence of significant negative health consequences from drinking. Additionally, we recruited a comparison group of drinkers with alcohol dependence, but no significant health problems, to sufficiently control for intake and severity of alcohol problems that may interact with executive functioning ability.

When assessing the role of executive functioning in our ALD sample, no supporting evidence was seen associating executive functioning with the overall recovery effects observed in the alcohol dependent and ALD samples in Chapter Three, or differences between the groups. However, as identified, these samples may represent the same subphenotype of severely dysregulated drinkers: both groups exhibited similar drinking profiles including severity of alcohol problems and experienced drinking consequences, albeit with ALD demonstrating higher consumption levels. Assessing these individuals as a combined sample may have been more informative, coupled with more comprehensive measurement of the frequency of negative consequences and physical outcomes of dysregulated drinking in these participants, as we identified that the lifetime DrInC lacked the sensitivity to capture the range of severe physical symptoms (e.g., pain, jaundice, bloating, vomiting blood) experienced by

ALD patients. Furthermore, consistently worse cognitive deficits were not seen in the ALD sample than in the alcohol dependent group. While ALD patients demonstrated worse Trails performance, there were no significant differences compared to the alcohol dependent patients for Stroop task performance (Chapter Three) or behavioural performance of the IGT task (reflecting decision-making processes) (Chapter Four). Both clinical samples were considerably impaired across the IGT task, with a significant proportion performing below other alcohol and substance use samples (Barry & Petry, 2008; Bechara & Damasio, 2002; Noël, Bechara, Dan, Hanak, & Verbanck, 2007) and comparably to VMPFC-lesioned patients who are severely impaired on the task (Bechara & Damasio, 2002; Bechara et al., 1999). This may reflect poor drinking choices toward immediate gratification through drinking over longer-term rewards associated with reducing consumption, and leading to difficulty in self-regulating drinking appropriately. Taken together, this suggests the ALD and alcohol dependent groups were not sufficiently delineated through neuropsychological executive functioning tasks, suggesting that these groups differ primarily in the negative outcomes experienced from their dysregulated drinking, rather than separate subphenotypes of drinkers.

An interesting finding was the impairment exhibited by our dysregulated drinker samples in anticipation of risky choices with potentially negative outcomes during the IGT in Chapter Four. Furthermore, the measurement of this anticipatory autonomic arousal (as indexed by skin conductance response) in expectancy of reinforcement from risky choices with potentially negative outcomes identified differences within the alcohol dependent drinkers accorded with experienced drinking consequences. These anticipatory responses were reduced for alcohol dependent participants who reported more negative drinking consequences, compared to alcohol dependent participants who reported with fewer negative consequences. Moreover, ALD patients demonstrated minimal autonomic responses overall. A similar pattern of impairment was also seen for responses after reinforcement signalling

negative outcomes. Taken together with the observed reduced anticipatory SCR to risky choices with negative outcomes, this suggests the alcohol dependent participants with significant experienced negative drinking consequences and ALD patients may not adequately identify or learn from negative consequences that may be used to inform future choices toward advantageous options (Bechara & Damasio, 2002).

This may reflect impairment in decision-making regarding drinking, resulting in poorer drinking choices and thus considerable negative outcomes (Bechara, 2005). Decision-making is a complex cognitive process that involves several executive functioning domains to appropriately assess and review choices while accounting for the wider context, to select the optimal response (L. Clark et al., 2004). Integrated learning and working memory processes are required to comprehend and encode task relevant negative outcomes, to inform future similar events requiring choices toward positive outcomes (L. Clark & Robbins, 2002; Rahman, Sahakian, Cardinal, Rogers, & Robbins, 2001; Séguin et al., 2007). Reduced emotional signalling after negative outcomes during the IGT may therefore serve as an index of dysfunctional learning of negative consequences, as lack of somatic arousal reaction suggests reduced capacity to react appropriately to negative outcomes. This may be mirrored in real-world drinking outcomes: individuals may not effectively learn from experienced negative drinking consequences, and thus not develop appropriate anticipatory responses to potentially risky choices with poor outcomes.

As these individuals do not perceive negative consequences of their choices (such as continued drinking), this may lead to dysregulated consumption and potentially recurring negative drinking consequences. Furthermore, the appetitive strength of cues inherent in drinking choices are robust when compared with controlling or resisting drinking which might lead to positive consequences that are less diffuse (e.g., maintaining jobs or relationships, avoiding hangovers), and this cue strength can lead to immediate gratification through

drinking over longer-term goals (Heatherton & Wagner, 2011). Resisting the temptation to drink involves reflective system processes to adequately select and plan strategies, weighing up and comprehension of available options, and dampening the responses from the impulsive system (Le Berre et al., 2017). Thus, the decision-making deficits and reduced physiological responses to risky choices and negative outcomes seen in the ALD participants, and in alcohol dependent samples concordant with a significant history of negative drinking experiences may indicate a maladaptive reflective system that does not adequately incorporate negative consequences of previous choices (such as dysregulated drinking occasions) to inform future decision-making situations (such as controlling consumption), in order to avoid further negative outcomes.

Converging executive functioning and neural correlates of prefrontal activity in regulation.

A consistent theme observed within the results was the association of Stroop task performance and responses during alcohol cue exposure—both for cue reactivity (Chapters Two, Three, and Five) and during regulation after cue offset (Chapter Two). Notably, greater Stroop interference scores was associated with poorer overall regulation to cues for participants with greater AUD severity in the non-clinical non-treatment-seeking drinkers (Chapter Two). Furthermore, clinical alcohol dependent participants with better Stroop performance exhibited dynamic cue reactivity parasympathetic responses during cue exposures, compared to those with worse performance and ALD patients who demonstrated little overall reactivity (Chapter Three). Finally, corresponding neural correlates of BOLD activity within alcohol dependent participants during the fMRI alcohol cue reactivity task (Chapter Five) showed reduced prefrontal activation in the right DLPFC of participants with worse Stroop performance that also had greater AUD severity, indicating a functional region

potentially significant in the effective regulation of cue-elicited impulsive system responses (Chapter Five).

The DLPFC has been implicated in several higher order executive functions crucial for decision-making and goal-directed behaviour, such as self-control in social contexts (Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006) and during choice selection (Hare, Camerer, & Rangel, 2009), future action planning (Mushiake, Saito, Sakamoto, Itoyama, & Tanji, 2006), and integration of time-dependent information (Barraclough, Conroy, & Lee, 2004); processes which are relevant to choices involving alcohol consumption and regulation of drinking behaviours. Furthermore, indirect evidence that DLPFC activity was negatively correlated with higher alcohol cue-activation in mesocorticolimbic reward and motivational structures (e.g., the caudate nucleus) observed in Chapter Five suggests that hypoactivation and/or dysregulation in the right DLPFC may be associated with increased impulsive, motivational responding to salient cues.

This distinction of DLPFC dysregulation has been demonstrated using functional connectivity analyses in alcohol dependent patients, whereby reduced modulation of right DLPFC and striatal connectivity during a fMRI reward task was associated with abnormal decision-making and predicted learning impairment and regulation of craving (S. Q. Park et al., 2010). Increased DLPFC activity was also evidenced when healthy participants were instructed to use explicit cognitive strategies to actively regulate reward expectations, with corresponding reduction in arousal when regulating versus merely attending to the reward stimulus, as indexed by skin conductance response (Delgado, Gillis, & Phelps, 2008). Additionally, increased DLPFC activity accorded with reciprocal reductions in striatal activity in smokers when instructed to deliberately cognitively regulate reactions to drug cues (Kober et al., 2010). Thus, reduced DLPFC activity may reflect impaired regulatory capacity for alcohol dependent participants with significant alcohol problems exhibited in Chapter Five,

though the lack of behavioural drinking outcomes limits the conclusive linking of these neural regions.

Relatedly, impairment in reward processing and anticipation of risky choices seen in Chapter Four has been linked with dysregulation of frontocortical areas, leading to suboptimal reward choices. Smaller immediate rewards were preferenced over longer-term rewards with greater gain in the ALD and alcohol dependent samples, reflecting incapacity to delay gratification which is commonly associated with alcohol and drug use disorders (Koob & Volkow, 2009). Considering the critical role the DLPFC has in reward processing and appropriate choice selection (Hare et al., 2009; S. Q. Park et al., 2010), the impaired decision-making seen in both alcohol dependent and ALD clinical samples during the IGT may relate to impairment in lateral frontal regions, as well as impaired somatic responses after punishment outcomes signalling incapacity to appropriately react to negative consequences. Future research implementing reward-based fMRI tasks in AUD samples, coupled with identification of somatic arousal as seen in Delgado et al.'s (2008) study may elucidate this suggested overlap of brain regions through concordant functional neural correlates. Interestingly, positive correlations between dysregulated drinking and alcohol-related decision-making in an AUD sample were associated with hyperactivation of the reward pathways rather than underactivity of regulatory neural systems (Stuke et al., 2016), demonstrating that further comprehensive measurement is required to elucidate the role of these systems. Furthermore, identifying overall impairment of regions such as the DLPFC to non-alcoholic cues may provide further support as to whether this dysfunction is limited to an alcohol-specific mechanism, or more likely overall regulatory mechanism is affected.

Conceptual models of regulation in addiction.

This converging neuropsychological and functional neuroimaging evidence implicating prefrontal regions accords with models of addiction. Koob and Volkow (2009)

outline the prominence of the DLPFC, along with the inferior frontal cortex and hippocampus, as key regions that undergo significant neuroadaptation across the stages of addiction (particularly the preoccupation/anticipation stage). Further, these regions are heavily involved in cognitive control, representation of drug-related memories, and appraisal and regulation of subjective states such as craving (Koob & Volkow, 2009). Relatedly, prefrontal cortex dysfunction is central to Goldstein and Volkow's (2002) impaired response inhibition and salience attribution (I-RISA) model of drug addiction, predicating a combination of increased drug cue salience attribution, decreased non-drug reward sensitivity, and reduced capacity to appropriately inhibit maladaptive or detrimental behaviours—thus leading to severely dyregulated drug-use. The relevance of this model was shown through a meta-analysis of imaging studies (fMRI and PET) that provided supporting evidence of activation across several task modalities comparing drug use samples and healthy controls, indicating activity changes related to neuropsychological features of addiction in functional regions of the prefrontal cortex (Goldstein & Volkow, 2011). In particular, executive functioning impairment (e.g., diminished inhibitory control) reduces an individuals' capacity to control alcohol intake, regulate motivational impulses signalling excessive craving, or successfully maintain abstinence (Goldstein & Volkow, 2011). Therefore, the common-executive functioning impairment demonstrated in our nonclinical drinker samples (Chapter Two), and neural modulation identified in the DLPFC of the clinical alcohol dependent participants (Chapter Five) may help explain the progression and maintenance of AUD, due to the reduced capacity to appropriately regulate responses to cues and consequently control impulses to consume alcohol.

The results of the cue reactivity tasks applied in Chapter Two and Chapter Three also provide some support of the two-system construct posited in dual-process model of addiction, as exhibited by the dysregulation of the impulsive system (i.e. increased psychophysiological

responses) through dysfunction of the reflective system (which includes executive functioning) (Bechara, 2005; Lubman et al., 2004; Wiers & Stacy, 2006b). However, while dual-process models have an appeal in the simplicity of theoretical explanation of opposing system processes, the findings of this body of research, and multiple components outlined by neurobiological models suggest there exists a complex interaction of these systems at many layers—comprising competing, complimentary, and potentially augmentative underlying processes. For example, while neural correlates revealed in alcohol dependent individuals in Chapter Five suggest the DLPFC may be a key functional area in the regulation of cue-elicited responses, as signalled by the impulsive system during alcohol cue reactivity, the versatility and functional heterogeneity of the prefrontal cortex allows for significant adaptation of other areas to compensate for dysfunctional regions (Chanraud et al., 2010; Dao-Castellana et al., 1998). Therefore, these recruited areas (such as the DLPFC) may subsequently fulfill the intended function through compensatory neural processing, which is indicated by different brain activation patterns both during tasks and when comparing drinking samples (Bates, Buckman, & Nguyen, 2013). This has been observed in both long-term abstinent alcohol dependent patients during resting state connectivity (Camchong, Stenger, & Fein, 2013b), including predicting relapse in short term abstainers at a 6-month follow-up (Camchong, Stenger, & Fein, 2013a); and shown during functional neuropsychological tasks (Chanraud, Pitel, Müller-Oehring, Pfefferbaum, & Sullivan, 2013; Chanraud et al., 2010) . Implementing techniques such as these in future research is therefore required to better understand the interaction of these theoretical impulsive and reflective systems, and to accurately associate functional processes to mechanisms of action (e.g., neural, cellular, neurotransmitter targets) which may be overlapping and/or supplementary. Optimistically, further integration of techniques within human populations combined with preclinical research will serve to elucidate mechanisms of action that interact at a micro (i.e.,

neurotransmitter, cellular) and macro (regional brain activation) level, as well as further converging evidence of multiple measurement techniques—such as those implemented in this program of research—will help to isolate specific processes and interactions.

Relatedly, there are also overlapping components underlying the neural structures involved in the integrative models of autonomic nervous system regulation for both cardiovascular and skin conductance psychophysiological indices, and the structural/functional neurocircuitry implicated in addiction models. The neurovisceral integration model posits a set of neural structures including the medial prefrontal cortex and extended amygdala in appropriately perceiving cued threats or stressors and appropriate downstream regulation of peripheral responses to galvanise an organism into action (Thayer et al., 2012). Similarly, the somatic marker hypothesis (Bechara & Damasio, 2005; Damasio, 1994) advocates this neurocircuitry in optimal decision-making through the representation of somatic states that guide advantageous choices, such as anticipatory response to risky choices which were impaired in our clinical AUD samples in Chapter Four. It unclear whether alcohol use affects these sets of neural structures directly via non-discriminatory structural brain damage and indirect processes (Butterworth, 1995a; Harper, 2009), or whether this reflects premorbid deficits in AUD individuals which may thus lead to progression of the disorder. However, reduced faculty of these neural networks to function effectively—for example, reduced anticipatory responses to risky choices and punishment responses in alcohol dependent and ALD clinical samples in Chapter Four—suggest that dysfunction of these processes can disrupt appropriate regulation, such as autonomic parasympathetic nervous system activity, and may lead to poorer drinking outcomes. The measurement of several physiological and psychophysiological indices in this thesis has identified that there are several underlying processes that are affected or dysfunctional in our AUD samples, and that there is some considerable overlap in the constructs of these models. In summary, it is

apparent that better identification of crucial and common components of these systems and their interactions across the stages of AUD, including further elucidating the role of executive functioning within these systems needs to be established.

Methodological considerations: Timescale of regulation.

A major strength of this thesis was the application of several measurement techniques to capture psychophysiological and functional neuroimaging indices of regulatory processes. This allowed us to identify several underlying processes that were related to regulation of cue-elicited responses to different cue modalities. Employing tangible water cues as a beverage control during the psychophysiological cue reactivity task in Chapters Two and Three provided specificity of the cue responses to help identify whether responses and subsequent regulation were specific to alcohol, or a general appetitive reaction to cues.

However, the timescale of regulation is unclear both within the studies, and when comparing the different indices measuring indirect underlying regulatory processes. We did not find evidence of an alcohol-specific delay or reduction in recovery effect that would have suggested impairment in regulatory responses to alcohol cues, rather exhibiting an overall appetitive response and consequent regulation. This may be due, in part, to the timescale dictating the measurement of regulation we employed. For example, HRV assessment in Chapter Two and Chapter Three measured the magnitude of HRV response as a mean of overall HF HRV parasympathetic activity. However, as demonstrated in Chapter Four using area under the curve analyses of SCR, psychophysiological responses to stimuli and reinforcers may be rapid; and regulation of impulsive responses may be transient, such as the cue-elicited brain activation identified by changes in BOLD activity which is apparent within several seconds of cue onset.

Accordingly, indices of regulation may not be identifiable across an averaged measurement period comprising several minutes, as applied during the psychophysiological

cue reactivity task version used in Chapter Two and Chapter Three. Spectral analytic techniques used to categorise high-frequency HRV require a minimum number of heart-beat oscillations for reliable measurement, with a recommendation of at least two minutes to confidently delineate heart rate frequency bands (Berntson et al., 1997; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Despite this, some studies have implemented event-related HRV measurement that ostensibly captures sufficient information within a much lower epoch (i.e., 8-sec), within social obedience tasks (Slater et al., 2006) and a study employing a cue reactivity task using alcohol advertisement cues in an alcohol dependent sample (Witteman et al., 2015). Although the reliability of the technique is not yet determined, and these studies are preliminary, this method may allow for the timecourse of regulation indexed with HRV to be measured, particularly after cue-offset. In conjunction with this, measuring the magnitude and length of the cardiovascular response is possible, which would provide information of the response time to cues over longer periods of time (Brosschot, Gerin, & Thayer, 2006). However, this requires more comprehensive measurement of the timecourse of cardiovascular markers across the day, pre- and post-cue presentation. This would provide an accurate representation of a true baseline as well as the full range and perseverance of cue responses (Pieper et al., 2010), and could be achieved in future studies using personal heart rate sensors to collect 24-hr beat-to-beat data, thus allowing better specificity of the timecourse of cue effects.

Cognitive Dysfunction in Alcohol Use Disorder

This research has demonstrated executive functioning is associated with regulation of motivational, impulsive responses in AUD. Further, we have specified discrete executive functioning domains, and functional neural correlates that may underlie incapacity for individuals with AUD to regulate these responses appropriately. However, this thesis cannot

clarify whether executive functioning dysfunction is a vulnerability factor that predicates AUD (e.g., impaired response inhibition), is the result of alcohol-related insult from chronic consumption (e.g., alcohol-related brain damage), or due to other causes. Investigating executive functioning as a predictor of alcohol use and alcohol-related problems from a developmental perspective, particularly using at-risk samples such as adolescents with family history of alcoholism is one avenue of research that may identify premorbid cognitive deficits. While some evidence suggests differences in cognitive functioning, such as response inhibition and working memory (Bjork, Hommer, Grant, & Danube, 2004; Nigg et al., 2004; Schweinsburg et al., 2004; Wetherill et al., 2013) may relate to AUDs, studies are often cross-sectional, comprising small sample sizes that limit definitive conclusions (D. B. Clark, Thatcher, & Tapert, 2008). Large-scale, prospective studies employing samples that have not developed alcohol use have found worse response inhibition in high-risk adolescents and predicted future alcohol-related problems (Nigg et al., 2006), and pre-existing working memory impairment was associated with later alcohol use frequency, mediated by impulsivity (Khurana et al., 2013). However, these observed effects were modest, and require further research. Indeed, there is mixed evidence delineating cognitive dysfunction resulting from alcohol use disorder versus existing premorbid or developmental deficits that are a vulnerability factor that can lead to the occurrence or progression toward disorders such as AUD (Schulte et al., 2014). Complimenting these neuropsychological measures with indices of psychophysiological responses to alcohol, such as an fMRI cue reactivity task (Brumback et al., 2015) and/or neuroimaging executive functioning task performance (Hu, Zhang, Chao, Krystal, & Li, 2016) in adolescent samples, and evaluating their associations with subsequent dysregulated alcohol behaviours may allow us to better identify whether executive functioning deficits at earlier stages of development predicate significant negative alcohol problems in at-risk samples.

A major contributing factor to consider in this program of research is the relationship between observed executive functioning deficits and biological impacts from alcohol consumption. Structural changes to both grey and white matter have been demonstrated in samples of differing severity and stages of AUD (Cardenas et al., 2005; De Bellis et al., 2005; Fein et al., 2002; Jernigan et al., 1991; O'Neill et al., 2001; Pfefferbaum et al., 1992; Pfefferbaum et al., 2009; Pfefferbaum et al., 1997; K. W. Smith et al., 2017), ostensibly through several direct (i.e., cellular/neuronal toxicity) and indirect (e.g., hepatic encephalopathy from liver damage, nutritional issues) pathways (Butterworth, 1995a, 2007; Harper, 2009; Harper & Matsumoto, 2005). To mitigate potential alcohol-related brain damage as a confounding factor, we employed a non-clinical sample with a range of consumption patterns when assessing domain-specific executive functioning in alcohol cue regulation in Chapter Two, yet we cannot rule out the potential for alcohol-related brain damage in this sample considering some participants reported significant AUD problems. Furthermore, there is a high likelihood of some alcohol-related damage in our severely dysregulated clinical ALD patients. This was controlled for using a matched sample of alcohol dependent participants with a similar history of alcohol consumption, and our sample exhibited relatively low disease severity on measures of liver function (Chapter Three and Chapter Four). Despite this, differences in psychophysiological indices and associations with executive functioning seen in the ALD patients may be due to brain damage to crucial areas within the prefrontal cortex, which is particularly vulnerable to damage from chronic consumption (Harper & Matsumoto, 2005), even at moderate levels (Topiwala et al., 2017). The possibility of alcohol-related brain damage is unavoidable to some extent when recruiting drinkers with a range of dysregulated drinking behaviours. However, it is a major caveat when considering conclusions of the associations of executive functioning and regulatory processes of AUD, as both can be uniquely impacted by this damage.

Clinical and treatment implications.

It is increasingly accepted that AUD is a heterogeneous syndrome, with a multitude of biological, environmental and genetic factors that predispose individuals to continue to consume alcohol, for different reasons, and in different patterns (Litten et al., 2015). Identification of subphenotypes of AUD is important, as individual subtypes may indicate different aetiology, and may respond better to specific treatment approaches (Litten et al., 2015). We have shown that psychophysiological indices can inform of impulsive system responses to cues, and subsequent reflective system regulatory processes across the studies comprising this program of research.

One implementation of cue reactivity tasks is in the evaluation of the efficacy and mechanisms of action in pharmacological treatments of AUD in attenuating symptoms such as craving, and reducing intake in several pharmacological targets (Hammarberg, Jayaram-Lindström, Beck, Franck, & Reid, 2009; Hutchison et al., 2005; Leggio et al., 2013; McGeary et al., 2006; Monti et al., 1999). However, they largely measure overall arousal (e.g., mean arterial pressure, (SCL), stress (cortisol) response and gross cardiac activity via HR; whereas we have shown that HRV better captures parasympathetic autonomic activity indicating underlying regulation of cue responses (Chapter Three).

Additionally, a recovery period following alcohol cue exposure is often omitted, which we have demonstrated can inform of specific alcohol-related reactivity and regulation versus overall arousal, or contrastingly, an overall attenuated response to eliciting cues reflecting overall regulatory dysfunction. Measuring regulation of alcohol cue responses in pharmacological treatment samples using cue reactivity paradigms may thus provide further confirmation of the effects of treatment response. Furthermore, as the direct (e.g., pharmacological action sites such as dopamine receptors) and indirect effects (e.g., sedation) of pharmacotherapies for AUD are varied and often non-specific, the identification of

regulation mechanisms that may be modulated by the treatment, and subsequent measurement of psychophysiological indices for changes during treatment regime may better inform treatment effectiveness and method of action. Alongside measurement of electropsychophysiological indices to inform treatment response, implementation of brain imaging cue reactivity tasks to investigate the functional modulation of drug treatments is also being explored (for a review, see Courtney, Schacht, Hutchison, Roche, & Ray, 2016; Langosch et al., 2012; Lukas et al., 2013; Mann et al., 2014; Schacht, Anton, Randall, et al., 2013). This indicates the increasing application of psychophysiological and neuroimaging biomarkers to augment standard biological measures and more comprehensively identify the neurocircuitry implicated in maintaining AUD.

There is also recent interest in developing strategies and interventions from the perspective of the dual-process model that aim to improve reflective system processes, either by addressing executive functioning deficits, or improving and augmenting existing executive functioning ability to control an overractive impulsive system (e.g., Brooks et al., 2017; Houben, Wiers, & Jansen, 2011; Wanmaker et al., 2017). The effectiveness of various techniques of "boosting" executive functioning to improve behavioural drinking outcomes have been mixed, partly due to an early reliance on traditional neuropsychological performance outcomes, differing treatment modalities, and the range of conceptual models which treatments were initially based upon (Bates et al., 2013). However, a shift toward a more holistic approach that incorporates other influencing factors (i.e., social, intrapersonal), measurement of long-term efficacy in both clinical and nonclinical drinker samples, and better identification of the wide range of alcohol-related problems within individuals that allow for tailored treatment approaches may lead to more considerable cognitive-based treatment outcomes.

Relatedly, accurate identification of potential executive functioning deficits in individuals with AUD is important, as treatment outcome may be influenced by executive functioning ability in AUD. Psychosocial interventions arguably require the engagement of complex cognitive processes (e.g., working memory, response inhibition) for comprehension and improving treatment adherence (Le Berre et al., 2017), although surprisingly there is limited research investigating this in AUD (Bates et al., 2013). Executive functioning deficits and/or neurocircuitry dysfunction resulting from chronic alcohol consumption may potentially compromise the effectiveness of psychosocial treatments, and lead to poorer outcomes, though factors influencing treatment outcomes are complex, and it can be difficult to isolate attributing effects of cognitive impairment (Bates et al., 2006). A study investigating coping skills treatment outcomes in participants with substance use disorder (Kiluk, Nich, & Carroll, 2011) found that better cognitive functioning assessed through tests prior to treatment related to better coping skills after eight weeks compared to treatment-as-usual. Additionally, a study examining motivational interviewing treatment efficacy versus a standard education intervention in alcohol- and marijuana-using adolescents (Houck & Feldstein Ewing, 2017) showed poorer treatment response for the standard intervention was associated with low working memory capacity for alcohol use only, whereas motivational interviewing outcomes were not affected by working memory capacity. Therefore, better identification of underlying regulatory mechanisms and associations with cognitive functioning, which was a primary aim in this thesis, will assist in understanding what factors may affect treatment efficacy and better inform these treatment techniques, which may help tailor treatments toward individuals who may be more receptive to specific approaches.

Relatedly, non-cognitive treatment approaches addressing regulation of AUDs that implement psychophysiological techniques are also being explored. Our research has added supporting evidence of the versatility of psychophysiological indices for informing of

underlying regulatory processes in individuals with AUD, including HRV and functional imaging indices. Biofeedback techniques that indicate a real-time change in these psychophysiological indices may increase regulatory processes linked to control of these physiological mechanisms. For example, instructing participants to try to regulate via downstream parasympathetic system modulation of heart rate, and indicated in real-time with HRV changes, has shown improved outcomes in biological and physiological health conditions such as asthma and hypertension (Lehrer et al.; McCraty, Atkinson, & Tomasino, 2003) and other mental disorders including depression and trauma (Karavidas et al., 2007; Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009). There has been little research investigating HRV biofeedback in AUD, though a recent pilot study of brief HRV feedback training in inpatient substance use disorder patients showed some potential reductions in reported craving than treatment-as-usual (Eddie, Kim, Lehrer, Deneke, & Bates, 2014), though the effect on craving was not conclusive, and the sample size was restrictive. Replication of this method within a randomised control trial using a large sample of AUD patients with similar dysregulated drinking profiles is a promising future research direction.

Similarly, implementation of real-time biofeedback has been adapted for functional imaging. This involves conveying a representation of real-time brain region activity visually to the participant, who is actively attempting to employ regulation strategies during fMRI while receiving feedback of corresponding BOLD signal to indicate “successful” changes in brain activity. Decreased ventral striatum activity during alcohol cue presentation was seen in heavy social drinkers receiving this mode of biofeedback versus a sham group (Kirsch, Gruber, Ruf, Kiefer, & Kirsch, 2016). This feedback presented was not real-time, however, but was delayed feedback of regional BOLD activity from preceding cue block modelled from traditional fMRI cue reactivity designs. However, an elegantly designed study of alcohol dependent patients undergoing single-session neurofeedback training (Karch et al., 2015)

implemented real-time feedback during cue presentation, using functional ROIs first identified using regional activity from a preceding cue reactivity stage—reduced neural activation was seen in prefrontal regions (ACC, medial frontal gyrus), insula, and temporal areas, with corresponding reduced self-reported craving. Determining any long-term effects of these techniques and concurring neural functioning with drinking outcomes is an important next step.

Other non-invasive imaging and neural modulation techniques may supplement these techniques identifying on-line regulation and allow us to better ascertain the proposed underlying neurocircuitry and further isolate specific effects of eliciting cues. For example, functional near-infrared spectroscopy is another measurement modality that provides information of cortical neural activity, yet is a portable and relatively cheaper technology than MRI that can potentially allow for testing outside the laboratory and confines of an MRI scanner (Bunce, Izzetoglu, Izzetoglu, Onaral, & Pourrezaei, 2006). Corroborating evidence of regulation and cortical activity (e.g., DLPFC activation) to alcohol cues has been shown in AUD participants (Ernst et al., 2014) and the modality's portability potentially allows for field research (such as a participants' favourite bar or during social drinking situations) increasing the ecological validity and range of the eliciting environmental cues. Advances in virtual reality technology within this decade also provides an immersive experience of cue exposure, again increasing the ecological validity of the cues while maintaining high experimental control, and has utility in treatment techniques such as cue exposure therapy (Hone-Blanchet, Wensing, & Fecteau, 2014). Virtual reality situations involving alcohol cues increased craving in drinkers and AUD samples of differing severity (Bordnick et al., 2008; Cho et al., 2008; Ryan, Kreiner, Chapman, & Stark-Wroblewski, 2010), and virtual reality has been adapted for MRI-compatible use to identify neural correlates to virtual reality cue responses in other substance use samples (Hone-Blanchet et al., 2014), which can be explored

in AUD samples. Lastly, employing transcranial magnetic/direct current stimulation techniques can allow for direct modulation of proposed key areas involved in regulation of cue-elicited responses to ascertain any changes attributed to stimulation of targeted areas (Cabrera et al., 2016). As this thesis has demonstrated, the integration techniques such as these in conjunction with the psychophysiological and neuropsychological measures such as those applied in this program of research may help further triangulate the structures involved in regulation of cue-elicited responses in AUD, and the role of executive functioning in these regulatory processes.

Limitations and Future Directions

This thesis contained significant methodological strengths that have produced innovative research questions, including: (a) sampling of range of nonclinical and clinical dysregulated drinkers; (b) employing a variety of methods including self-report, psychophysiological, functional neuroimaging, neuropsychological, and behavioural measures; (c) the application of theoretical frameworks of executive functioning and regulatory processes. However, there were some evident limitations within the empirical studies that will be subsequently addressed in greater detail.

A primary limitation of the studies within this thesis involves the small sample sizes that restrict generalisability of the findings. Practical considerations including the costs of funding larger samples, restrictive inclusion and exclusion criteria, and issues recruiting patient groups that present with severely dysregulated drinking problems and related health issues were factors that contributed to the sample sizes employed in this thesis. While the sample sizes are reflective of those reported in research literature employing similar methodologies, replication of these findings in larger representative samples should be conducted.

Another notable limitation was the lack of a control group of drinkers that represent a population who successfully regulate their consumption, which would have allowed us to examine whether executive functioning ability influenced better regulation capacity. Abstinent samples are inadequate as controls due to several changes resulting from detoxification, including time-dependent changes in mood, neurotransmitter and cellular function, and some recovery of cognitive function (Bates et al., 2013; Oscar-Berman et al., 2014). However, capturing samples of regulated drinkers that match the consumption levels of those exhibited by our dysregulated alcohol dependent and ALD drinker samples is difficult, particularly as our samples were consuming alcohol at significantly high levels per drinking day. Recruiting heavy binge drinkers who demonstrate some capacity for drinking regulation (e.g., only weekend drinking) may be a potential solution as recruited clinical samples for this study were chronic heavy drinkers, and often daily consumers. Additionally, ALD patients can suffer significant physical consequences from their condition that can deleteriously impact upon executive functioning ability and regulatory processes. Employing a sample of ALD drinkers that manage to regulate their consumption, such as post-operative transplant patients that have resumed drinking, but have not relapsed may provide a suitable comparison control.

Relatedly, the clinical samples employed in this body of research were treatment-seeking participants involved in a randomised control trial of pharmacotherapy baclofen to attenuate craving in AUD (Morley et al., 2013), which may affect self-reported craving and regulatory processes of interest. However, sampling of participants within a treatment program is common in substance use disorder research, and access to severely dysregulated patient groups can be restrictive, with patients often only approachable in treatment when more amenable to research outcomes. Further, there are clear ethical considerations in the planned recruitment of a sample of participants that may present with severe AUD without

offering a baseline treatment as a minimum. Attempts were made to limit analyses only to participants receiving the placebo treatment in the relevant studies, but restrictive numbers within the treatment trial due to drop-out and practical considerations would have reduced our sample size even further, and interactions with craving were controlled for within the statistical models to assess the effect of treatment where possible.

The focus of regulation in this thesis primarily investigated underlying processes of regulation in AUD, rather than deliberate attempts to control impulses or urges to drink, or explicit regulation strategies. Therefore, we did not account or control for explicit cognitive regulation strategies that may have been initiated by participants during the cue reactivity tasks. Research has shown that instructing participants to explicitly cognitively regulate their impulses and feelings elicited by salient cues reduced self-reported craving, and increased brain activity in regulatory regions of alcohol dependent samples (S. Q. Park et al., 2010), and in smokers (Kober et al., 2010). Future research implementing active and passive regulation stages within the cue reactivity task may reveal differences in indices of regulation according to explicit regulation strategies.

The findings presented in this thesis highlight several future research directions in addition to those already discussed. Future research employing larger samples that synthesise simultaneous, multimodal, psychophysiological and functional measurement (e.g., SCR, HRV, functional correlates) with longitudinal approaches examining cue reactivity across stages of drinking (e.g., pre- versus post-abstinence) may elucidate concurrent, competing, or complementary processes that underlie appropriate regulation in AUD individuals. Capturing the timecourse of regulation rather than the magnitude or change in regulation may reveal differences within severely dysregulated AUD samples specifically related to cognitive processes, which was not evidenced between our alcohol dependent and ALD samples. Furthermore, application of novel techniques may be useful to examine and/or isolate

components of regulatory networks in these dysregulated AUD samples: employing functional connectivity, either during resting state or during cue reactivity tasks; optogenetics to identify neural networks and downstream inhibitory processes, both in animal models and potentially in clinical samples in the future; and computer neural circuit modelling to attempt to replicate the neural networks and interactions between processes, such as any associations between decision-making deficits and regulatory parasympathetic cue-elicited deficits. Finally, taking advantage of data derived from large-scale, consortium-driven, multicentre studies investigating these factors using an array of techniques within large samples of younger populations using a longitudinal, developmental design will likely identify predictive factors that underlie subphenotypes of AUD. This includes the European-led IMAGEN study (Schumann et al., 2010), which measures neuropsychological, functional and structural imaging, and genomic techniques in adolescents to evaluate how the interaction of biological, genetic and environmental factors may predicate neuropsychiatric disorders such as AUD. Similarly, the National Consortium on Alcohol and NeuroDevelopment in Adolescence (Brown et al., 2015) in the United States focuses specifically on AUD, utilising similar methodology and oversampling adolescents at-risk samples of alcohol use problems to identify associations of developmental factors, neurocognitive development and functioning that may influence future alcohol use. The results of these large-scale studies will serve to further clarify the role of cognitive functions such as executive functioning, including executive functioning deficits as a vulnerability factor for adolescents with a family history of AUD. Further, prospective studies examining cognitive functioning prior to significant alcohol use may reveal mechanisms that predicate development of alcohol problems, and potentially identify and effectively treat of AUD in individuals with these risk factors.

Conclusion

Difficulties in self-regulating responses to alcohol cues appropriately may explain why people continue to consume alcohol at risky levels even after experiencing severe or frequent negative consequences that, unchecked, may lead to significant adverse effects to their physical and mental health, as well as social and financial problems. The studies comprising this thesis used various methods and applied cognitive and regulatory frameworks to comprehensively identify regulatory processes that underlie appropriate regulation of cue-elicited responses in AUD. This thesis reveal relationships between cognitive processes and numerous layers of underlying regulatory processes through the application of multimodal measurement of psychophysiological and functional neuroimaging indices. Gaining better understanding of how individuals with AUD may have difficulty in self-regulation of drinking through the examination of underlying regulatory processes, and key components associated with appropriate regulation of cue-elicited responses such executive functioning capacity is valuable in elucidating the progression and maintaining factors of the disorder. This body of work contributes to the literature involved in elucidating potential neurocircuitry components and underlying neurocognitive mechanisms involved in dysfunctional regulation in AUD, which are integral to better inform therapeutic interventions and identify potential neurocognitive and neuropsychological targets to advance our understanding of why individuals with this disorder continue to drink when consequences can be so deleterious.

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Appendix A

Ethics Approvals

MACQUARIE UNIVERSITY

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16 April 2014

Associate Professor Andrew Baillie
Department of Psychology
Faculty of Human Sciences
Macquarie University NSW 2109

Dear Associate Professor Baillie

RE: *The relationship between executive functioning, cue reactivity and alcohol consumption in social drinkers*

Thank you for submitting the above application to the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)) for ethical and scientific review.

The HREC (Medical Sciences) considered your application at its meeting held on 27 March 2014 and ethical and scientific approval of the above application has been granted.

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007).

Details of this approval are as follows:

Reference No: 5201400315

Approval Date: 27 March 2014

This letter constitutes ethical and scientific approval only.

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Documents reviewed	Version no.	Date
Macquarie University Human Research Ethics Committee Application Form	2.3	July 2013
Macquarie University Participant Information and Consent Form entitled *The relationship between cognition, alcohol cue reactivity and alcohol consumption in social drinkers*	1	31/02/2014
Contact email for study participation	1	31/02/2014
Task Description	1	31/02/2014
AUDIT – 10 [PSYC104 Screener 2014]	1	12/03/2014

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH DEVELOPMENT OFFICE
ROYAL PRINCE ALFRED HOSPITAL
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TELEPHONE: (02) 9515 6766
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REFERENCE: X11-0154 & HREC/11/RPAH/223
5.0/4.5/JUN11

NSW GOVERNMENT Health
Sydney Local Health Network

15 June 2011

Professor P Haber
C/- Dr S Leung
Drug Health Services
Level 6, Building 13
Royal Prince Alfred Hospital

Dear Professor Haber,

Re: Protocol No X11-0154 & HREC/11/RPAH/223 - "Exploring the efficacy and biobehavioural basis of Baclofen in the treatment of alcoholic liver disease"

I refer to Dr S Leung's correspondence of 14 June 2011.

Please be advised that the Ethics Review Committee (RPAH Zone) expressed a favourable opinion of the above study and, subject to provision by you of acceptable responses to the issues raised in the Committee's correspondence of 10 June 2011, will give ethics approval of the study.

Yours sincerely,

Lesley Townsend

Lesley Townsend
Executive Officer
Ethics Review Committee (RPAH Zone)

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NSW GOVERNMENT Health
Sydney Local Health District

14 August 2012

Professor P Haber
C/- Dr K Morley
Drug Health Services
Level 6, Building 13
Royal Prince Alfred Hospital

Dear Professor Haber,

Re: Protocol No X11-0154 - "Exploring the efficacy and biobehavioural basis of Baclofen in the treatment of alcoholic liver disease"

HREC/11/RPAH/223 **SSA/12/RPAH/350**

Thank you for submitting a Site Specific Assessment Form for this study. I am pleased to inform you that authorisation has been granted for it to be undertaken at the Royal Prince Alfred Hospital.

The approved information and consent documents for use at this site are:

- Information for Participants -Treatment Program (Master Version 3, 24 July 2012)
- Participant Consent Form - Treatment Program (Master Version 2, 28 June 2011)
- Information for Participants - Pharmacokinetic substudy for patients (Master Version 2, 28 June 2011)
- Participant Consent Form - Pharmacokinetic substudy for patients (Master Version 2, 28 June 2011)
- Information for Participants - Pharmacokinetic substudy for healthy volunteers (Master Version 2, 28 June 2011)
- Participant Consent Form - Pharmacokinetic substudy for healthy volunteers (Master Version 2, 28 June 2011)

- Information for Participants – Reactivity (Version 2, 12 March 2012)
- Participant Consent Form – Reactivity (Version 1, 12 March 2012)

The following conditions apply to this research study. These are additional to those conditions imposed by the human research ethics committee (HREC) that granted ethical approval:

1. This trial will be conducted under the CTN Scheme. It cannot commence until it has been notified to the Therapeutic Goods Administration (TGA) and a copy of the TGA acknowledgement letter has been received by the Research Governance Officer.

2. Proposed amendments to the research protocol or conduct of the research, which may affect the ethical acceptability of the study and which are submitted to the lead HREC for review, must be copied to me.

3. Proposed amendments to the research protocol or conduct of the research, which may affect the ongoing site acceptability of the study, must be submitted to me.

I wish you every success in your research.

Yours sincerely,

Lesley Townsend

Lesley Townsend
Research Governance Officer
SLHD (RPAH Zone)

RGO - Lesley\CORRES\X11-0154

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NSW GOVERNMENT Health
Sydney
Local Health District

19 June 2014

Professor P Haber
C/- Dr K Morley
Drug Health Services
Level 6, Building 13
Royal Prince Alfred Hospital

Dear Professor Haber,

Re: Protocol No X11-0154 & HREC/11/RPAH/223 - "Exploring the efficacy and biobehavioural basis of Baclofen in the treatment of alcoholic liver disease"

The Executive of the Ethics Review Committee, at its meeting of 22 May 2014 considered your correspondence of 9 May 2014 and subsequently Dr K Morley's emailed correspondence of 19 June 2014, and gave its approval of the following:

- Brain imaging side-arm study (protocol, as described in your correspondence of 9 May 2014)
- Information for Participants – Reactivity: Brain Imaging (Master Version 2, 19 June 2014)
- Participant Consent Form – Reactivity: Brain Imaging (Master Version 2, 19 June 2014)
- MRI Pre-Booking Checklist Screener – Reactivity: Brain Imaging (Master Version 1, 9 May 2014)

Yours sincerely,

Lesley Townsend

Lesley Townsend
Executive Officer
Ethics Review Committee (RPAH Zone)

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Appendix B

Audio Vignettes for Cue Reactivity Task

Audio Vignettes for CR task

Control recording

"You are sitting alone on the beach. You look up, and a good friend of yours is walking towards you! They tell you they've brought you a beach towel – you can see it in their hand. You notice the smell of the laundry soap coming from the orange beach towel. You sit on the towel, and it feels rough against your skin, but it reminds you of holidays so it relaxes you. You pick up a bottle of sunscreen and the bottle is slightly greasy in your hand. You squirt some more into your hand and you can smell it, it smells like coconut. The bottle makes a noise as you squirt more onto your palm. You want to put the sunscreen on quickly, you think you might get burnt soon. Suddenly you feel like everything's just right – here you are with your friend, sitting on the sand, and it's just so easy. The warmth from the sun is making your skin tingle a bit. This is such a relief, you've needed this break. You rub the cool, creamy sunscreen across your shoulders, onto your arms, down your legs, and it feels good against your skin. You stretch out on the sand and feel all of your muscles relaxing as the tension just melts away. You think about how much you enjoy being able to just take a break, and suddenly you can't wait to have more fun. This is exactly what you've needed; it feels better than anything has all week. You haven't even been here long before you're thinking about getting into the water."

Alcohol recording

"You are sitting alone in a bistro. You look up and a good friend of yours is walking towards you! They tell you they've brought you your favourite alcoholic drink – you can see it in their hand. You think about how you weren't going to drink, you've tried so hard not to. Maybe you'll just leave it sitting there. You sit down together and start to have a chat. In spite of yourself, you find yourself reaching forward and taking the drink – you feel how smooth the glass feels against your hand, and the thought of it is making your mouth water. You bring it to your lips and suddenly you can smell it, its right there in front of you. You can hear the drink moving around in the glass, and you're really looking forward to it. You can't wait to taste it; your mouth is watering a lot now. Suddenly you feel like everything's just right – here you are with your friend, having a chat and a drink, and it's just so easy. The drink hits your tongue and it's wonderful – you can feel it moving around in your mouth and there's that taste, the taste you've been waiting for. Such a relief. You can feel the liquid all around your mouth, around the inside of your cheeks; haven't you tried so hard at being good? You swallow, and suddenly you can't wait for the next mouthful. You take another mouthful and it's just as good, no, better than the last. You haven't even swallowed this mouthful before you are thinking about the next."

Appendix C

Supplementary Tables: Chapter Five

Supplementary Table 1

*Main effects of BOLD activation for contrast Alcohol > Control for the Whole Sample (*N = *36), Whole Alcohol Dependent sample (*n = *27), and Healthy Controls (*n = *9)*

Participants	Area	Side	Cluster Size	Z	x	y	z
Whole Sample	Inferior Occupital Gyrus	L	3044	6.37	-36	-86	12
		R	2472	5.76	38	-76	2
	Insula	R	285	4.65	30	24	-18
	Middle Temporal Gyrus	R	109	4.43	58	-30	-8
	Superior Frontal Gyrus	L	826	4.38	12	20	62
		R	995	4.29	0	64	14
	Posterior Cingulate Gyrus	R	718	3.97	-4	-44	24
	Middle Frontal Gyrus	L	81	3.80	-20	56	30
		R	16	2.84	44	8	56
	Insula	L	175	3.50	-32	20	-22
	Middle Temporal Gyrus	L	112	3.33	-58	-50	-2
	Transverse Temporal Gyrus	R	50	3.29	48	-24	18
	Angular Gyrus	R	71	3.21	54	-60	34
	Medial Frontal Gyrus	L	38	3.19	-6	30	36
	Precuneus	R	89	3.18	2	-62	64
	Superior Temporal Gyrus	R	28	3.12	46	-32	4
				3.05	66	-24	14
				2.80	50	-2	2
				2.99	62	-50	0
Whole AD Sample	Inferior Occupital Gyrus	L	2780	5.74	-36	-86	12
		R	2624	5.07	48	-74	-6
	Middle Temporal Gyrus	R	252	4.64	58	-30	-8
		L	307	4.26	-58	-50	-2
	Fusiform Gyrus	L	250	4.54	-30	-48	-10
	Posterior Cingulate	R	858	4.43	-6	-42	24
	Insula	R	418	4.18	30	24	-18
	Medial Frontal Gyrus	R	1255	4.17	-4	56	14
		L	44	2.99	-2	32	34
		R	479	3.58	6	12	72
	Supplementary Motor Area	L	155	3.55	-16	38	56
	Paracentral Lobule	L	285	3.53	2	-42	72
	Insula	L	206	3.52	-32	22	-18
	Middle Frontal Gyrus	L	124	3.42	-20	58	30
	Lingual Gyrus	L	40	3.21	-20	-76	-6
	Amygdala	R	22	3.12	14	-6	-18
	Superior Frontal Gyrus	R	33	3.02	20	46	34

Supplementary Table 1 Continued

Participants	Area	Side	Cluster Size	Z	x	y	z
HC	Middle Temporal Gyrus	R	33	4.32	52	-46	18
			43	3.47	46	-36	-2
	Middle Frontal Gyrus	L	67	4.10	-34	8	38
	Inferior Occupital Gyrus	L	214	3.51	-42	-80	-4
		R	127	3.47	42	-84	2
	Fusiform Gyrus	L	48	3.07	-34	-60	-18
	Supplementary Motor Area	R	47	3.03	12	20	58
		L	28	2.84	-14	6	62
	Cuneus	L	16	2.87	-8	-90	2
	Lingual Gyrus	L	20	2.81	-20	-76	-12

Note. Corrected at $p < .005$, voxel threshold $k > 15$; AD = Alcohol dependent; HC = Healthy controls; Z = Z-value; x, y, z = MNI coordinates; L = left; R = right.

Supplementary Table 2

*Whole Brain Regression Analysis for Contrast Alcohol>Control, Showing Correlations with Stroop Interference score and ADS score Within the Reduced Alcohol Dependent Sample (*n = *17)*

	Area	Side	cluster size	Z	x	y	z
Stroop							
Positive							
	Postcentral Gyrus	L	76	3.98	-58	-2	34
	Supramarginal Gyrus	R	55	3.61	50	-20	30
	Precuneus	R	215	3.24	28	-62	12
	Middle Temporal Gyrus	L	36	3.05	-56	-34	8
	Middle Frontal Gyrus	L	28	2.97	-32	44	20
	Inferior Frontal Gyrus	R	21	2.84	26	12	28
		L	29	2.79	-48	20	26
Negative							
	Supplementary Motor Area	L	671	3.98	-30	40	42
	Insula	R	47	3.93	32	24	-18
	Inferior Parietal Lobule	R	99	3.69	46	-60	38
	Middle Frontal Gyrus	R	149	3.48	26	20	56
		R	155	3.43	36	36	36
		R	19	2.93	24	54	30
	Precuneus	L	32	3.42	-12	-52	46
	Middle Occupital Gyrus	R	29	3.28	50	-72	0
	Hippocampus	R	51	3.14	50	-38	-12
	Superior Temporal Gyrus	R	36	3.11	42	20	-24
	Medial Frontal Gyrus	R	22	3.08	10	28	36
	Inferior Parietal Lobule	L	33	2.99	-52	-52	42
				2.99	-38	-62	40
ADS							
Positive							
	No significant clusters						
Negative							
	Middle Frontal Gyrus	R	239	4.14	32	42	36
	Postcentral Gyrus	R	846	4.07	56	-18	38
	Middle Occupital Gyrus	L	105	3.72	-52	-72	4
	Superior Parietal Lobule	L	595	3.58	-22	-56	62
	Superior Parietal Lobule	R	58	3.19	20	-52	60
	Occupital Lobe	L	99	3.56	-28	-74	8
	Inferior Parietal Lobule	R	66	3.55	46	-60	38
	Inferior Parietal Lobule	L	20	2.89	-46	-26	44
	Superior Frontal Gyrus	L	15	3.35	-12	18	40
	Precuneus	R	20	3.33	26	-80	40

Supplementary Table 2 Continued

Area	Side	cluster size	Z	x	y	z
Precuneus	R	22	3.01	14	-64	48
Precentral Gyrus	L	56	3.31	-56	-4	36
		34	3.25	-36	0	42
		101	3.13	-38	-18	38
Precentral Gyrus	R	15	2.84	16	-24	74
Middle Temporal Gyrus	R	37	3.20	54	-58	2
Precuneus	R	28	3.10	4	-38	48
Supramarginal Gyrus	L	21	3.07	-58	-24	24
Postcentral Gyrus	R	83	3.06	40	-42	62
Postcentral Gyrus	R	16	2.89	14	-48	72
Anterior Cingulate Cortex	R	101	3.01	2	20	34

Note. Corrected at $p < .005$, voxel threshold $k > 15$; ADS = Alcohol dependence Scale; Z = Z-value; x, y, z = MNI coordinates; L = left; R = right.

Supplementary Table 3

*Whole Brain Regression Analysis for Contrast Alcohol>Control, Showing Correlations with Trails Difference Score and ADS score within the Reduced Alcohol Dependent sample (*n = *17)*

	Area	Side	Cluster size	Z	x	y	z
Trails							
Positive							
	Cuneus	R	68	4.47	18	-96	14
	Inferior Frontal Gyrus	L	706	4.24	-26	4	28
	Postcentral Gyrus	R	90	3.93	28	-24	48
	Postcentral Gyrus	R	404	3.66	44	-18	30
	Middle Occupital Gyrus	L	42	3.47	-30	-90	16
	Postcentral Gyrus	L	46	3.43	-26	-28	48
	Anterior Cingulate Cortex	R	60	3.34	-2	50	14
	Lingual Gyrus	R	25	3.25	26	-50	-8
	Midcingulate Cortex	L	28	3.14	-4	-6	42
	Superior Occupital Cortex	R	15	3.01	24	-76	16
	Middle Frontal Gyrus	R	24	2.99	44	18	34
Negative							
	Middle Frontal Gyrus	R	74	4.22	28	56	24
			40	3.41	28	32	34
			55	3.08	36	36	48
	Middle Occupital Gyrus	L	203	4.16	-30	-56	0
	Middle Temporal Gyrus	R	407	4.12	56	-34	-8
	Precuneus	L	88	3.68	-8	-72	50
	Superior Frontal Gyrus	L	18	3.43	-28	64	-4
		R	15	2.87	24	64	-8
	Cuneus	R	94	3.33	10	-80	44
	Superior Temporal Gyrus	R	47	3.29	56	12	-12
		L	48	2.91	-54	10	-12
	Inferior Parietal Lobule	R	41	3.13	46	-52	46
ADS							
Positive							
	No significant clusters						
Negative							
	Middle Frontal Gyrus	R	1001	4.09	54	-14	24
		R	29	3.44	32	42	34
	Parahippocampal Gyrus	R	33	3.59	28	-24	-16
	Postcentral Gyrus	L	720	3.48	-56	-24	52
		L	40	2.85	-22	-32	66
	Supplementary Motor Area	R	488	3.41	-6	-16	54
	Insula	R	32	3.25	34	-22	22
		L	15	3.17	-26	24	16
	Precentral Gyrus	L	21	3.16	-36	0	42
	Midcingulate Cortex	R	25	2.96	4	-40	48
	Middle Temporal Gyrus	L	19	2.91	-46	-68	6
	Precuneus	R	19	2.78	0	-48	52

Note. Corrected at $p < .005$, voxel threshold $k > 15$; ADS = Alcohol Dependence Scale; Z = Z-value; x, y, z = MNI coordinates; L = left; R = right.

Supplementary Table 4

Whole brain regression analysis of the negative correlation between increasing activation during Contrast Alcohol>Control and lower f-ROI right DLPFC activity in the reduced alcohol dependent sample (n = 17)

Area	Side	cluster size	Z	x	y	z
Olfactory Cortex	L	10	2.98	-6	30	-2
Caudate	L	26	2.96	-20	-4	24
	L	73	2.93	-20	-34	18
	R	12	2.66	22	8	22
Insula	R	139	2.79	28	-34	18
Inferior Frontal Gyrus, pars Opercularis	L	22	2.77	-34	6	22
Medial Frontal Gyrus	L	23	2.76	-14	50	16
Inferior Parietal Lobule	L	49	2.69	-38	-46	28
Superior Occupital Gyrus	R	7	2.59	24	-74	18
Thalamus		45	2.56	-2	-18	4

Note. Corrected at $p < .01$, voxel threshold $k > 5$; Z = Z-value; x, y, z = MNI coordinates; L = left; R = right.