An investigation of mechanisms underpinning substance dependence and novel interventions

Submitted by Lorna Hardy to the University of Exeter as a thesis for the degree of Doctor of Philosophy in Psychology, August 2018.

I certify that all material in this thesis which is not my own work has been identified and that any material that has previously been submitted and approved for the award of a degree by this or any other university has been acknowledged.

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Abstract

A number of theories have attempted to explicate mechanisms underpinning the transition from recreational drug use to substance dependence. A highly reliable correlate of dependence is the value ascribed to the drug. However, supernormal drug valuation may be insufficient to fully account for a subgroup of dependent individuals for whom the course of dependence is chronic and relapsing and who persist in drug use in the face of devastating costs. Three candidate secondary mechanisms for dependence are considered in this thesis: cue reactivity, cost discounting, and sensitivity to negative affect. Neither cue reactivity nor cost discounting were found to be significantly associated with severity of alcohol dependence in samples of young adult drinkers. By contrast, induced negative affect was found to be reliably associated with augmented alcohol motivation, and sensitivity to this effect was related to symptoms of depression and self-reported drinking to cope with negative affect: both risk factors for the development of dependence. These findings delineate a particular subset of dependent individuals for whom negative affect may represent a substantial trigger to continued drug use.

There are a lack of brief interventions to abolish or limit negative affect driven drug motivation. This thesis trialled three potential interventions. A natural walk intervention in hazardous drinkers showed no evidence of limiting this effect in two experiments. Brief instruction in acceptance-based coping showed no evidence of limiting annoyance in response to an aversive noise induction procedure in an alcohol dependent population, and was therefore also eliminated as a potential intervention. However, engagement with pleasant environmental images, as a proxy for environmental enrichment, significantly reduced negative affect driven alcohol choice in student drinkers who reported a desire to visit the locations shown (high liking), compared to low-liking individuals and controls. This provides preliminary evidence for the efficacy of environmental enrichment type interventions, justifying further trials. In treatment of dependence more generally, interventions to increase access to healthy, non-drug sources of positive reinforcement may prove effective.

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I am especially thankful to my friends in the department, and all the people I've been lucky enough to share an office with during my PhD - Amy, Maisy, Will, Kathryn, Lucy, Will, Joff, Alex and Asha. Particular thanks to Maddie, who has been a constant source of support since the very first day of undergraduate.

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Author's Declaration

Experiments within Chapters 3, 4, 5, 6, 7 and 8 have been published as papers. All experiments were run at the University of Exeter.

For Chapter 3 (Hardy et al. 2017) I collected and analysed data, and wrote the manuscript with edits from my co-authors. Data originally contributed to a BSc from the University of Exeter, and was re-analysed and written up for publication during my PhD. In Chapter 4 (Hogarth and Hardy 2018a) I collected and analysed data as part of a group of undergraduate research project students (Olivia Bryan, Imogen Bodimeade, Laura Collins, Matthew Hobbs, Victoria Howells, Charlotte Oldroyd, and Emma Zeitlyn), wrote the first draft of the manuscript and contributed further edits. Data originally contributed to a BSc from the University of Exeter, and was re-analysed and written up for publication during my PhD. For Chapter 5 (Hardy et al. 2018a) I designed the two experiments, collected and analysed data, and wrote the manuscript, with additional edits from my co-authors.

For Chapter 6 I designed the experiment, collected and analysed data, and wrote the manuscript with edits from my co-author (Hardy and Hogarth 2017). Data originally contributed to an MSc from the University of Exeter, and was re-analysed and written up for publication during my PhD. In Chapters 7 and 8 I contributed substantially to study design and the manuscripts (Hogarth et al. 2018a; Hogarth and Hardy 2018b). Data for the experiments in Chapters 7 and 8 were collected by undergraduate research project students (Charles Carter-Esdale, Nicole Gasson, Amy-Louise Holloway, Anna Hulme, Amy Kane, Samuel Lansley, Hayley Nicholls, and Georgia Persad).

An additional publication which arose from our collaboration with the Exeter Drug Project is reproduced in Appendix A (Hardy et al. 2018b). For this paper I collected and analysed data, and wrote the manuscript with edits from my co-authors.

Papers have been reproduced as published and only edited to ensure sequential numbering of tables and figures throughout the thesis.

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Chapter 1. Introduction

Substance dependence is typically defined as a chronic and relapsing disorder (e.g. Leshner 1997; McLellan 2002). However, evidence suggests that the majority of people who meet criteria for substance dependence in the general population resolve their dependence in the absence of formal treatment (Copersino et al. 2006; Cunningham and Breslin 2004; Cunningham et al. 2000; Cunningham and McCambridge 2012; Sobell et al. 1996; Toneatto et al. 1999), and infrequently experience a re-occurrence of this disorder (Dawson et al. 2007; Dawson et al. 2005; de Bruijn et al. 2006). There does, however, appear to be a subgroup of treatment-seeking dependent individuals who experience a chronic course of dependence with frequent relapses (Heyman 2013; McLellan et al. 2000; McLellan 2002; Witkiewitz and Marlatt 2007), and continue to use the drug in the face of rising adverse consequences (Altman et al. 1996; Koob and Simon 2009; Worley et al. 2015). These individuals often present with additional psychiatric comorbidities (Chan et al. 2008; Cunningham and McCambridge 2012; Grant et al. 2004). It is crucial to clarify the mechanisms by which dependence is initiated and maintained in this population, and develop effective interventions.

The economic benefits of intervention in substance dependence are well established, especially when interventions are preventative (Knapp 2012; Knapp et al. 2011; Whelan et al. 2014). However, funding of drug and alcohol treatment services in the UK fell from £877m in 2013/14 to £716m in 2017/18 (Rhodes 2018). There is therefore a need for cost-effective, evidence-based interventions to target dependence (Magidson et al. 2011). The optimum treatment strategy for a high-risk, treatment-seeking population has not yet been established. The purpose of this introductory chapter is to introduce the content of each chapter that follows, and site it within a larger body of research.

1.1 Overview of theories of dependence

A number of theories have aimed to explicate mechanisms underpinning the transition from recreational drug use to substance dependence. In negative reinforcement models (e.g. Wikler 1948) drug-seeking behaviour is sustained because it removes an aversive state of withdrawal. Opponent process theories (Koob et al. 1993; Solomon and Corbit 1974), for example, postulate that the transition from recreational use to dependence is underpinned by a shift in control of behaviour from positive to negative reinforcement.

While self-administration behaviour is initially established by the positive hedonic state engendered by the drug, continued use in dependence is increasingly driven by an opposing, negative hedonic state of withdrawal (Koob et al. 1997; Koob et al. 1993; Solomon and Corbit 1974). However, this account is undermined by the fact that periods of drug craving or self-administration do not always coincide with withdrawal (Childress et al. 1988; Ehrman et al. 1992; Meyer 1988; Robinson and Berridge 1993; Wise and Bozarth 1987), and relapse often occurs after long periods of abstinence, at which time any overt withdrawal syndrome should have abated (Robinson and Berridge 1993; Wikler 1948).

Positive reinforcement accounts propose alternative mechanisms. In cue reactivity accounts, drug cues increasingly come to elicit drug-seeking behaviour automatically (Tiffany 1990). Within this class of accounts, incentive salience theory proposes that drug use is mediated by two independent processes – 'liking' and 'wanting' (Robinson and Berridge 1993; Vollstadt-Klein et al. 2010). While initial drug use may be driven by liking – subjective experience of the drug as pleasurable – continued use is increasingly controlled by a motivational dopaminergic 'wanting' system, which promotes attention to drug cues and inflexible, cue-driven drug-seeking behaviour (Berridge and Robinson 2016). The independence of these two systems arguably explains why drug use continues even when dependent individuals report no longer liking the drug (Robinson and Berridge 1993). However, while this account presumes that dependence is maintained by enhanced attentional bias to drug cues, it is undermined by the fact that retraining of this attentional bias has not proven reliable in promoting abstinence (Begh et al. 2015; Field et al. 2009).

Finally, executive/habit system dysfunction accounts have built on these theories to propose that chronic drug use leads to reduced control by executive inhibitory mechanisms (Jentsch and Taylor 1999; Lubman et al. 2004) and/or enhanced control by habit-based mechanisms (Sjoerds et al. 2013; Vollstadt-Klein et al. 2010), facilitating automatic drug-seeking behaviours which are resistant to modification (Redish et al. 2008). However, there is evidence that dependent drug users do not significantly differ from controls in their capacity for goal-directed control over action selection (Hogarth et al. 2018b), undermining excessive habit accounts.

Importantly, none of these theories can account for the fact that the correlates of quitting in substance dependence are typically those factors which attend intentional decision-making more generally: concerns regarding the impact of drug use on family and quality of relationships, finances, and job prospects (Heyman 2013; Jorquez 1983; Kennett et al. 2013; Klingemann et al. 2010; Robins 1993; Stinson et al. 2005; Tuchfeld 1981). Frequency of drug use can also be reliably reduced in dependent individuals by providing monetary incentives which are contingent on continued abstinence (Davis et al. 2016; Prendergast et al. 2006). It is unclear why these factors should promote abstinence in habit-based models, in which drug-seeking behaviour becomes increasingly automated and thus insensitive to changes in reward value (Kennett and McConnell 2013). These findings can, however, be explained by means of a behavioural economic model of substance dependence.

1.2 Specific theories of dependence addressed in this thesis

1.2.1 Behavioural economics and supernormal drug valuation

Behavioural economic accounts argue that continued drug use in dependence is not automatic, but rather based on the application of a cost-benefit analysis which compares the relative availability and reinforcement value of the drug to that of alternative rewards (Bickel et al. 2014b; Bickel et al. 1998; Correia et al. 2010). In this model, dependent individuals repeatedly make intentional decisions to consume (or not consume) the drug based on their expectation of its value, and the value of available alternatives (Correia et al. 2010). For example, getting a new job might provide an alternative source of reinforcement to drug use, lowering the drug's relative value. If this job requires mandatory drug testing, it may also raise the costs associated with drug use (loss of employment). Integration of this information into a cost-benefit analysis should reduce choice of the drug reward. In this way, a behavioural economic model can account for the fact that dependent individuals remain sensitive to the consequences of drug use.

Vulnerabilities within this behavioural economic decision-making system may promote continued drug use in a manner which appears compulsive (Bickel et al. 2014b). One significant way in which dependent individuals may differ from those who are not dependent within this model is in ascribing an abnormally high value to

the drug. This value may consistently exceed costs associated with the drug, promoting continued use (MacKillop 2016). Supernormal valuation of the drug may arise from a wide range of factors, including genetic variation, developmental history, psychiatric comorbidities, and social context, which jointly determine the relative reinforcement value of the drug (MacKillop 2016).

Supernormal drug valuation has proved the most reliable correlate of dependence across multiple accounts of addiction. In demand tasks, participants report the amount of the drug that they would hypothetically consume across a range of increasing prices (e.g. Murphy and MacKillop 2006). In these tasks, intensity of demand (consumption of the drug at zero or low cost) represents a relatively pure index of drug value. This measure correlates with a number of metrics of dependence, including frequency of drug use and drug-related problems (MacKillop and Murphy 2007; Murphy and MacKillop 2006; Murphy et al. 2009). An alternate metric of drug value is provided in concurrent choice tasks, in which participants choose between a drug reward and a concurrently-available alternative reward across a series of trials. Rewards may be points, pictures, or actual consumption of the drug or alternative reward. Percent choice of the drug in these tasks reliably correlates with tobacco (Chase et al. 2013; Hogarth and Chase 2011) and cocaine dependence (Moeller et al. 2013; Moeller et al. 2009). Overall, greater severity of dependence is reliably associated with higher valuation of the drug.

A methodological concern from a behavioural economic perspective is that current measures of drug value are not optimised for use by clinically dependent populations. Demand tasks (e.g. MacKillop and Murphy 2007) are demanding and time consuming for participants, and require a minimum level of literacy, while points and consumption-based tasks (e.g. Amlung et al. 2012; Hogarth and Chase 2012; Hogarth et al. 2015b) in which participants either expect to consume the reward or do consume it during the experimental procedure are ethically inappropriate for treatment-seeking participants attempting to maintain abstinence. A pictorial choice measure, in which participants choose concurrently between drug images and alternative pleasant images, may circumvent these issues. Chapter 5 of this thesis therefore aimed to

develop a picture-based behavioural assay of drug value, and validate this method in clinically-dependent populations.

Based on the above evidence, we might presume that supernormal drug valuation is the primary mechanism underpinning dependence. However, this mechanism alone may be insufficient to fully account for the subgroup of treatment-seeking, dependent individuals for whom the course of dependence is chronic and relapsing (Heyman 2013; McLellan et al. 2000; McLellan 2002; Witkiewitz and Marlatt 2007), and who persist in drug use despite reporting a wish to quit (Hogue et al. 2010; MacKillop et al. 2011) and in the face of devastating costs which appear to clearly outweigh any reported benefits (Heyman 2013; Kennett et al. 2013; Kennett and McConnell 2013). There may therefore be an additional, secondary process by which drug use is maintained in such populations. This thesis investigates three candidate secondary mechanisms.

1.2.2 Cue reactivity

The first candidate mechanism is cue reactivity. Theories of cue reactivity were developed based on the observation that dependent individuals are more likely to relapse in the presence of cues related to prior drug use (Carter and Tiffany 1999). In experimental cue reactivity paradigms, dependent individuals are presented with drug-related cues, typically either as images or *in vivo*, and subsequent drug motivation measured (Carter and Tiffany 1999). Exposure to drug-related cues has been found to reliably augment self-reported drug craving (Carter and Tiffany 1999; Cooney et al. 1997; Witteman et al. 2015), and actual consumption behaviours including latency to use the drug and intensity of use (Conklin et al. 2015; Hogarth et al. 2010), although not always (see Shiffman et al. 2013a; Shiffman et al. 2013b).

There are two opposing classes of account by which drug cues promote craving and drug-seeking behaviour. Automatic accounts propose that experience of the drug reinforces an association between the stimulus (i.e. the context in which a drug-seeking response was made) and the response itself. Subsequent re-exposure to the stimulus directly elicits the associated response, without reference to the drug outcome itself (Hogarth et al. 2007; Hull 1943). A second class of goal-directed theories propose that drug cues, instead of automatically priming drug-seeking behaviour, instead elicit an

expectation of the drug outcome, and it is this expectation which promotes subsequent drug-seeking (Hogarth and Duka 2006; Stewart et al. 1984). Evidence for goal-directed accounts comes from Pavlovian to instrumental transfer (PIT) tasks which, by their design, exclude control of behaviour by S-R associations. Drug cues have been shown to reliably augment drug-seeking in PIT tasks (Garbusow et al. 2014; Hogarth and Chase 2011; 2012; Hogarth et al. 2007; Martinovic et al. 2014), effectively excluding an S-R account of cue reactivity. However, it is less clear by what goal-directed mechanism drug cues might promote drug-seeking.

If cue reactivity contributes substantially to dependence, we would expect sensitivity to cues to increase as a function of dependence severity. However there is little evidence that this is the case, with some positive (Niaura et al. 1989; Sjoerds et al. 2014), but largely null findings (Hogarth and Chase 2011; 2012; Perkins 2009; Perkins 2012; Rohsenow et al. 1994; Vollstadt-Klein et al. 2011; Witteman et al. 2015). The experiment presented in Chapter 3 therefore aimed to test a goal-directed account of cue reactivity, and the relationship between this mechanism and dependence severity.

1.2.3 Insensitivity to cost

A plausible explanation for continued drug use in dependence is that individuals fail to accurately incorporate drug-associated costs into a cost-benefit analysis (i.e. they discount or are insensitive to costs) (Belin et al. 2008; Bickel et al. 2014a; Mitchell 2003). Evidence for cost insensitivity in dependence comes primarily from animal models, in which persistence of drug use is measured under conditions of concurrent shock punishment (Deroche-Gamonet et al. 2004). Rats that have received extended access to the drug, or are impulsive (and are therefore notionally dependent or dependence-prone) show weaker suppression of drug self-administration by contingent shock punishment, despite comparable baseline self-administration rates to control animals (Belin et al. 2009; Belin et al. 2008; Deroche-Gamonet et al. 2004; Economidou et al. 2009; Pelloux et al. 2007; Pelloux et al. 2015; Vanderschuren and Everitt 2004). This suggests that the transition to dependence, at least in notionally dependent rats, is underpinned by increasing insensitivity to drug-associated costs.

In humans, evidence for cost insensitivity is less clear. In cost discounting paradigms a drug related cost is introduced and/or manipulated, and subsequent drug motivation

measured. Drug motivation has been shown to be sensitive to opportunity cost (i.e. the value of an alternative reward foregone if the drug is chosen) (Bickel et al. 1993; Bickel et al. 1995; Higgins et al. 1994; Johnson and Bickel 2003; Nader and Woolverton 1991), the delay to receiving the drug (temporal availability) (Bickel and Marsch 2001; Ito and Nakamura 1998; Vuchinich et al. 1987), and resources expended to receive the drug (including money and effort) (Bickel et al. 1991; Johnson and Bickel 2003; Murphy and MacKillop 2006). In demand tasks, breakpoint, or the price at which drug consumption drops to zero, is presumed to reflect sensitivity to cost (MacKillop and Murphy 2007). Evidence in this area has been mixed, with one study finding that increased dependence severity predicts higher breakpoints (i.e. lower sensitivity to cost) (Murphy and MacKillop 2006), but another finding no significant relationship (MacKillop et al. 2010a). Evidence for cost insensitivity from demand tasks is therefore equivocal.

An additional strand of evidence comes from delay discounting tasks, in which dependent individuals choose between a smaller immediate or larger delayed reward (either the drug or an alternative reinforcer such as money) (Lim et al. 2017). Greater severity of dependence is consistently associated with preference for the smaller immediate reward (Lim et al. 2017; MacKillop et al. 2011; Petry 2001b; Vuchinich and Simpson 1998), with some null findings (Robles et al. 2011). One interpretation of these findings is that dependent individuals are in fact hypersensitive to delay costs, since their valuation of rewards declines steeply with increasing delay (MacKillop et al. 2011). A second interpretation, however, is that dependent individuals are insensitive to delayed or long-term negative consequences (particularly those associated with drug use - Baker et al. 2003; Madden et al. 1997; Petry 2001b) perhaps due to a restricted temporal horizon (MacKillop et al. 2011; Petry et al. 1998) and/or a deficiency in abstract imagination of future outcomes (Griffiths et al. 2012; Yi et al. 2017). Therefore, it is unclear whether delay discounting in dependence signifies enhanced or reduced sensitivity to costs.

Overall, then, research from animal models, demand tasks, and delay discounting procedures has not established definitively whether greater severity of dependence is associated with enhanced insensitivity to costs. The aim of Chapter 4 was to test

whether dependence severity is associated with insensitivity to delay and opportunity costs imposed on a drug reward.

1.2.4 Negative reinforcement and sensitivity to negative affect

A final candidate mechanism is sensitivity to negative affective triggers. While traditional models of negative reinforcement focused on withdrawal as the primary motivator of drug use, newer formulations of this account argue that negative affect is in fact the core motivational component of withdrawal (Baker et al. 2004; Kenford et al. 2002). By this account, experience of a negative affective state, either within a withdrawal syndrome or in isolation, acutely raises drug motivation to mitigate this aversive state (Koob 2013). Drug-seeking behaviour may become increasingly controlled by negative reinforcement in greater severity of dependence, as chronic drug use promotes a persistent state of negative affect and increased sensitivity to affective triggers (Baker et al. 2004; Heilig et al. 2010; Koob and Le Moal 1997). By this account, the relative reinforcing value of the drug may be acutely raised in dependent individuals under conditions of negative affect, promoting continued use in spite of drug-associated costs and/or intentions to quit.

The contribution of negative reinforcement to dependence is supported by evidence that dependent individuals retrospectively attribute negative mood as their reason for relapsing more frequently than any other (Brown et al. 1990; Hodgins et al. 1995; Marlatt 1996; Marlatt and Friedman 1981; Strowig 2000). It is possible, however, that this data reflects post-hoc rationalisation of relapse (Hall et al. 1993). More convincingly, experimental induction of negative mood reliably promotes drug motivation and drug-seeking behaviour as measured on a number of metrics (e.g. Birch et al. 2004; Cooney et al. 1997; Cyders et al. 2016; Rousseau et al. 2011). If negative reinforcement theory is correct, dependence severity (and risk factors for dependence formation and maintenance) should be associated with increased sensitivity to negative affective triggers for drug-seeking (Heilig et al. 2010). There is some indication that sensitivity to this effect of negative mood predicts relapse in dependent drinkers (Brady et al. 2006; Cooney et al. 1997; Sinha et al. 2011). Self-reported tendency to use drugs to address negative affect is also reliably associated with the development of dependence and subsequent relapse (Beseler et al. 2008; Crum et al. 2013b; Holahan et

al. 2001; Merrill et al. 2014). However, these predictions of negative reinforcement theory require further testing.

There are a number of mechanisms by which negative affect might motivate drug use which, as in cue reactivity, can be broadly divided into automatic and goal-directed accounts. In automatic accounts (e.g. Baker et al. 2004), experience of the drug as particularly reinforcing under conditions of negative affect strengthens a direct link between negative mood and the motor sequence through which the drug is obtained and/or consumed (i.e. a stimulus-response association) (Hogarth et al. 2015a; Hull 1943). Experience of negative affect thus elicits drug-seeking behaviour without reference to outcome value. Intentional accounts, by contrast, argue that it is the expectation of enhanced drug value under conditions of negative affect that primarily motivates use. In an incentive learning account, for example, dependent individuals learn that, under conditions of negative affect, the drug is highly reinforcing. Subsequent experience of this state retrieves an expectation that the drug currently has a high value (Dickinson and Balleine 2010). This expectation is integrated with goal-directed knowledge of the response-outcome relations operating in the current context, allowing execution of an appropriate drug-seeking response (Hogarth et al. 2015a; Trask and Bouton 2014). Evidence for intentional, as opposed to automatic, accounts comes from findings that negative mood can prime a novel drug-seeking response in the absence of experience of the drug reinforcer (i.e. in extinction) (Hogarth et al. 2015a). This is inconsistent with S-R accounts, in which changes in drug-seeking are driven by direct experience of the outcome as more or less reinforcing (Dickinson 1985). Instead, participants in this study may have integrated knowledge concerning the heightened value of the drug under conditions of negative affect with the response-outcome contingency in force. However, this finding requires replication.

The aim of Chapters 6, 7, and 8 was therefore to test whether greater dependence severity (and associated risk factors for dependence) is associated with greater sensitivity to the motivational effect of negative mood on drug choice. A secondary aim was to test whether this motivational effect of negative mood is primarily underpinned by automatic or goal-directed mechanisms (addressed in Chapter 8).

1.3 Interventions for substance dependence

Interventions for substance dependence are typically developed from a specific theoretical position regarding the mechanisms underpinning dependence (Morgenstern and McKay 2007). However, the majority of trials do not include mediation analyses to determine whether the mechanism of interest is in fact changed by the intervention. The few studies which have included such analyses typically find that therapeutic effects are not mediated by changes in the psychological construct on which the intervention is predicated (Morgenstern and McKay 2007). For example, a review by Morgenstern and Longabaugh (2000) found little evidence that improvements in alcohol dependence as a function of cognitive behavioural therapy (CBT) were mediated by skill acquisition: a core tenet of CBT. Given recent cuts to funding of drug and alcohol treatment services in the UK, there is a need for brief, cost-effective interventions which are targeted and evidence-based in the sense that they modify specific mechanisms known to underpin dependence. A range of interventions, based on the mechanisms of dependence discussed above, are considered in turn below.

1.3.1 Interventions for supernormal drug valuation

Interventions based on behavioural economic principles typically aim to raise the value of alternative, non-drug reinforcement. In contingency management, dependent individuals are offered monetary or voucher-based incentives in exchange for objective evidence of abstinence, thus introducing a significant opportunity cost to drug use (Alessi et al. 2011). Contingency management has proved highly effective in reducing drug use during treatment (Dutra et al. 2008; Lussier et al. 2006; Prendergast et al. 2006). However, the durability of this therapeutic effect is less clear: improvements are often not sustained in the long term following termination of treatment (Alessi and Petry 2014; Dunn et al. 2010; Rawson et al. 2002; Rohsenow et al. 2017; Sayegh et al. 2017), although some longer term benefits have been observed (Petry and Martin 2002). Contingency management also presents practical challenges in being expensive to implement, and requiring frequent drug testing of clients during treatment (Petry 2010).

Other interventions have aimed to introduce alternative, high value sources of reinforcement in a more naturalistic manner. Behavioural activation (BA) – a therapy

initially developed for depression –aims to increase engagement with positively reinforcing activities unrelated to substance use (Daughters et al. 2008; Lewinsohn and Graf 1973). Brief BA-based interventions have proved effective in reducing alcohol use in young adult drinkers (Correia et al. 2005; Murphy et al. 2012). In more dependent populations, longer term interventions have aimed to address comorbid depression and substance dependence by helping clients identify drug-unrelated forms of positive reinforcement, and schedule pleasant activities in their daily routine (e.g. Daughters et al. 2008; MacPherson et al. 2010; Ross et al. 2016). Preliminary trials have reported improvements in depressive symptoms, abstinence, and retention in treatment compared to treatment as usual (Daughters et al. 2008; Daughters et al. 2018; MacPherson et al. 2010; Magidson et al. 2011). The success of these types of interventions provides a direct translation from animal models: rats reared in complex, novel environments with plentiful sources of positive reinforcement show decreased drug self-administration and drug-seeking as compared to rats reared in standard housing (Bardo et al. 2001; Green et al. 2002; Puhl et al. 2012; Stairs et al. 2006). This is arguably because environmental enrichment of this type reduces the relative reinforcing value of the drug (Marianno et al. 2017). Overall, then, interventions to limit the relative value of the drug are effective in promoting abstinence, but typically require significant resources and/or time. There may be a gap in the current range of treatments for substance dependence for additional brief rescue interventions based on behavioural economic principles.

1.3.2 Interventions for cue reactivity

Cue reactivity interventions are typically designed to extinguish the association between cues and drug-seeking behaviour. Cue-exposure therapy (CET), for example, aims to reduce conditioned drug-seeking by exposing dependent individuals to motivating cues, and then preventing drug use in a process of repeated non-reinforced exposure (Drummond et al. 1990; Marlatt 1990; Mellentin et al. 2017). While these treatments reliably reduce cue-elicited craving in experimental settings (Price et al. 2010; Staiger et al. 1999), systematic reviews have found little evidence for the efficacy of CET in maintenance of abstinence (Conklin and Tiffany 2002; Martin et al. 2010; Mellentin et al. 2017), perhaps due to poor generalisation of learning across contexts

(Collins and Brandon 2002; Thewissen et al. 2006). On this basis, cue reactivity does not appear a promising target of brief interventions. Societal-level interventions to limit exposure to cues in the natural environment (for example, plain packaging policies: Hogarth et al. 2015b) might prove more effective in targeting this mechanism.

1.3.3 Interventions for cost insensitivity

Cost insensitivity interventions in dependence typically target delay discounting. If dependence is underpinned by an inability to attend to abstract, future drug-related costs, then interventions which encourage conceptualisation of these costs in more immediate terms might prove effective (Yi et al. 2017). Episodic future thinking (EFT) training encourages dependent individuals to imagine future events in a concrete and vivid manner (Atance and O'Neill 2001). EFT training has proved effective in reducing delay discounting in dependent individuals (Chiou and Wu 2016; Snider et al. 2016; Stein et al. 2016). However, such interventions may prove less effective in more severely dependent populations (Snider et al. 2016), perhaps because this group exhibit specific deficits in autobiographic memory which may prove resistant to training (D'Argembeau et al. 2006; Griffiths et al. 2012). While EFT training therefore appears a promising intervention, further investigation is required to determine its applicability across treatment-seeking populations.

1.3.4 Interventions for negative affect driven drug motivation

Interventions which aim to protect against negative affective triggers to drug use are typically either pharmacological or cognitive behavioural. Antidepressant agents, which aim to limit negative affect, have proved minimally effective in promoting abstinence in dependent individuals with comorbid depression (Kranzler et al. 2006; Pettinati 2004; Pettinati et al. 2001). By contrast, there is a strong body of evidence for the efficacy of cognitive behavioural interventions in substance dependence (Dutra et al. 2008; Magill and Ray 2009). Relapse prevention (RP) therapy, for example, aims to identify high risk situations for relapse (which might include experience of negative affect), and provide dependent individuals with the cognitive and behavioural coping skills to respond adaptively (Larimer et al. 1999; Marlatt and Gordon 1985; Witkiewitz and Marlatt 2004). There is reliable evidence for the efficacy of RP compared to no

treatment (Carroll 1996; Irvin et al. 1999), but little evidence of superiority compared to other active treatments (Brown et al. 2002; Thakker and Ward 2010).

Original models of relapse prevention were criticised for promoting control over or avoidance of negative affect (Thakker and Ward 2010). In experimental trials, acceptance as opposed to avoidance or suppression is associated with more efficient regulation of negative affect (Campbell-Sills et al. 2006; Singer and Dobson 2007; 2009), and reduced negative affect driven drug seeking (Tull et al. 2015). In response, a number of treatment programmes have been developed which foster an acceptance-based approach to negative affect (Vieten et al. 2010). Mindfulness-based relapse prevention (MBRP) retains the core components of RP but in addition incorporates mindfulness practices to increase non-evaluative awareness and tolerance of unpleasant internal states (Bowen et al. 2009). However, evidence for this intervention is relatively weak: a systematic review of MBRP found little evidence for the efficacy of this treatment compared to other active treatments such as CBT or standard RP (Grant et al. 2015). Other acceptance-focused treatment programmes such as Acceptance and Commitment Therapy (ACT) and Acceptance Based Coping for Relapse Prevention (ABCRP) have shown promising results in improving treatment outcomes (Lee et al. 2015) and in reducing negative affect and emotional reactivity in dependent individuals (Vieten et al. 2010) but further high-quality research in this area is required.

Finally, epidemiological evidence supports a negative correlation between physical activity and drug use (Iannotti et al. 2009; Liangpunsakul et al. 2010; Strohle et al. 2007). On this basis, a number of exercise-based interventions have been developed as adjunctive treatments for substance dependence. A review by Zschucke et al. (2012) indicated strong evidence for exercise in smoking cessation, and more recent studies have indicated improved treatment outcomes in other dependent populations (Brown et al. 2014; Brown et al. 2010; Buchowski et al. 2011; Roessler 2010).

There are a number of mechanisms by which exercise might improve outcomes in substance dependence (Linke and Ussher 2015). A plausible possibility is that exercise limits negative affect driven drug motivation by driving a global improvement in affective state: enhancing positive affect (Dua and Hargreaves 1992; Reed and Ones 2006), reducing negative affect (Babyak et al. 2000; Penninx et al. 2002) and anxiety

(Breus and O'Connor 1998; Wipfli et al. 2008), and protecting against negative affective symptoms of withdrawal (Taylor et al. 2007; Williams et al. 2011). However, a therapeutic effect of exercise on negative affect driven drug motivation has not been established.

1.4 Concluding remarks

On review of the literature, the behavioural marker most reliably associated with dependence severity is valuation of the drug. However, this mechanism in isolation may be insufficient to fully account for a subgroup of treatment-seeking individuals for whom the course of dependence is chronic and relapsing and in whom continued drug use appears compulsive or irrational. This thesis considers three candidate secondary mechanisms: cue reactivity (Chapter 3), cost discounting (Chapter 4), and sensitivity to negative affective triggers (Chapters 6, 7, and 8). Current measures of drug value are not optimised for use in clinically dependent populations, and therefore a novel pictorial choice measure is validated in Chapter 5.

A wide range of interventions have been proposed for substance dependence. However, it remains unclear whether the therapeutic effects observed in these interventions are driven by the proposed underpinning mechanisms. While interventions which aim to limit the relative value of the drug by providing alternative reinforcement have proved particularly effective, these typically require significant resources and/or time. There is therefore a need for brief, cost-effective, and evidence-based interventions which modify specific mechanisms known to underpin dependence. As it stands, there is a lack of brief interventions targeting negative affect as a motivator for drug use. Given that negative affect acutely raises drug motivation (Birch et al. 2004; Cooney et al. 1997; Cyders et al. 2016; Rousseau et al. 2011), brief and easily implemented rescue interventions to limit this effect may prove valuable in protecting against relapse. This thesis focuses on three novel interventions for negative affect driven drug motivation, derived from exercise (Chapter 10), acceptance-based coping (Chapter 11), and environmental enrichment research (Chapter 12).

Chapter 2. Summary of Thesis

The first aim of this thesis was to investigate the contribution of three candidate mechanisms to dependence: cue reactivity, cost discounting, and sensitivity to negative affective triggers. Having demonstrated that negative affect driven drug-seeking appears to represent an individual risk factor for dependence, the second aim was to use a novel experimental model to trial interventions to limit or abolish this effect.

A literature review is presented in **Chapter 1.** On the basis of evidence presented, supernormal drug valuation appears to be the primary mechanism underpinning dependence. Chapters 3 and 4 investigated two secondary candidate mechanisms: cue reactivity and insensitivity to drug costs. **Chapter 3** demonstrated that alcohol dependence severity was not significantly associated with cue-driven alcohol choice in a Pavlovian to instrumental transfer task. **Chapter 4** demonstrated that alcohol dependence severity was not significantly associated with insensitivity to delay and opportunity costs in a points-based concurrent choice task. Both experiments found that greater severity of alcohol dependence was, however, significantly associated with greater relative value ascribed to alcohol, indexed by percent choice of the drug over alternative reinforcement. These studies suggest that drug cue reactivity and insensitivity to costs may not contribute substantially to dependence, and instead emphasise the role of raised drug value, consistent with behavioural economic theories. However, current measures of drug value are not optimised for use with clinically-dependent populations. **Chapter 5** found that a novel pictorial concurrent choice procedure provided a reliable behavioural assay of drug value in two treatment-seeking dependent populations: recently-hospitalised smokers and treatment-engaged drinkers.

The third candidate mechanism for dependence, derived from negative reinforcement theories, is sensitivity to the motivational effect of negative mood on drug use. Chapters 6 to 8 aimed to quantify the effect of induced negative mood on alcohol motivation and identify individual differences in sensitivity to this effect. **Chapter 6** demonstrated that induction of negative mood augmented motivation to drink in hazardous drinkers. **Chapters 7 and 8** replicated this finding in two samples of student drinkers, and found that depression and drinking to cope with negative affect

predicted greater sensitivity to this effect. These findings delineate a particular subset of dependent individuals for whom negative affect may represent a substantial trigger to continued use. **Chapter 8** demonstrated that negative affect promoted a novel alcohol-seeking response in extinction, suggesting that negative affective states control drug-seeking by a goal-directed, as opposed to automatic, mechanism. In our favoured goal-directed account, expectation of raised drug value under conditions of negative affect is integrated with knowledge of response-outcome contingencies in a process of incentive learning.

Chapter 9 aimed to establish this model of negative affect induced drug motivation in a population of recently-hospitalised smokers. Choice of smoking images showed no evidence of modulation under induced negative affect, and we found no evidence that individuals with depression or who smoked to cope with negative affect were particularly sensitive to this effect. These null findings may be attributed to our use of an intermixed mood induction procedure which incorporated both positive and negative affective statements, reducing our power to detect an effect.

The second half of the thesis trialled brief interventions to abolish or limit negative affect driven drug motivation. Interventions were designed to be brief and inexpensive, with prior evidence of efficacy. In **Chapter 10**, a natural walk intervention in hazardous drinkers showed no evidence of limiting negative affect driven alcohol motivation in two experiments. In **Chapter 11** brief instruction in acceptance-based coping showed no evidence of limiting negative affect driven alcohol motivation in a treatment-engaged alcohol dependent population. These two interventions were therefore eliminated as potential interventions. In **Chapter 12**, engagement with pleasant environmental images, as a proxy for environmental enrichment, significantly reduced negative affect driven alcohol choice in individuals who reported a desire to visit the locations shown (high liking), compared to low liking individuals and controls. This provides preliminary evidence for environmental enrichment type interventions. These findings are consistent with behavioural economic conceptions of dependence which predict that raising the value of competing alternative reinforcement should limit drug-seeking behaviour.

Chapter 13 provides a general discussion of findings, implications, and future directions for research. Overall, while dependence may be primarily underpinned by supernormal drug valuation, sensitivity to negative affective triggers may confer additional risk, particularly in individuals who are depressed and use the drug to cope with negative affect. The most effective brief interventions to protect against this acute motivational effect of negative mood may be those which raise the value of alternative reinforcement.

Finally, appendices enclose an additional publication arising from our collaboration with the Exeter Drug Project, assessing a brief CBT-based intervention for alcohol-related violence (**Appendix A)**. This work was undertaken to facilitate access to client groups for the main experimental studies.

Chapter 3. Drug cue reactivity involves hierarchical instrumental learning: Evidence from a biconditional Pavlovian to instrumental transfer task

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3.1 Abstract

Rationale: Drug cue reactivity plays a crucial role in addiction yet the underlying mechanisms are poorly understood. According to the binary associative account, drug stimuli retrieve an expectation of the drug outcome, which in turn elicits the associated drug-seeking response (S-O-R). By contrast, according to the hierarchical account, drug stimuli retrieve an expectation that the contingency between the drug-seeking response and the drug outcome is currently more effective, promoting performance of the drug-seeking response (S:R-O). *Methods*: The current study discriminated between these two accounts using a biconditional Pavlovian to instrumental transfer (PIT) task with 128 alcohol drinkers. A biconditional discrimination was first trained in which two responses produced alcohol and food outcomes respectively, and these response-outcome contingencies were reversed across two discriminative stimuli (SDs). In the PIT test, alcohol and food cues were compounded with the two SDs to examine their impact on percent alcohol choice in extinction. *Results*: It was found that alcohol and food cues selectively primed choice of the response that earned that outcome in each SD (p<.001), and this effect was associated with participants' belief that cues signalled greater effectiveness of that response (p<.0001). *Conclusions*: The alcohol stimulus could not have selectively primed the alcohol-seeking response though binary S-O-R associations because the drug outcome was equally associated with both responses. Rather, the alcohol stimulus must have retrieved an expectation that the response-alcohol contingency available in the current context was more likely to be effective (S:R-O), which primed performance of the alcohol-seeking response.

3.2 Introduction

Drug cue reactivity is a central construct in addiction research, and there have been numerous attempts to elucidate the underlying learning mechanisms (e.g. Carter and Tiffany 1999). Drug cue reactivity was originally attributed to the formation of a direct association between the stimulus and the response (Wikler 1984), but later theories accepted that drug cues might elicit expectations of the drug, which drive drug-seeking behaviour (Stewart et al. 1984). Several sources of evidence are consistent with this latter view. First, drug conditioning studies have found that drug-paired conditioned stimuli (CS) only elicit craving and drug consumption if participants possess knowledge of the predictive relationship between the conditioned stimulus (CS) and the drug (Hogarth and Duka 2006). More decisively, conditioned craving to CS can be immediately established by instructions stating that the CS predicts drug availability, and abolished by instructions stating that the CS no longer predicts drug availability (Dols et al. 2000; Field and Duka 2001). Such instruction effects on human non-drug conditioning have been extensively reported (Mitchell et al. 2009). Thus, drug expectancies appear to contribute causally to drug cue reactivity.

The Pavlovian to instrumental transfer (PIT) procedure provides a key method for studying the role of drug expectancies in drug-seeking behaviour. In a typical human drug PIT design, participants undergo instrumental training in which one response (R1) earns a drug reward outcome (O1), and another response (R2) earns a food outcome (O2) (R1-O1, R2-O2) (Hogarth et al. 2007). In a separate phase, participants learn that two Pavlovian stimuli differentially predict those same outcomes (S1-O1, S2-O2). In the transfer test, the Pavlovian stimuli are presented while participants freely choose between the two responses in extinction (S1:R1/R2, S2:R1/R2). It has been found that each cue selectively augments choice of the response that earns the same (congruous) outcome (S1:R1>R2, S2:R1<R2) (Hogarth et al. 2007). The capacity of the drug stimulus to selectively prime the drug-seeking response cannot be attributed to the formation of an S-R association (habit learning) because the Pavlovian stimulus and the instrumental response are trained in separate stages and so are never paired prior to testing. Rather, to explain this effect, the drug stimulus must retrieve an expectation

(or representation) of the drug outcome with which it was paired, to specifically prime the response that was paired with the same outcome.

There are two variants of this expectancy based account of PIT. The S-O-R account argues that the PIT effect is driven by a chain of binary associations between stimuli, outcomes and responses (de Wit and Dickinson 2009). Specifically, in the Pavlovian phase, each stimulus forms a binary association with (and can elicit an expectation of) its associated outcome (S1-O1, S2-O2). Similarly, in the instrumental training phase, each response forms a binary association with its associated outcome (R1-O1, R2-O2). Crucially, these R-O links are bidirectional such that an S-elicited expectation of a particular O can elicit the associated R through the chain of S-O-R links. Thus, each S selectively primes one R through an expectation of the outcome, shared by both the S and R.

The hierarchical account, by contrast, argues that the PIT effect is driven by stimuli retrieving an expectation (or representation) of which R-O relationship is currently in force (S:R-O) (Dickinson 1997; Rescorla 1991). In the context of cue reactivity, the presence of particular drug stimuli (e.g. a bar or pub open sign) retrieves an expectation that a particular drug-seeking response (walk in and buy a drink) is likely to be effective in producing the drug (a drink), raising the propensity to perform this response. To explain the PIT effect, the hierarchical account argues that S:R-O relations are learned in both the Pavlovian and instrumental phases. In the Pavlovian phase, S1 and S2 signal that a common tacit response (e.g. hopper entry, saccade, approach etc.) produces access to O1 and O2 respectively. By contrast, in the instrumental phase, a common contextual stimulus signals that R1 and R2 produce access to O1 and O2 respectively. The PIT effect in the transfer test is produced by a combination of (inference between) the S:R-O relations acquired in these two stages. That is, S1 is inferred to signal that the R1-O1 contingency is in force, whereas S2 is inferred to signal that the R2-O2 contingency is in force. These expectancies drive performance of the viable response. In other words, each stimulus elicits a goal-directed expectation that the R-O contingency for the shared O is more likely to be effective, which primes performance of that R (Hogarth et al. 2014; Seabrooke et al. 2015).

The binary versus hierarchical explanations of PIT can be distinguished using a biconditional discrimination task. This task has demonstrated that animals are capable of hierarchical learning (e.g. Bradfield and Balleine 2013; Colwill and Rescorla 1990; Trask and Bouton 2014), but has rarely been used in humans (Declercq and De Houwer 2009). The current study employed a novel human biconditional PIT task with alcohol and food outcomes to test whether drug stimulus control of drug-seeking is underpinned by binary or hierarchical learning. In the biconditional training phase, participants learned that in one discriminative stimulus (SD1) R1 earned alcohol O1, and R2 earned food O2 (SD1: R1-O1, R2-O2). These response-outcome contingencies were reversed in the second SD (SD2: R1-O2, R2-O1). In the transfer test, an alcohol or food image was presented together with each SD. The purpose of this phase was to test whether the alcohol and food stimuli could selectively prime the response which earned the congruous outcome in the current SD (a biconditional PIT effect).

This biconditional PIT effect could not be explained by binary S-O-R associations because all binary associations between SDs, outcomes and responses are equated by the biconditional schedule (the original purpose of this procedure: Rescorla 1991). That is, the S-O-R account predicts that when the alcohol stimulus is presented at test it will elicit an expectation of the alcohol outcome (S-O). However, because this outcome has been equally associated with both responses, it should prime both responses equally through the O-R link, creating no selective choice of the response which earns the alcohol outcome in the current SD (no biconditional PIT effect). The same is true for the food stimulus. By contrast, the hierarchical account anticipates that alcohol and food stimuli will produce a biconditional PIT effect on the grounds that these stimuli retrieve knowledge of hierarchical S:R-O contingencies, i.e. knowledge of which response produces the congruous outcome in the current SD, because they are functionally similar to (have acquired equivalence with) the SD used in the training stage (Hall et al. 2003). Arguably, the alcohol and food stimuli elicit an expectation that the response which earns the congruous outcome in the current SD is more likely to be reinforced, which selectively primes that response. This claim was further tested by asking participants after the PIT test to rate the extent to which they thought that the alcohol and food stimuli signalled that the congruous response was more likely to be reinforced. A correlation between these expectations and the biconditional PIT effect

would support the claim that the biconditional PIT effect is underpinned by hierarchical knowledge of S:R-O relations. Evidence for a hierarchical account of drug cue reactivity would have implications for treatment strategy.

3.3 Method

3.3.1 Participants

One hundred and twenty-eight students who reported drinking at least occasionally (50% male) were recruited at the University of Exeter. There were no other inclusion criteria. Ethical approval was obtained from the University of Exeter Research Ethics Committee.

3.3.2 Questionnaires

Participants reported age, gender, and alcohol use/alcohol-related problems in the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al. 2001).

3.3.3 Biconditional training

Participants were instructed that "In this task, you can earn beer and chocolate to take away at the end. In each trial, press the left or right key to win a point for these rewards. Different arrow shapes indicate which key earns which reward. It is your task to learn this. Press any key to begin". Participants were shown the alcohol reward (a 275ml bottle of Becks) and the food reward (a 45g bar of Dairy Milk), and these remained in sight. This was a deception. All participants were given a small chocolate bar at the end of testing.

Sequential training established the biconditional contingencies (Table 3.1). The first block of 8 trials began with SD1, a particular arrow symbol (black or blue) pointing in both directions signalling that either a left or right key press response could be made. Participants were free to press either the left or right arrow keyboard key. Pressing a key presented the outcome text "You earn beer" (O1) or "You earn chocolate" (O2) below the arrow symbol for one second prior to an random inter-trial-interval (ITI) of 350-750msec. SD1 signalled that response 1 (R1) earned alcohol and response 2 (R2) earned food: SD1:R1-O1, R2-O2. These response-outcome contingencies were deterministic, that is, they produced their relevant outcome with 100% probability on a

fixed ratio 1 schedule. In the next block of 8 trials, the arrow symbol SD2 was presented, which signalled that the reverse R-O mappings were in effect, i.e. SD2: R1-O2, R2-O1. Whether black or blue arrow symbols functioned as SD1 or SD2 in the two blocks was counterbalanced between-subjects, as well as the left/right responses that functioned as R1 and R2. Following these 16 trials, participants reported their knowledge of the biconditional contingencies in four questions in which SD1 and SD2 were presented twice, along with the questions (in random order): "When this arrow was present, which key earned [beer/chocolate] the LEFT or RIGHT key?" Participants were deemed to have acquired knowledge of the biconditional contingencies when they got all four questions correct, and sequential training blocks continued until this criteria was met. Participants then experienced intermixed training, in which SD1 and SD2 trials were randomly intermixed across each set of 16 training trials. Training continued until all four contingencies questions were correctly answered.

3.3.4 Transfer test phase

Participants were instructed: "In this part of the task, you can earn beer and chocolate in the same way as before. However, you will only be told how much you have earned at the end of the experiment. Press any key to begin." This phase was conducted in nominal extinction to test the effect of cues in the absence of feedback from outcomes (Table 3.1). In each trial, the arrow symbol SD1 or SD2 was displayed with a picture of either alcohol (two beer glasses being tapped together), food (close-up of chocolate chunks), or a blank grey image, located above the arrow symbol. Participants then made a left or right key press but received no feedback about the outcome earned, and instead the ITI of 350-750msec launched before the next trial. There were 48 transfer trials, comprising four cycles of 12 trials, in which the two arrow symbols (SD1, SD2), were presented with each of the three stimuli (alcohol, food, blank) twice for each combination. Alcohol and food images were expected to augment choice of the arrow key which produced the congruous outcome in that context.

Biconditional training	Transfer test	Expectancy test
SD1:R1-O1, R2-O2 SD2:R1-O2, R2-O1	AlcoholS+SD1: R1/R2 AlcoholS+SD2: R1/R2 FoodS+SD1: R1/R2 FoodS+SD2: R1/R2 BlankS+SD1: R1/R2 BlankS+SD2: R1/R2	AlcoholS/FoodS: 'When this picture was presented, to what extent did you think that the [beer/chocolate] key was more likely to be rewarded?

Table 3.1 shows the arrangement of the training, test and expectancy phases. SD1 and SD2 were blue and black arrow keys which signalled the reversal of two response-outcome (R-O) contingencies. R1 and R2 were left or right keyboard arrow presses. O1 was beer points, O2 was chocolate points. AlcoholS was a picture of beer, FoodS was a picture of chocolate, and BlankS was a grey square.

3.3.5 Expectancy scores

Participants' expectations that stimuli signalled effective R-O relations were then measured in two questions. Participants were told "We would now like to examine your thoughts about the beer and chocolate pictures. Please think carefully about your answers. Press any key to begin". Participants were presented with the alcohol and food stimuli individually in separate trials in random order. Upon presentation of the alcohol stimulus they were asked: "When this picture was presented, to what extent did you think that the beer key was more likely to be rewarded? Press a key from 1 to 7', with a Likert scale from 1 (not at all) to 7 (very much). Upon presentation of the food stimulus they were asked: "When this picture was presented, to what extent did you think that the chocolate key was more likely to be rewarded? Press a key from 1 to 7'. Finally, participants' knowledge of the biconditional contingencies was tested as before.

3.3.6 Analysis

ANOVA first tested whether the alcohol and food stimuli increased choice of the response for the congruous outcome, collapsed across the two SDs. An ANCOVA then tested whether the biconditional PIT effect increased with mean expectancies that

stimuli signalled greater efficacy of the corresponding response (mean expectancy scores in the beer and chocolate stimulus were collapsed because they were so highly correlated, r=.74, p<.001). This effect would suggest that cue reactivity is driven by knowledge of hierarchical relations. A similar ANCOVA was run to determine if the biconditional PIT effect varied with alcohol use/ problems, indexed by the AUDIT.

3.4 Results

3.4.1 Participants

Of 128 participants, eight participants reported inaccurate knowledge of the biconditional contingencies following the transfer test and were excluded (Hogarth et al. 2007; Trick et al. 2011). One participant was excluded for requiring an outlying number of sequential training blocks to acquire contingency knowledge (10 sixteen-trial blocks). The mean for the remaining 119 participants (54% male) was 1.3 blocks, range=1-4. The mean number of intermixed blocks required to report accurate knowledge was 1.2 (range 1-5). The remaining sample had a mean age of 20.7 (range=19-38), and a mean AUDIT score of 13.4 (range=1-30).

3.4.2 Transfer test

Figure 3.1A shows the percent choice of alcohol over food in alcohol, food and blank stimulus trials, collapsed across SD1 and SD2. ANOVAs on these data yielded a significant main effect of stimulus, F(2,236)=70.71, p<.001, eta^2=.37, where alcohol differed from food, F(1,118)=99.15, p<.001, eta^2=.46, and blank, F(1,118)=44.55, p<.001, eta^2=.27, and food differed from blank, F(1,118)=45.90, p<.001, eta^2=.28. The extent to which alcohol and food stimuli primed their corresponding responses relative to blank trials was comparable, F(1,118)=.77, p<.38, eta^2=.01. Thus, cues were highly effective in promoting the response which produced the congruous outcome in the discriminative context (SD1 and SD2), supporting a hierarchical account of cue reactivity.

Figure 3.1B shows that the biconditional PIT effect varied with expectations that cues signalled greater efficacy of the corresponding response. ANCOVA on these data revealed a significant interaction between stimulus and expectancy, F(2,234)=16.79, p<.0001, eta^2=.13, and no main effect of expectancy, F(1,117)=1.84, p=.17, eta^2=.02, indicating that overall alcohol choice did not increase with expectancy. The interaction

between stimulus and expectancy was reliable when the model was restricted to alcohol and food trials, $F(1,117)=24.92$, $p<.0001$ $eta^2=.18$, alcohol and blank trials, $F(1,117)=10.65$, $p=.001$ $eta^2=.08$, and food and blank trials, $F(1,117)=9.60$, $p=.002$ $eta^2=.08$. These findings suggest that cue reactivity is associated with knowledge of hierarchical relations.

Figure 3.1C shows that the biconditional PIT effect varied with alcohol use/problems (AUDIT) scores. There was a main effect of AUDIT, $F(1,117)=13.23$, $p<.001$ $eta^2=.10$, indicating that alcohol use/problems was associated with greater alcohol choice overall. There was also a significant interaction between stimulus and AUDIT, $F(2,234)=5.04$, $p=.007$ $eta^2=.04$, suggesting that the PIT effect varied with alcohol use/problems. However, the interaction between stimulus and AUDIT was not reliable when the model was restricted to alcohol and blank trials, $F(1,117)=0.01$, $p=.93$ $eta^2<.01$, suggesting the alcohol PIT effect is constant across alcohol use/problems. By contrast, the interaction between stimulus and AUDIT was reliable when the model was restricted to food and blank trials, $F(1,117)=12.37$, $p=.001$ $eta^2=.10$, and alcohol and food trials, $F(1,117)=5.51$, $p=.02$ $eta^2=.05$, suggesting that the food PIT effect was compressed in low-dependent individuals because baseline food responding in blank trials was near maximal. Finally, AUDIT and expectancy scores were not significantly correlated, $r=.09$, $p=.33$.

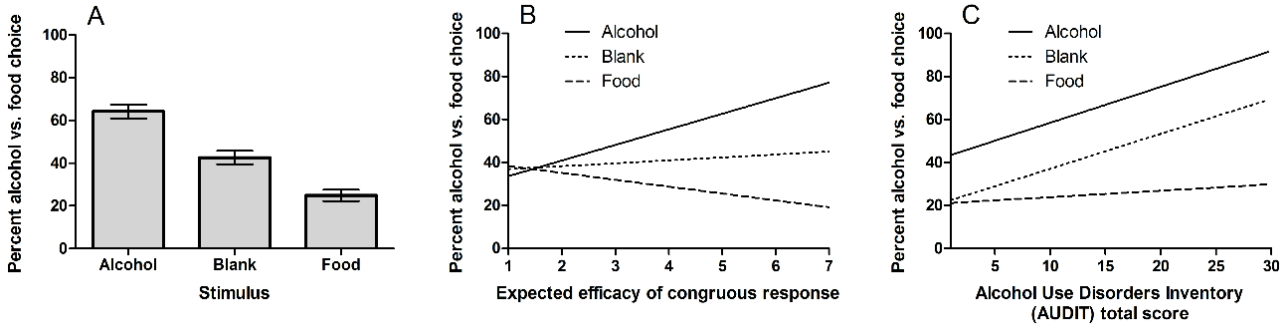

Fig 3.1A Bar chart showing the mean percent choice of alcohol in alcohol, blank, and food stimulus conditions of the transfer test. Fig 3.1B Regression slopes plotting the percent choice of alcohol in the alcohol, food and blank stimuli of the transfer test, against the mean expectancy score (1-7) that stimuli signalled greater efficacy of the congruous response-outcome relation. Fig 3.1C Percent choice of alcohol in the alcohol, food and blank stimuli of the transfer test plotted against the alcohol use/alcohol-related problems (AUDIT) scores.

3.5 Discussion

The current study tested whether the capacity of alcohol cues to specifically promote alcohol-seeking behaviour is driven by binary S-O-R links or hierarchical S:R-O knowledge, using a biconditional PIT task. A biconditional discrimination was trained in which two SDs signalled the reversal of two R-O contingencies for alcohol and food outcomes respectively (SD1:R1-O1, R2-O2. SD2:R1-O2, R2-O1). The transfer test found that alcohol and food stimuli presented with these SDs selectively primed performance of the response which earned the congruous outcome in each SD. This biconditional PIT effect cannot be explained by the S-O-R account because the binary associations between SDs, Os and Rs were all equivalent in the biconditional schedule. Specifically, because the alcohol and food outcomes have equal binary associations with both responses, the S-O-R account anticipates that the retrieval of an alcohol outcome expectancy by the alcohol stimulus would activate both Rs equally, producing no preferential selection between the two responses (the same is true for the food stimulus). Rather, for the alcohol and food stimuli to have selectively primed the congruous response, they must have retrieved hierarchical knowledge of which response produced that outcome in each SD (S:R-O). The finding that the magnitude of the PIT effect increased with participants' expectations that alcohol and food stimuli signalled greater effectiveness of the congruous response supports the view that this effect is underpinned by hierarchical knowledge of S:R-O relations.

Several other findings support the hierarchical account of PIT. First, PIT effects are larger when R-O contingencies are partially reliable (33%) compared to fully reliable (100%) (Cartoni et al. 2015). S-O-R theory anticipates the opposite finding because the O-R link is weaker in the unreliable condition and so should produce a smaller PIT effect. By contrast, the hierarchical account anticipates this finding because PIT effects should be greater when cues resolve uncertainty about the effectiveness of R-O contingencies. Second, PIT effects are generally larger with cues that have been trained as SDs compared to Pavlovian stimuli (Rescorla 1994; Troisi 2006). The S-O-R account predicts the opposite finding because discriminative training (S:R-O) should lead to overshadowing by the R, producing a weaker S-O link compared to Pavlovian training. By contrast, the hierarchical account anticipates this finding because stimuli that have

been trained as SDs initially should be more readily treated as SDs in the PIT test (Hall et al. 2003). Finally, PIT effects are extinguished more rapidly if stimuli undergo discriminative extinction where the S signals that the R-O relation is not in force, compared to Pavlovian extinction where the S signals that the O will not occur (Delamater 1996; Gámez and Rosas 2005; Hogarth et al. 2014; Rescorla 1992; Rosas et al. 2010). Again, the S-O-R account predicts the opposite finding because Pavlovian extinction should more readily degrade the S-O link. In contrast, the hierarchical account anticipates this finding because discriminative extinction degrades the hierarchical S:R-O relations which underpin the PIT effect. Finally, the PIT effect can be abolished by verbal instructions that stimuli do not signal which response is more effective, or created by instructions stating that stimuli signal which response is more likely to be effective, suggesting that hierarchical knowledge of S:R-O relations is sufficient to drive the PIT effect (Hogarth et al. 2014; Seabrooke et al. 2015). However, it should be noted that although hierarchical knowledge underpinned the current biconditional PIT effect, it remains possible that simpler associative structures, such as S-R habit learning or binary S-O-R learning could play a role in cue reactivity when biconditional contingencies are not in effect, and the current study cannot rule out this possibility.

The hierarchical account has implications for the treatment of cue reactivity. Studies have attempted to extinguish drug-seeking by means of Pavlovian extinction, where drug cues are presented without drug consumption, or instrumental extinction, where mock drug-taking does not produce drug reinforcement. Although these procedures reduce cue-elicited craving in the laboratory (Conklin and Tiffany 2002; Price et al. 2010; Xue et al. 2012), they do not abolish PIT effects (Delamater 1996; Hogarth et al. 2014; Rosas et al. 2010) or produce long-term improvements in abstinence (Conklin and Tiffany 2002). The hierarchical account anticipates these clinical failures because extinguishing binary S-O and R-O relations leaves hierarchical S:R-O relations intact. One might argue, therefore, that interventions should seek to degrade hierarchical knowledge using discriminative extinction training procedures (S:R-no O). These procedures are more effective at abolishing PIT in the laboratory (Delamater 1996; Gámez and Rosas 2005; Hogarth et al. 2014; Rescorla 1992; Rosas et al. 2010). However, the more intractable problem is that extinction learning generalises poorly between

contexts (Collins and Brandon 2002; Thewissen et al. 2006), and there is no evidence that discriminative extinction would be any less susceptible to this problem. A possible solution could be the implementation of discriminative extinction training in the user's natural environment with ecologically valid stimuli and responses. However, clients' knowledge that bars and pubs signal the viability of alcohol-seeking behaviour is veridical with environmental contingencies, and may not be susceptible to modification by cognitive behaviour therapy or gamified tasks. Psychologists might therefore be tempted to abandon retraining of cue reactivity in the natural environment, and instead focus on minimising the pervasiveness of environmental drug cues by evaluating plain packaging policy (Hogarth et al. 2015b) or the regulation of advertising (Jernigan et al. 2017), for example.

AUDIT scores were not associated with the alcohol PIT effect: the extent to which the alcohol stimulus primed alcohol-seeking above the blank condition. Such null associations between drug PIT and severity of drug use/problems have been found previously for alcohol (Garbusow et al. 2014; Martinovic et al. 2014) and tobacco (Hogarth 2012; Hogarth and Chase 2011; 2012). In addition, cue-elicited craving also shows no association with dependence level (Perkins 2009) or relapse (Perkins 2012), suggesting that drug cue reactivity is not associated with severity of addiction. The hierarchical account anticipates these null associations because all drug users should rapidly acquire comparable knowledge that drug cues signal the viability of drug-seeking behaviour. This means that drug cues should prime drug-seeking over baseline to a comparable extent irrespective of an individual's level of drug use severity.

Higher AUDIT scores were associated with an overall increased preference for alcohol over food. Such associations between drug dependence severity and overall preferential drug choice have been consistently reported (Hogarth 2012; Hogarth and Chase 2011; 2012; Moeller et al. 2013; Moeller et al. 2009), and suggest that drug dependence severity is underpinned by the ascription of greater relative value to drugs over other reinforcers (Ahmed 2010; Bickel et al. 2014; Heyman 2013; MacKillop 2016). By contrast, expectancy scores were not associated with an overall increase in alcohol choice.

The study reported a double dissociation: expectancy scores were associated with PIT but not overall alcohol choice, whereas AUDIT scores were associated with overall alcohol choice but not PIT. There was also no correlation between AUDIT and expectancy scores. The implication is that drug-seeking is governed by two independent processes (Cartoni et al. 2013; Hogarth 2012). Whereas the expected value of alcohol (indexed by AUDIT) determines the overall preference for alcohol, the expected viability of the alcohol-seeking response in the alcohol stimulus (indexed by expectancy scores) determines the alcohol PIT effect. This dual-process account of drug-seeking suggests that treatments must simultaneously address cue reactivity and expected drug value in order to improve therapeutic outcomes.

One unexpected result was that the magnitude of the food PIT effect was smaller in less dependent individuals. This was presumably due to food choice nearing maximal in blank trials in low-dependent individuals (approx. 80%), leaving little room for increase following food stimulus presentation. By contrast, alcohol choice peaked at around 60% in blank trials in more dependent individuals, and there was no reduction in the difference between alcohol and blank conditions as dependence increased, suggesting that the alcohol PIT effect was not similarly constrained by a ceiling effect.

In conclusion, the study used a biconditional PIT procedure to support a hierarchical learning account of drug cue reactivity. On this view, drug cues elicit an expectation that drug-seeking responses available in the current context are more effective, thus priming those responses. The study excluded the S-O-R account of cue reactivity which argues that drug expectancies directly elicit the drug-seeking responses with which they have been paired. Treatments which aim to reduce cue reactivity might therefore attempt to modify hierarchical knowledge that certain drug-seeking responses are viable in particular stimulus contexts. However, there remains the question as to what extent hierarchical knowledge, compared to simpler associative structures such as S-R or S-O-R, contribute to drug cue reactivity in the natural environment. Resolving this issue is crucial for determining which form of knowledge to target therapeutically.

Chapter 4. Alcohol use disorder symptoms are associated with greater relative value ascribed to alcohol, but not greater discounting of costs imposed on alcohol

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4.1 Abstract

Rationale: Alcohol dependence is characterised by persistent drinking despite health, social and economic costs. Behavioural economics has proposed two explanations for the persistence of alcohol use despite costs. Dependent individuals may (a) ascribe excessively high value to alcohol, such that costs associated with alcohol are exceeded, and/or (b) they may discount (neglect) the costs associated with alcohol. **Methods:** To test these predictions, the current study recruited 127 student drinkers who reported varied alcohol use disorder symptom severity in the Alcohol Use Disorders Inventory Test (AUDIT; mean=11.17, 69% above the hazardous cutoff). Participants made concurrent forced choices between alcohol and food points under conditions that manipulated the magnitude of points (1, 2 or 3) and the delay to receive points (0 or 3 seconds). Alcohol value was indexed by preferential choice of alcohol versus food points, whereas sensitivity to costs was indexed by the decrease in alcohol choice when food points were of greater magnitude (sensitivity to opportunity costs) and when alcohol points were delayed (sensitivity to delay costs). **Results**: Percent choice of alcohol over food varied consistently with the relative magnitude of points offered (p<.001) and with time delays imposed on these rewards (p<.001). AUDIT scores were associated with greater alcohol versus food choice across all conditions (p=.001). As alcohol use disorder symptom severity increased, the sensitivity of alcohol choice to the relative magnitude of points (p=.29) and time delays (p=.62) remained unchanged, suggesting no differential discounting of opportunity or delay costs imposed on alcohol. In contrasts of AUDIT categories, there was comparable sensitivity to costs across groups defined as low-risk (N=39), hazardous (n=57), harmful (n=20) and

possible dependent drinkers (n=11). **Conclusions**: Alcohol use disorder symptom severity is associated with greater relative value ascribed to alcohol, but not with greater discounting of opportunity or delay costs imposed on alcohol. Despite limitations of the current study, it may be concluded that cost discounting plays a lesser role in dependence than previously thought.

4.2 Introduction

A key diagnostic feature of alcohol dependence is that dependent individuals will continue to drink even when doing so brings about negative health, social and economic consequences (American Psychiatric Association 2013). Behavioural economic theory has proposed two explanations for continued drinking in the face of rising costs in dependent individuals. First, more dependent drinkers may ascribe excessively high value to alcohol, such that costs associated with alcohol are exceeded, so drinking persists despite costs (MacKillop 2016). The second possibility is that more dependent drinkers discount (i.e. neglect) the costs associated with drinking in their decision-making, such that drinking persists despite costs (Belin et al. 2008; Bickel et al. 2014; Mitchell 2003). It is important to distinguish these two possibilities to clarify the psychological mechanism(s) underpinning dependence. The purpose of the current study was to test, using a novel concurrent choice procedure, whether alcohol use disorder symptom severity in student drinkers would be associated with greater relative value ascribed to alcohol, and/or greater discounting of costs imposed on alcohol.

Evidence that alcohol dependence is associated with greater value ascribed to alcohol comes from human demand tasks. In these tasks, drinkers report the amount of alcohol they would hypothetically consume across increasing prices. The intensity of demand (maximum consumption at zero or low cost) is considered to be a relatively pure index of the value of alcohol unaffected by sensitivity to costs, whereas peak expenditure (or Omax) and elasticity may reflect both alcohol value and cost sensitivity. Intensity of demand for alcohol correlates with various proxies for dependence, including drinks consumed per week (MacKillop and Murphy 2007), episodes of heavy drinking per week (Murphy and MacKillop 2006), and alcohol related problems (Murphy et al. 2009). Similarly, in concurrent choice procedures, where drinkers choose between alcohol and food rewards (points or pictures), preference for the alcohol reward is associated with alcohol use disorder symptom severity in both hazardous drinkers recruited from the community (Hardy and Hogarth 2017) and student drinkers (Hardy et al. 2017; Hogarth et al. 2018a). These demand and choice data fit with the prediction

of economic theory, that drinkers with greater dependence symptoms ascribe greater relative value to alcohol, which could underpin persistent drinking despite costs.

In demand tasks, breakpoint – the price at which alcohol consumption drops to zero – is thought to index the extent to which drinkers incorporate price costs into their decision to drink, with higher breakpoints indicating greater cost discounting (MacKillop and Murphy 2007). Evidence is mixed as to whether alcohol dependence is associated with higher breakpoints. Higher breakpoints have been found to be associated with drinking heaviness in students (Murphy and MacKillop 2006), but not with alcohol dependence symptom severity in adults (MacKillop et al. 2010a). Importantly, a meta-analysis of this literature found that proxies for alcohol dependence correlated more consistently across studies with measures of intensity than with breakpoint (MacKillop et al. 2015), suggesting that alcohol dependence may be driven by higher value ascribed to alcohol rather than cost discounting. However, one key study found that student drinkers with a family history of alcoholism were less sensitive to the effect of imagined next-day responsibilities on reducing alcohol demand (Murphy et al. 2014) supporting the claim that dependence vulnerability may be linked to discounting costs associated with alcohol.

Another potential source of evidence for cost discounting in alcohol dependence comes from delay discounting tasks. In these tasks, drinkers choose between smaller immediate and larger delayed rewards (alcohol or money). It is typically found that alcohol use disorder symptoms are associated with a greater preference for the smaller immediate reward (Lim et al. 2017; MacKillop et al. 2011; Petry 2001b; Vuchinich and Simpson 1998). One interpretation of this result is that dependence is associated with greater sensitivity to time delay costs (not cost discounting), because the value of the reward declines more steeply with delay. However, the typical interpretation is that reduced choice of the delayed reward reflects a restricted temporal horizon, i.e. neglect of future outcomes in decision making, which arguably includes neglect of future costs associated with drinking (MacKillop et al. 2011). However, this possibility remains to be demonstrated directly. Thus, steeper temporal discounting provides only ambiguous evidence for greater cost discounting as a function of alcohol dependence symptoms.

Deficits in reversal learning can be interpreted as evidence for greater discounting of punishment contingencies in dependent individuals. In the reversal learning task, participants first learn that one response choice has a higher payoff than the alternative choice, before these response-reward contingencies are reversed. Drug users show deficits in reversal learning despite comparable acquisition of the initial contingencies (Ersche et al. 2008; Fortier et al. 2008; Reiter et al. 2016; Vanes et al. 2014). One explanation of these findings is that drug users are less sensitive to punishment of the incorrect choice, enabling persistence of that choice in reversal. However, reversal learning deficits could be due to impaired prediction error coding, cognitive inflexibility or general task disengagement. Furthermore, because the reward and punishment contingencies are confounded in the reversal task, impaired reversal learning cannot be unequivocally attributed to punishment discounting (Ersche et al. 2008).

Perhaps the best evidence that dependence is driven by cost discounting comes from animal studies. Several studies have shown that rats that are impulsive or have been given extended access to the drug (and so are notionally dependence prone), show weaker suppression of drug self-administration by contingent shock punishment, despite comparable baseline self-administration rates to control animals (Belin et al. 2008; Economidou et al. 2009; Pelloux et al. 2007; Pelloux et al. 2015; Vanderschuren and Everitt 2004). These effects suggest that the nominally dependent rats do not ascribe higher value to drugs at baseline, but rather, selectively discount the costs associated with drug self-administration (but see the Discussion for counter arguments). The implication is that drug choice in more dependent humans should also be less sensitive to the suppressive effects of costs (i.e. they should discount costs imposed on the drug).

Concurrent choice procedures offer a method for measuring the relative value ascribed to alcohol, and sensitivity to costs imposed on alcohol. In concurrent choice procedures, participants choose between a drug reward and a concurrently available natural reward alternative across a series of trials (the two rewards may be points-based, pictures or actually consumed/administered depending on the method). The claim that percent drug choice indexes the relative value ascribed to the drug versus

natural reward, is supported by the finding that percent drug choice reliably increases with the severity of dependence to alcohol (Hardy and Hogarth 2017; Hardy et al. 2017; Hogarth et al. 2018a), cocaine (Moeller et al. 2013; Moeller et al. 2009) and tobacco (Chase et al. 2013; Hogarth and Chase 2011). Importantly, concurrent choice procedures can also index sensitivity to opportunity costs, quantified by the decrease in drug choice that occurs when the magnitude of the competing alternative reward is increased. This measure reflects sensitivity to the cost imposed on the drug choice by the potential loss of the valuable alternative reward (Bickel et al. 1995; Campbell and Carroll 2000; Carroll and Lac 1993; Carroll et al. 1989; Ginsburg and Lamb 2018; Hatsukami et al. 1994; Higgins et al. 1994; Higgins et al. 1996; LeSage 2009; Nader and Woolverton 1991; 1992a; Stevens Negus 2003). Finally, concurrent choice procedures can index sensitivity to delay costs, quantified by the decrease in drug choice that occurs when a delay is imposed between the choice and receipt of the drug (Ito and Nakamura 1998; Woolverton and Anderson 2006).

The purpose of the current experiment was to test, using a novel concurrent choice procedure, whether alcohol use disorder symptom severity in student drinkers would be associated with greater relative value ascribed to alcohol indexed by greater percent choice of alcohol versus food. Secondly, the study tested whether alcohol choice could be modified by imposing opportunity and delays costs on alcohol, to demonstrate that alcohol choice is an economic decision based on the weighing of rewards and costs. Thirdly, and most importantly, the study tested whether alcohol use disorder symptom severity is associated with greater discounting of opportunity costs on alcohol choice (smaller decrease in alcohol choice when the magnitude of the competing alternative is increased), and greater discounting of delay costs on alcohol choice (smaller decrease in alcohol choice when a delay is imposed on the receipt of alcohol). As far as we are aware, only two experiments have utilised such a method (Vuchinich and Tucker 1983; Vuchinich et al. 1987). In these studies, drinkers completed a concurrent choice procedure for alcohol and money, across conditions where money was manipulated in magnitude and delay. Alcohol choice decreased as the magnitude of the money alternative increased demonstrating the sensitivity of alcohol choice to opportunity costs. Furthermore, alcohol choice increased when a delay was imposed on receipt of the money reward, demonstrating sensitivity to delay

costs. However, these studies did not test whether individual differences in alcohol use disorder symptom severity were associated with greater alcohol preference, or the sensitivity of alcohol choice to opportunity and delay costs. The present study re-evaluated this concurrent choice design to determine whether alcohol use disorder symptom severity is associated with greater alcohol preference and/or greater discounting of opportunity and delay costs imposed on alcohol.

4.3 Method

4.3.1 Participants and questionnaires

One hundred and twenty seven students who reported drinking at least occasionally (49% male) were recruited at the University of Exeter. Participants were aged between 18 and 51 (*M*=21.4). At baseline, participants completed the Alcohol Use Disorders Identification Test (AUDIT) to index alcohol use disorder symptom severity (Babor et al. 2001) and the Timeline Follow Back (TLFB) questionnaire to index typical number of units of alcohol consumed per week (Sobell and Sobell 1992). AUDIT total scores were calculated by summing the 10 items of that questionnaire, can range from 0-40, and are commonly split into the following categories: low-risk (0-7), hazardous (8-15), harmful (16-19) and possible dependent (20-40). The sample as a whole reported a mean AUDIT total score of 11.17 (*SD*=6.03, range=1-32), i.e. the mean was above the hazardous cutoff. Based on the AUDIT categories, there were 39 (31%) low-risk subjects, 57 (45%) hazardous subjects, 20 (16%) harmful subjects, and 11 (9%) possible dependent subjects. The TLFB questionnaire indicated that the sample as a whole consumed an average of 14.17 units of alcohol per week (*SD*=14.08, range=0-75) estimated from the two weeks prior to testing. This average is right on the limit of 14 units per week proposed by the UK chief medical officers' guidelines. Of the sample, 81 (64%) subjects drank less than this limit, and 46 (36%) drank more than this limit. There was a significant correlation between AUDIT total scores and average units per week as estimated by the TLFB questionnaire, r=.69, p<.001. These findings suggest that the student sample contained a substantial proportion of drinkers above the hazardous cutoff (69%), and that the AUDIT total score was a valid estimate of alcohol use. Ethical approval was obtained from the University of Exeter Research Ethics Committee and subjects provided informed written consent.

4.3.2 Concurrent choice task

Figure 4.1 shows the on-screen instructions which informed participants about the nature of the task. Physical rewards were present on the desk between the screen and the keyboard: two 275ml bottles of Becks beer and two 45g bars of Dairy Milk chocolate. On-screen instructions stated that participants could earn points for the alcohol and chocolate rewards, and that 'points will be drawn from a lottery at the end of the experiment'. This statement was framed to give participants the impression that their response choices in the task had a direct impact on their chances of receiving the two rewards at the end. However, this instruction was a deception – all participants received a small chocolate bar at the end of testing irrespective of their choices.

For a random half of participants the left key produced the alcohol reward and the right key produced the chocolate reward. These response-reward contingencies were reversed for the remaining half of participants. The position of rewards on the instructions page (Figure 4.1) was congruous with the response-reward contingencies in the task. Participants completed 90 choice trials. At the start of each trial, participants were presented with two vertical bars in the left or right position which represented the magnitude of the alcohol and chocolate rewards on offer (small=1, medium=2 and large=3 points). If an hourglass symbol was also present next to the bar, this indicated that a delay of 3 seconds would be imposed on receiving the reward (participants ultimately received the reward after the delay, so the cost of selecting the delayed choice was a lengthening of the study procedure by three seconds). Participants then made a choice between the left or right key response, and the reward was presented. If the alcohol choice was selected, a picture of a 275ml bottle of Becks beer was presented, whereas if the chocolate choice was selected, a picture of a 45g bar of Dairy Milk chocolate was presented. The picture of the selected reward was accompanied by a number, +1, +2 or +3, which represented the number of points earned for that reward (corresponding to the height of the grey bar at the start of the trial). Finally, if the selected grey bar had an hourglass symbol next to it at the start of the trial, a 3 second delay was imposed between the choice of that option and the presentation of the reward picture and points (given that participants believed that the actual physical rewards – beer and chocolate – would be given to them at the end of

the task, the delay to obtain the actual rewards imposed by choosing the delayed options, was the sum of the 3 second delays).

There were 30 trials in which no delay was imposed on either reward (no hourglass symbol next to either grey bar). Across these 30 trials, there were five conditions that manipulated the magnitude of the alcohol and chocolate points on offer. Alcohol could be worth two fewer points than chocolate (1/3; six trials), 1 less point (1/2, 2/3; three trials each) equal points (1/1, 2/2, 3/3; two trials each), 1 more point (2/1, 3/2; three trials each) or 2 more points (3/1; six trials). These five conditions were coded as -2, -1, 0, +1 and +2 respectively, reflecting the relative difference in the alcohol versus chocolate points on offer. There were 30 identical trials with the delay imposed on the alcohol choice, and another 30 identical trials with the delay imposed on the chocolate choice. The 90 trials were selected at random without replacement. The dependent variable was percent choice of alcohol over chocolate in the five conditions that manipulated the relative magnitude of alcohol points (-2, -1, 0, +1, +2) and three conditions that manipulated delay to reward points (delay alcohol, no delay, delay chocolate).

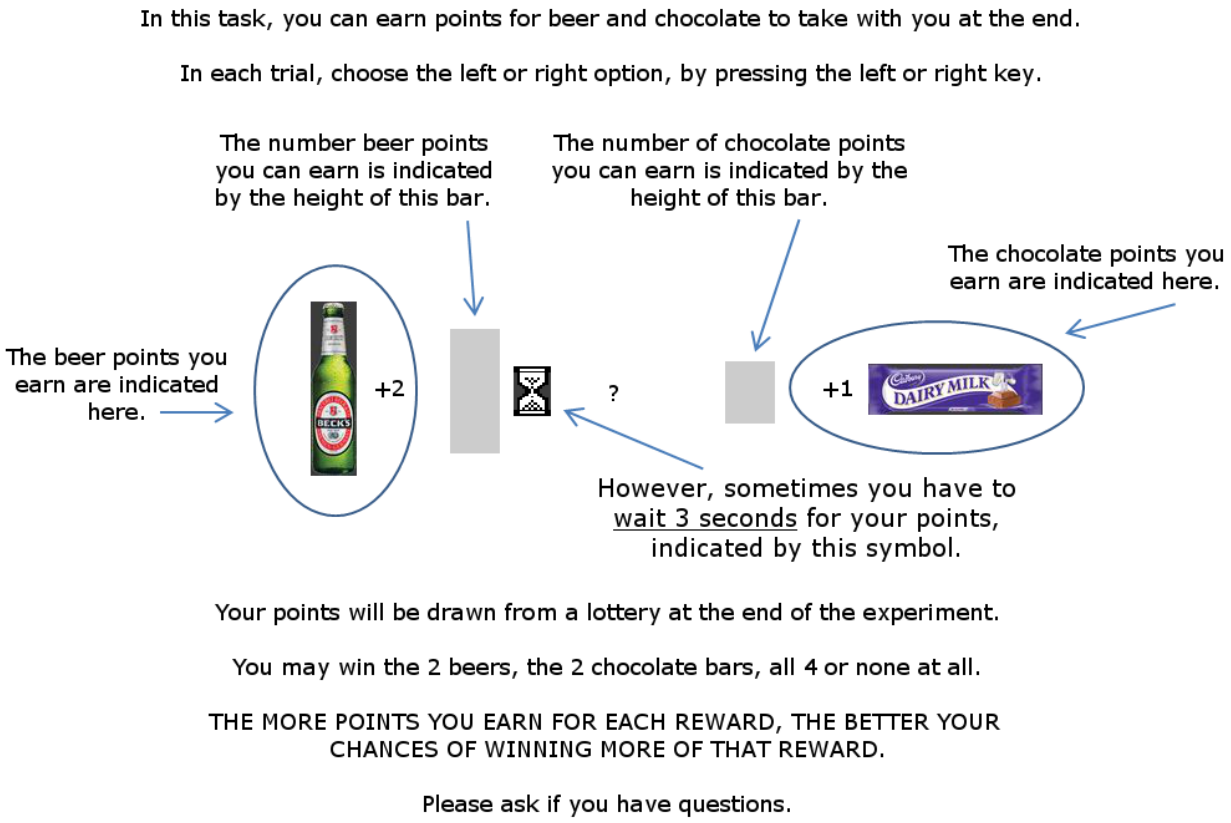

Figure 4.1 shows the instruction screen presented to participants at the start of the concurrent choice task. The left and right arrow keys were used to choose alcohol or chocolate points on offer (response-reward contingencies were counterbalanced between-subjects). The magnitude of the alcohol and chocolate points on offer was signalled by the height of the two grey bars. An hourglass symbol signalled whether a three second delay would be imposed on the receipt of the alcohol or chocolate reward, or neither. Following choice of the left or right option, a picture of the selected reward was displayed alongside the number of points earned for that reward (after a delay if this was imposed). Reward points were +1, +2 or +3 signalled by the height of the grey bar. The relative magnitude of alcohol versus chocolate points was manipulated across five conditions (-2, -1, 0, +1, +2), and delay was manipulated across three conditions (delay alcohol, no delay, delay chocolate).

4.4 Results

4.4.1 Effect of the relative magnitude of alcohol points on alcohol choice

Figure 4.2A shows the percent choice of alcohol over chocolate in the five conditions that manipulated the relative magnitude of alcohol versus chocolate points (-2, -1, 0, +1, +2) as a function of AUDIT scores. A general linear model (GLM) was performed on these data, incorporating percent choice of alcohol over chocolate as the dependent variable, relative magnitude of alcohol points as the within-subjects variable, and

AUDIT total scores as a continuous predictor variable. There was a significant main effect of the relative magnitude of alcohol points on percent alcohol choice, $F(4,500) = 20.79$, $p < .001$, $\eta p^2 = .143$, indicating that alcohol choice tracked the relative magnitude of the alcohol points. As can be seen in Figure 4.2A, percent alcohol choice increased with the relative magnitude of alcohol versus chocolate points offered in the five conditions: -2 (M=18.24, SD=22.32), -1 (M=22.27, SD=23.54), 0 (M=33.55, SD=28.22), +1 (M=47.42, SD=32.23), and +2 (M=55.07, SD=33.22). Within-subjects ANOVAs contrasting all possible pairs of the five relative magnitude conditions indicated all contrasts were significant, Fs(1,126) > 12.25, ps ≤ .001, ηp^2s > .089.

In the overall GLM, there was also a main effect of AUDIT, $F(1,125) = 11.75$, $p = .001$, $\eta p^2 = .086$, indicating that alcohol use disorder symptom severity was associated with an increased preference for alcohol over chocolate, across conditions. The Pearson correlation between AUDIT scores and overall percent alcohol choice was $r = .29$, $p = .001$.

Finally and most importantly, in the overall GLM there was no significant interaction between AUDIT scores and the relative magnitude of alcohol points, $F(4,500) = 1.25$, $p = .289$, $\eta p^2 = .010$. This finding indicates that as alcohol use disorder symptom severity increased, there was no difference in the sensitivity of alcohol choice to manipulation of the relative magnitude of alcohol points. Both the decrease in alcohol choice when alcohol was worth relatively less (the -1 and -2 conditions; i.e. impact of opportunity costs), and the increase in alcohol choice when alcohol was worth relatively more (+1 and +2 conditions), compared to the 0 condition (where rewards were of equal magnitude), were comparable as a function of alcohol use disorder symptom severity. These findings suggest that alcohol use disorder symptoms are not associated with greater discounting of opportunity costs imposed on alcohol.

4.4.2 Effect of delay on alcohol choice

Figure 4.2B shows the percent choice of alcohol over chocolate in the three conditions of the delay manipulation (delay alcohol, no delay, delay chocolate), as a function of AUDIT scores. A GLM was performed on these data, incorporating percent choice of alcohol over chocolate as the dependent variable, delay condition as the within-subjects variable, and AUDIT scores as a continuous predictor variable. There was a

significant main effect of delay condition on percent alcohol choice, $F(4,250) = 24.17$, $p < .001$, $\eta p^2 = .162$, indicating that choice was modified by the delays imposed on rewards. As can be seen in Figure 4.2B, percent alcohol choice was lowest when the delay was imposed on alcohol (M=19.97, SD=22.86), intermediate with no delay (M=31.34, SD=28.64), and the greatest when the delay was imposed on chocolate (M=54.62, SD=31.17). Within-subjects ANOVAs contrasting all possible pairs of the three delay conditions indicated that every contrast was significant, Fs(1,126) > 44.73, ps ≤ .001, ηp^2s > .262.

In the overall GLM, there was also a main effect of AUDIT identical to the GLM that tested the relative magnitude of points, above. Finally, and most importantly, there was no significant interaction between AUDIT scores and delay condition, $F(2,250) = 0.48$, $p = .622$, $\eta p^2 = .004$. This finding indicated that as alcohol use disorder symptom severity increased, there was no difference in the sensitivity of alcohol choice to the delays imposed on alcohol and chocolate rewards. Both the decrease in alcohol choice when alcohol was delayed (i.e. the impact of delay costs), and the increase in alcohol choice when chocolate was delayed, relative to the no delay condition, were comparable as a function of alcohol use disorder symptom severity. These findings suggest that alcohol use disorder symptoms are not associated with greater discounting of delay costs imposed on alcohol.

4.4.3 Specific contrasts to test a priori predictions

Specific contrasts were undertaken to test directly the prediction that alcohol use disorder symptoms are associated with greater discounting of opportunity and delay costs on alcohol choice. Figure 4.2C shows the percent choice of alcohol over chocolate in conditions where alcohol and chocolate points were of equal magnitude (the 0 condition), and where alcohol was worth two fewer points than chocolate (the -2 condition). This comparison tests the effect of opportunity costs (the possible loss of a valuable alternative) on alcohol choice. The horizontal axis shows the sample split into AUDIT categories reflecting alcohol use disorder symptom severity, to better explore performance difference within each category. An ANOVA was performed on these data with percent alcohol choice as the dependent variable, relative magnitude condition as the within-subjects factor (0, -2), and AUDIT category as the between-

subjects factor (4). There was a significant main effect of relative magnitude, $F(1,123) = 40.01$, $p < .001$, $\eta p^2 = .245$, a significant main effect of AUDIT category, $F(3,123) = 4.51$, $p = .005$, $\eta p^2 = .099$, but no significant interaction between relative magnitude and AUDIT category, $F(3,123) = 1.36$, $p = .258$, $\eta p^2 = .032$. These findings confirm the conclusions of the primary analysis (in Figure 4.2A), that increasing the relative magnitude of the alternative reward (opportunity costs) decreased alcohol choice, and crucially, that alcohol use disorder symptom severity was not associated with greater discounting of opportunity costs on alcohol choice.

Figure 4.2D shows the percent choice of alcohol over chocolate in conditions where no delay was imposed on rewards, and when alcohol was delayed, to test the specific effect of delays costs on alcohol choice. ANOVA was performed on these data with percent alcohol choice as the dependent variable, delay condition as the within-subjects factor (no delay, delay alcohol), and AUDIT category as the between-subjects factor (4). There was a significant main effect of delay condition, $F(1,123) = 41.55$, $p < .001$, $\eta p^2 = .253$, a significant main effect of AUDIT category, $F(3,123) = 3.14$, $p = .028$, $\eta p^2 = .071$, but no significant interaction between delay condition and AUDIT category, $F(3,123) = 1.53$, $p = .211$, $\eta p^2 = .036$. These findings confirmed the conclusions of the primary analysis (in Figure 4.2B), that imposing a delay on alcohol reduced alcohol choice, and crucially, that alcohol use disorder symptom severity was not associated with greater discounting of delay costs imposed on alcohol.

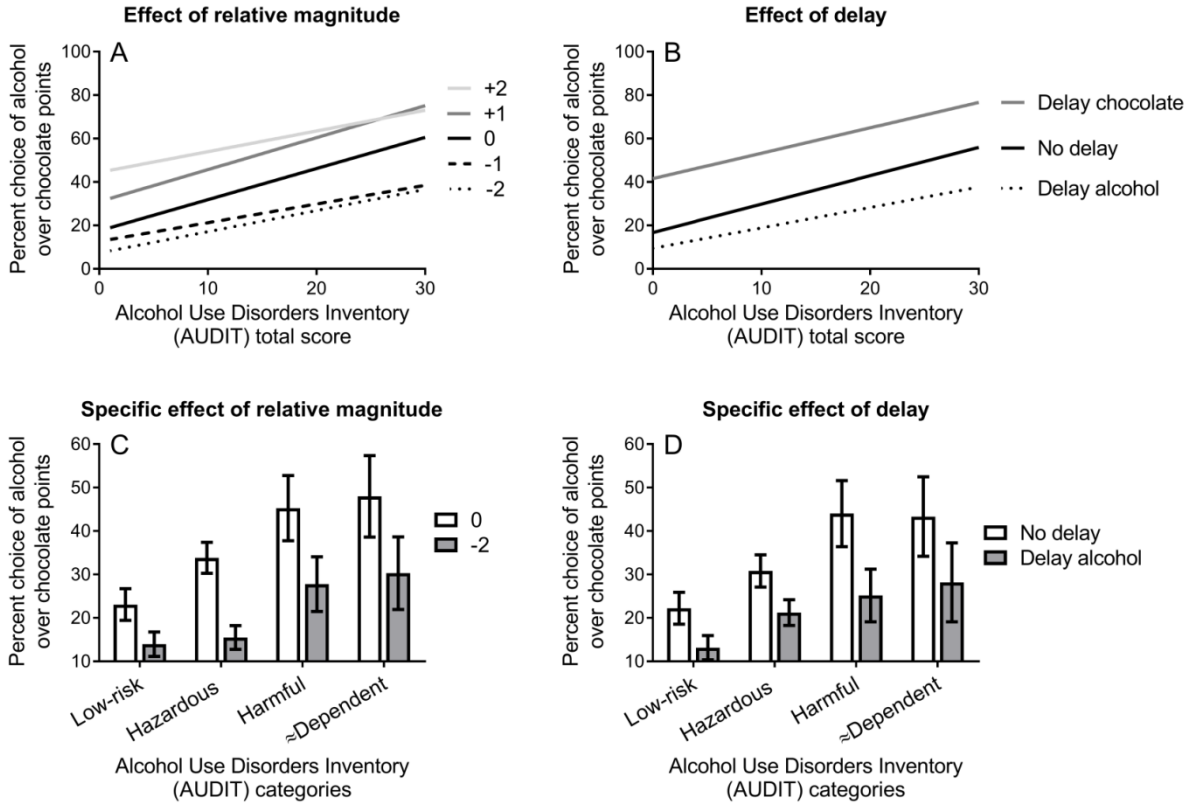

Figure 4.2A shows the percent choice of alcohol over chocolate in five conditions that manipulated the relative magnitude of the alcohol versus chocolate points (-2, -1, 0, +1, +2), as a function of alcohol use disorder symptom severity as a continuous variable. Figure 4.2B shows the percent choice of alcohol over chocolate in three conditions that manipulated the delay imposed on receipt of these rewards (delay alcohol, no delay, delay chocolate), as a function of alcohol use disorder symptom severity as a continuous variable. Figure 4.2C shows the percent choice of alcohol over chocolate in two conditions where alcohol and chocolate points were of equal magnitude (the 0 condition), and where alcohol was worth two fewer points than chocolate (the -2 condition), to explore the extent to which opportunity costs (the possible loss of a valuable alternative) reduced alcohol choice. The sample was split into AUDIT categories reflecting alcohol dependence symptom scores, to better explore performance difference within each category: low-risk = scores 0-7; hazardous = scores 8-15; harmful = scores 16-19; and possible (≈) dependent = scores 20-40. Figure 4.2D shows the percent choice of alcohol over chocolate when no delay was imposed on rewards and when alcohol was delayed, to test the specific effect of delay costs on alcohol choice. The sample was split into AUDIT categories reflecting dependence symptom severity.

4.5 Discussion

The current study found that alcohol use disorder symptom severity indexed by the AUDIT was associated with increased choice of alcohol over chocolate in a concurrent choice procedure. This finding replicates previous studies which have also found that alcohol use disorder symptoms are associated with preferential alcohol choice (Hardy and Hogarth 2017; Hardy et al. 2017; Hogarth et al. 2018a), and accords with studies which have found that cocaine dependence symptoms are associated with preferential

cocaine choice (Moeller et al. 2013; Moeller et al. 2009), and that tobacco dependence symptom severity is associated with preferential tobacco choice (Chase et al. 2013; Hogarth and Chase 2011). These findings provide powerful, converging support for the prediction of behavioural economic theory that drug dependence is driven by the ascription of greater relative value to drug rewards (Bickel et al. 2014; Hursh et al. 2005; MacKillop 2016). On this account, drug use might persist despite costs simply because drug value exceeds the costs (Heyman 2013).

The study also found that alcohol choice could be effectively modified by manipulating the relative magnitude of the competing alternative reward (chocolate), and by imposing delays upon the two rewards, suggesting drug choice is an economic decision based on the weighing of rewards and costs. These findings are consistent with previous concurrent choice studies which have demonstrated that alcohol choice can be lawfully modified by manipulating the magnitude and delay of the alternative money reward (Vuchinich and Tucker 1983; Vuchinich et al. 1987). Additionally, concurrent choice studies with drugs other than alcohol have also modified drug choice by manipulating the relative magnitude of the alternative natural reward (Bickel et al. 1995; Campbell and Carroll 2000; Carroll and Lac 1993; Carroll et al. 1989; Ginsburg and Lamb 2018; Hatsukami et al. 1994; Higgins et al. 1994; Higgins et al. 1996; LeSage 2009; Nader and Woolverton 1991; 1992a; Stevens Negus 2003) and by imposing a delay on either reward (Ito and Nakamura 1998; Woolverton and Anderson 2006). Precisely how the rewards and costs associated with two different reinforcers are commensurated to determine choice between them remains to be resolved (Rangel et al. 2008; Redish et al. 2008). Such knowledge will be crucial for developing future decision-based interventions.

The most important contribution of the current study was to demonstrate that alcohol use disorder symptoms severity was not associated with greater discounting of opportunity or delay costs imposed on alcohol choice. Specifically, the reduction in alcohol choice produced by either the increased value of chocolate points or delay imposed on alcohol reward did not show any statistical decline as a function of either continuous or categorical AUDIT scores. It is particularly salient that the 20 harmful and 11 possible dependent participants showed no evidence of reduced sensitivity to

opportunity or delay costs compared to the 57 hazardous or 39 low-risk drinkers, in the analysis of categorical AUDIT groups. It is an empirical question as to whether the failure to detect cost insensitivity in more severe student drinkers would generalise to older drinkers with a clinical diagnosis of alcohol dependence. However, the current study does clearly suggest that hazardous campus drinking, which is a problem in its own right, is probably not driven by greater cost discounting, but rather, by greater relative value ascribed to alcohol.

The failure to demonstrate costs insensitivity with increasing AUDIT scores is at odds with four lines of evidence which suggest that dependence is linked to cost discounting. First, alcohol dependence symptoms are sometimes associated with higher breakpoints in demand tasks, suggesting dependence is associated with the discounting of price costs (MacKillop et al. 2015), and student drinkers with a family history of alcoholism are less sensitive to the effect of imagined next-day responsibilities on reducing alcohol demand (Murphy et al. 2014). Second, alcohol dependence symptoms are associated with a steeper delay discounting of rewards, which could theoretically extend to neglect of future costs associated with alcohol (Lim et al. 2017; MacKillop et al. 2011; Petry 2001b; Vuchinich and Simpson 1998). Third, drug users show deficits in reversal learning which could be driven by insensitivity to punishment of the incorrect response during reversal (Ersche et al. 2008; Fortier et al. 2008; Reiter et al. 2016; Vanes et al. 2014). Finally, rats that are impulsive or have had extended access to the drug are less sensitive than control rats to the suppression of drug self-administration by contingent shock punishment, despite comparable baseline self-administration rates, suggesting equivalent drug valuation and selective discounting of costs (Belin et al. 2008; Economidou et al. 2009; Pelloux et al. 2007; Pelloux et al. 2015; Vanderschuren and Everitt 2004).

Several limitations of the current study might explain the failure to demonstrate greater cost discounting with alcohol use disorder symptoms, and hence the inconsistency with previous evidence. First, our student subjects, despite being categorized as harmful or possibly dependent by their AUDIT scores, may not have acquired the same deficit in decision making that drives persistent alcohol use in clinically diagnosed drinkers. This proposal could be tested straightforwardly by

running clinically diagnosed drinkers on the current procedure to determine if they show greater cost discounting than matched non-dependent controls. Second, the costs imposed on alcohol (loss of chocolate points or three seconds delay) may not have been strong enough to reveal individual differences, such as those found with shock punishment in animals. This could be tested straightforwardly by using shock within the current paradigm. Third, our use of chocolate as the alternative reinforcer may have increased variance in the preferential choice measure due to individual differences in chocolate liking, thereby reducing sensitivity to individual differences in cost discounting. Future studies might negate this risk by utilising an alternative reinforcer for which there is more homogenous liking, such as money. Fourth, participants were deceived that they could earn alcohol and chocolate rewards contingent on their choices in the task. This deception could have been communicated between participants, which would increase variance in the preferential choice measure, thereby reducing sensitivity to individual differences in the cost discounting. Finally, our lab procedure may have failed to detect individual differences in cost discounting because the costs imposed were too specific and were not a ecologically valid. For instance, alcohol dependence may be associated with discounting of real delayed costs such as negative educational, career, health or legal consequences, but because the three second delay manipulation did not adequately model this cost, we failed to detect differential sensitivity to cost discounting. By contrast, demand tasks measure hypothetical alcohol consumption under costs such as price (MacKillop et al. 2015) or imagined next day responsibilities (Murphy et al. 2014), which may have greater ecological validity and therefore greater sensitivity to individual differences in cost discounting. Employing more ecologically valid costs within the current model, for example, by having participants pay for rewards, or by measuring alcohol choice under conditions of imaged next day responsibilities, it might be possible to detect reliable individual differences in cost discounting. Altogether, the limitations of the current model suggest that cost discounting could be found to play a role in dependence if different procedures or participants were studied.

Alternatively, if one accepted the current data and concluded that alcohol use disorder symptoms are not associated with greater cost discounting, then one would have to explain the apparent published evidence supporting this claim. Accordingly, the

finding that at-risk drinkers have higher breakpoints (MacKillop et al. 2015) or reduced sensitivity to next-day responsibilities (Murphy et al. 2014) could reflect the greater relative value ascribed to alcohol compared to money or next day responsibilities. Second, the steeper delay discounting of dependent drinkers might be a strategy developed through experience of unpredictable environments, rather than reflecting a constitutional neglect of future costs of alcohol. Third, drug users' reversal deficits may stem from a general impairment (e.g. reduced prediction error coding, cognitive inflexibility, task disengagement), rather than a specific deficit in punishment sensitivity. Finally, insensitivity to the suppressive effects of shock on drug self-administration found in impulsive or extended drug access rats may not reflect cost discounting per se, but rather, may reflect greater value ascribed to the drug which was not effectively assessed by the single lever self-administration procedures used in previous studies (Bentzley et al. 2014; Pelloux et al. 2015). Altogether, this analysis and the current data weaken support for the claim that human drug dependence is driven by discounting costs associated with drug use. However, replication of the current effects with different participants and conditions is needed to substantiate this conclusion.

The current findings have clinical implications. The finding that alcohol choice is an economic decision based on weighing the rewards and costs of alcohol versus competing non-drug alternatives suggests that alcohol treatments should focus on (a) decreasing the value of alcohol, (b) increasing the costs of alcohol, (c) increasing the value of competing rewards, and (d) decreasing the costs of competing rewards. There are many interventions which address these four decision variables including health education (Kleinot and Rogers 1982), taxation/minimum price policies (Chaloupka et al. 2002), contingency management (Higgins et al. 2004; Regier and Redish 2015), behavioural activation (Ross et al. 2016) and community-reinforcement (Meyers et al. 2011). The current study suggests that decision-oriented treatment research should focus on interventions that address all four decision variables simultaneously.

Chapter 5. A concurrent pictorial drug choice task marks multiple risk factors in treatment-engaged smokers and drinkers

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5.1 Abstract

Concurrent choice tasks, where subjects choose between a drug versus natural reward, predict dependence vulnerability in animals and humans. However, the sensitivity of concurrent choice tasks to multiple risk factors in treatment-engaged drug users has not been comprehensively tested. In Experiment 1, 33 recently-hospitalised smokers who were engaged with the smoking cessation service made forced choices between enlarging pictures of people smoking versus not smoking. In Experiment 2, 48 drinkers who were engaged with an outpatient alcohol treatment service made forced choices between enlarging pictures of alcohol versus food. In these experiments, percent drug picture choice was significantly associated with dependence severity, craving, self-reported reasons for drug use (negative coping and cued craving), depression, anxiety, withdrawal intolerance, drug use frequency prior to treatment, and current abstinence status (coefficients ranged from r=.39 to r=.66). The concurrent pictorial drug choice task is sensitive to multiple risk factors in clinical, treatment-engaged drug users, and may be used to identify individuals requiring more support, to test experimental treatment manipulations, and to translate to animal concurrent self-administration procedures.

5.2 Introduction

Substance dependent individuals typically ascribe greater value to their drug of preference than individuals who are less dependent. The supernormal valuation of drugs in more dependent individuals is thought to arise from a wide range of risk factors, including neurophysiological constitution, developmental history, drug use history, psychiatric comorbidities, psychosocial attainment and social networks (MacKillop 2016). These risk factors are thought to increase the experienced reinforcement value of the drug, which gives rise to the expectation that the drug has greater reinforcement value, which promotes a higher frequency of drug use behaviour relative to alternative activities (Leventhal and Schmitz 2006). Drug value is therefore thought to be conjointly determined by a wide range of risk factors.

Demand tasks provide an important assay of drug value in humans. In demand tasks, participants report their hypothetical consumption of the drug across a range of prices. Drug value is indexed by intensity (maximum consumption at low price), elasticity (decline in consumption with increasing price), Omax (maximum expenditure), and breakpoint (price at which consumption drops to zero) (MacKillop 2016). These indices of drug value have been shown to robustly correlate with severity of dependence in both subclinical (MacKillop and Murphy 2007; Murphy and MacKillop 2006; Murphy et al. 2009) and clinical samples (Bruner and Johnson 2014; MacKillop and Tidey 2011; Petry 2001a), and to predict treatment outcomes (MacKillop and Murphy 2007; Murphy et al. 2005), and actual consumption of the drug (Amlung et al. 2012), across a range of drugs, including alcohol, tobacco and cocaine. Furthermore, the economic value ascribed to drugs indexed by the demand task has been shown to be increased by withdrawal (MacKillop et al. 2012; Madden and Bickel 1999), stress induction (Owens et al. 2015b), impulsivity (Gray and MacKillop 2014) depression and anxiety (Murphy et al. 2013), schizophrenia (MacKillop and Tidey 2011) and drug related cues (MacKillop et al. 2010b). These data suggest that the value ascribed a drug in the demand task is determined conjointly by a diverse range of risk factors.

There are known methodological issues with the demand task which limit its clinical utility. First, there is uncertainty about which of the various metrics derived from the demand task provides the best index of drug value and whether these metrics are

dissociable (Amlung et al. 2015). Second, calculating elasticity from demand tasks requires the application of an exponential model, which is statistically demanding and thus limits uptake of the task by research groups (Owens et al. 2015a). The exponential model may also provide a suboptimal fit to the observed data (Amlung et al. 2015). The area under the curve metric has been developed to simplify the quantification of drug value but this metric requires further validation (Amlung et al. 2015). The demand task is also effortful/time consuming for participants, requiring completion of a large number of items, limiting its application with vulnerable populations. In response, a brief, 3-item questionnaire measure has been developed to capture intensity, Omax, and breakpoint, but again, this requires further validation (Owens et al. 2015a). The objective in the above research has been to validate a simple, clinically useful, assay of drug value to assist addiction research.

Concurrent choice tasks provide an alternative index of drug value. In the animal model, two response levers are provided which deliver the drug and natural reinforcer (e.g. sucrose), respectively. Preferential choice of the drug is found in a small proportion of 'vulnerable' animals (Ahmed 2010; Panlilio et al. 2015), which can be increased by extended drug exposure, suggesting development of dependence (Lenoir et al. 2013; Russo et al. in press). Preferential drug choice is also marked by a greater number of orbitofrontal cortical neurons that selectively encode the drug versus natural reward (Guillem and Ahmed 2017; Guillem et al. 2017), and can be lawfully modulated by changing the relative magnitude, delay or effort associated with the drug or the natural alternative (Campbell and Carroll 2000; Nader and Woolverton 1991; 1992b; Woolverton and Anderson 2006). These findings suggest that the concurrent choice model is a valid assay of the drug's relative economic value in animals.

In human concurrent choice tasks, participants make forced choices between a drug and a natural reinforcer over a series of trials. The two rewards might be points (Hogarth and Chase 2011), pictures (Hardy and Hogarth 2017; Hogarth et al. 2017, 2018; Miele et al. 2018; Moeller et al. 2013; Moeller et al. 2009) or actual consumption of rewards during the task (Bickel et al. 1995; Hart et al. 2000; Stoops et al. 2012) depending on the method. The claim that percent drug choice indexes the relative

value ascribed to the drug versus natural reward is supported by the finding that percent drug choice reliably increases with the severity of dependence to cocaine (Moeller et al. 2013; Moeller et al. 2009), alcohol (Hardy and Hogarth 2017; Hardy et al. 2017; Hogarth and Hardy 2018a; Hogarth and Hardy 2018b; Hogarth et al. 2018a), and tobacco (Chase et al. 2013; Hogarth and Chase 2011; Miele et al. 2018). Furthermore, percent drug choice increases with withdrawal (Hogarth et al. 2017), negative mood induction (Hardy and Hogarth 2017; Hogarth and Hardy 2018b; Hogarth et al. 2017, 2018a), depression symptoms and self-reported drinking to cope with negative affect (Hardy and Hogarth 2017; Hogarth and Hardy 2018b; Hogarth et al. 2018), and the presentation of drug cues (Hardy et al. 2017; Hogarth and Chase 2012). Percent drug choice can also be decreased by health warnings and satiety (Hogarth 2012; Hogarth and Chase 2011; Johnson and Bickel 2003), by raising the magnitude of the alternative reward (Bickel et al. 1995; Hatsukami et al. 1994; Higgins et al. 1994; Higgins et al. 1996), or the response requirements on the drug response (Ito and Nakamura 1998). The implication is that the value ascribed to the drug in the concurrent choice task, much like the demand task, is determined conjointly by a diverse range of risk factors. Concurrent choice and demand tasks also correlate, suggesting they commonly tap the value of the drug (Chase et al. 2013).

Only a small number of human studies have tested whether preferential drug choice is associated with risk factors in clinical drug users. Such data is necessary to demonstrate the utility of the concurrent choice task in clinical research. Two studies have shown that, in a sample of current cocaine addicts, preferential choice of cocaine over pleasant images predicted current and future drug use frequency (Moeller et al. 2013; Moeller et al. 2009). Another study showed that in hazardous drinkers recruited from the community, preferential choice of alcohol versus food images was associated with alcohol dependence severity, drinking to cope with negative affect and depression symptoms (Hardy and Hogarth 2017). Another study found that, amongst cancer patients enrolled in a smoking cessation program, preferential choice of tobacco over food pictures was associated with tobacco dependence symptoms, age of starting smoking, craving, withdrawal intolerance, and all reasons for smoking, including addiction, stimulation, negative affect, and physiological need (Miele et al. 2018). Finally, one study had daily smokers who desired to quit complete a concurrent choice

task between nicotine versus placebo nasal spray (Perkins et al. 2002). Preferential choice of nicotine did not correlate with tobacco dependence severity, but did predict latency to relapse. Thus, there is promising but limited evidence that the concurrent choice task is sensitive to multiple risk factors in clinical drug users.

We undertook two experiments to test whether the pictorial choice task (PCT) is associated with multiple risk factors in treatment-engaged drug users. In Experiment 1, recently hospitalised smokers who were engaged with a smoking cessation service completed a concurrent choice task in which they chose to enlarge pictures of people smoking versus people not smoking (Hogarth et al. 2017). In Experiment 2, drinkers who were engaged with an out-patient psychosocial alcohol cessation intervention provided by drug-treatment services completed a concurrent choice task in which they chose to enlarge pictures of alcohol versus food (Hardy and Hogarth 2017). Participants in these experiments completed a range of questionnaires assessing risk factors including dependence severity, depression and anxiety symptoms, reasons for drug use, drug use frequency, and current abstinence status. It was expected that preferential pictorial drug choice would be associated with these risk factors demonstrating the utility of the task as an index of drug value in clinical drug users.

Methods

5.3 Experiment 1

5.3.1 Participants

Participants were 33 treatment-enrolled smokers, recruited from the Royal Devon and Exeter (RD&E) hospital smoking cessation service. Participants had been admitted to hospital for a range of chronic and acute illnesses, including myocardial infarction, chronic obstructive pulmonary disease, and stroke. While in hospital they all received a short smoking cessation intervention, delivered by a stop smoking advisor. Testing took place either on the RD&E site in the Clinical Research Facility (CRF) or at the participant's home. Participants were recompensed with £15. This study was granted NHS Research Ethics Committee (REC) and Health Research Authority (HRA) approval.

5.3.2 Questionnaires

Participants reported age and gender (male = 1, female = 2). Questionnaires were as follows: (1) The Fagestrom Nicotine Tolerance Questionnaire (NTQ) to measure nicotine dependence (Fagerström 1978). The NTQ is composed of six items, and total mean scores have category labels of low dependence (1-2), low to moderate dependence (3-4), moderate dependence (5-7), and high dependence (8+). (2) The Questionnaire of Smoking Urges (QSU) to measure craving (Tiffany and Drobes 1991). The QSU comprises two factors: one measuring desire and intention to smoke, and the second measuring anticipated relief from negative affect when smoking. For the purposes of this study, we used a total QSU measure comprising an average of these two factors. (3) The Beck Depression Inventory (BDI-II), with the suicide item 9 removed, to measure current symptoms of depression (Beck et al. 1996b). This scale comprises 20 items, and total sum scores have category labels of minimal depression (0-13), mild depression (14-19), moderate depression (20-28), and severe depression (29-63). (4) The Reasons for Drinking Questionnaire (RFDQ), adapted for smoking (Westerberg et al. 1996). The RFDQ has three subscales reflecting smoking to cope with negative affect, social pressure, and cued craving. We adapted the RFDQ because the drinking to cope subscale in the original version correlated with percent alcohol picture choice in two earlier studies (Hardy and Hogarth 2017; Hogarth et al. 2018a), and adaptation required only replacement of the words 'drink, 'drinking' and 'alcohol' with 'smoke', 'smoking' and 'cigarettes' respectively. Participants also completed information on smoking history including self-reported current abstinence status ("Are you currently smoking or have you quit?": abstinent=0, smoking=1), number of previous quit attempts, number of cigarettes smoked per day prior to any current quit attempt, years smoked, and age initiated.

5.3.3 Pictorial tobacco choice task

On-screen instructions stated: 'In this task, you can view different faces by choosing the LEFT or RIGHT thumbnail to enlarge. Press the space bar to begin'. On each trial, participants were presented with two greyscale thumbnail images, both of which showed a close up of a person's face (sometimes including shoulders). In each trial, the person in one thumbnail was smoking, while the alternate person in the other thumbnail was not smoking, randomly in the left or right location. Pictures of people

smoking were used because they have been shown to be more rewarding than other types of smoking pictures (Mucha et al. 2008). However, because faces are themselves rewarding (Aharon et al. 2001), the alternative pictures also contained faces to control this factor. Thus, participants made choices between two rewarding face pictures, in one of which the person was smoking. Participants pressed the left or right arrow key to select one thumbnail, which enlarged in position for 2 seconds, and caused the other thumbnail to vanish, before a random inter-trial interval of between 1 and 2 seconds prior to the next trial. There were a total of 16 choice trials. Each trial sampled the smoking image from a set of 12 and the non-smoking image from a set of 12, randomly with replacement. Each image set was half male and half female. Different people featured in the smoking and non-smoking image sets. Percent choice of the smoking versus non-smoking image was the dependent variable.

5.3.4 Analysis

Spearman's rank order correlations were used to test the relationship between percent choice of smoking versus non-smoking pictures and risk factors assessed by questionnaires. Spearman's was chosen to account for the significant skew (non-normality) in a number of key variables in our data (including percent choice of smoking images). This non-normality is common in many psychological constructs, for example, depression (Zimmerman et al. 2004). Rank biserial correlations were used to test the relationship between percent smoking image choice and the binary variables abstinence status and gender.

5.4 Experiment 2

The purpose of Experiment 2 was to confirm the sensitivity of the concurrent pictorial choice task to multiple risk factors in a sample of treatment-engaged alcohol dependent individuals, generalising the utility of the task across drug user groups. Forty-eight treatment-engaged drinkers completed a concurrent choice task in which they chose between enlarging pictures of alcohol versus pictures of food. Questionnaires measured two new constructs compared to Experiment 1, anxiety symptom severity and intolerance to alcohol withdrawal, in addition to alcohol dependence, depression, reasons for drinking and current abstinence status. We expected these risk factors to

predict preferential alcohol choice, confirming the utility of the choice task as an index of alcohol value.

5.4.1 Participants

Participants were 48 treatment-enrolled drinkers, recruited from the Exeter Drug Project (EDP) Weymouth alcohol service UK. The majority of participants were, at the time of testing, attending a weekly, CBT-based group intervention to target hazardous drinking and encourage controlled drinking or abstinence. Testing took place on site. Participants were recompensed with £15. This study was granted approval by the University of Exeter Psychology ethics board.

5.4.2 Questionnaires

Initial questions recorded age, gender (male = 1, female = 2) and self-reported current drinking status ("Are you currently abstinent from alcohol?" Abstinent = 0, somewhat abstinent = 1, drinking = 2). Questionnaires were as follows: (1) The Alcohol Use Disorders Identification Test (AUDIT) to measure alcohol dependence (Babor et al. 2001). This questionnaire comprises 10 items scored from 0-4, and total sum scores have the following category labels, mild (0-7), hazardous (8-15), harmful (16-19) and possibly alcohol dependent (20+). (2) The Patient Health Questionnaire (PHQ-9) (Kroenke and Spitzer 2002; Kroenke et al. 2001), with the suicide item removed, leaving 8 items scored from 0 (not at all) to 3 (nearly every day). Total sum scores have the following category labels, no or minimal depression (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27). (3) The General Anxiety Disorder questionnaire (GAD-7) (Spitzer et al. 2006). This questionnaire comprises 7 items scored from 0 (not at all) to 7 (nearly every day). Total sum scores have the following category labels, no or minimal anxiety (0-4), mild (5-9), moderate (10-14), and severe (15+). (4) Drinking to cope with negative affect was measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) measure of coping expectancies adapted for alcohol (Edelen et al. 2014; Shadel et al. 2014). This questionnaire comprised 12 items scored from 1 (never) to 5 (always). This questionnaire was used (rather than the RFDQ used in Experiment 1) to support the PROMIS initiative by reporting the concurrent validity of the new questionnaire (i.e. its correlation with established questionnaires including the AUDIT, PHQ-9, GAD-7). (5)

The withdrawal intolerance subscale of the Intolerance for Smoking Abstinence Questionnaire (adapted for drinking - IDQ) (Sirota et al. 2010). This scale comprises 12 items scored from 1 (strongly disagree) to 5 (strongly agree). The IDQ was included on the basis that intolerance of withdrawal has been shown previously to predict latency to relapse in smokers (Sirota et al. 2010), and may therefore represent a significant marker of risk in the present sample.

5.4.3 Pictorial alcohol choice task

On-screen instructions stated: 'In this task you can choose to view images of alcohol and food using the left and right arrow keys. Press the space bar to begin'. Each trial presented a pair of thumbnail images, where one thumbnail was alcohol and the other was food, randomly in the left and right position. The thumbnail pair remained on-screen until the left or right arrow key was chosen. This response enlarged the chosen image in place for 2 seconds, and caused the other image to vanish, before a random inter-trial interval of between 1 and 2 seconds prior to the next trial. There were a total of 24 choice trials. Each trial sampled an alcohol image from a set of 28 (which included images of beer, wine and spirits) and sampled the food image from a set of 28 (which were all typical UK dinners). Percent choice of alcohol versus food images was the dependent variable.

5.4.4 Analysis

Spearman's rank order correlations were used to test the relationship between percent choice of alcohol versus food images and risk factors assessed by questionnaires. Abstinence status was treated as a three level ordinal variable and subjected to a Spearman's correlation. A rank biserial correlation was used with the binary variable gender.

Results

5.5 Experiment 1

5.5.1 Participants

Participant characteristics are shown in Table 5.1. The proportion of participants in the four NTQ categories were low dependence (0%), low to moderate (18.2%), moderate

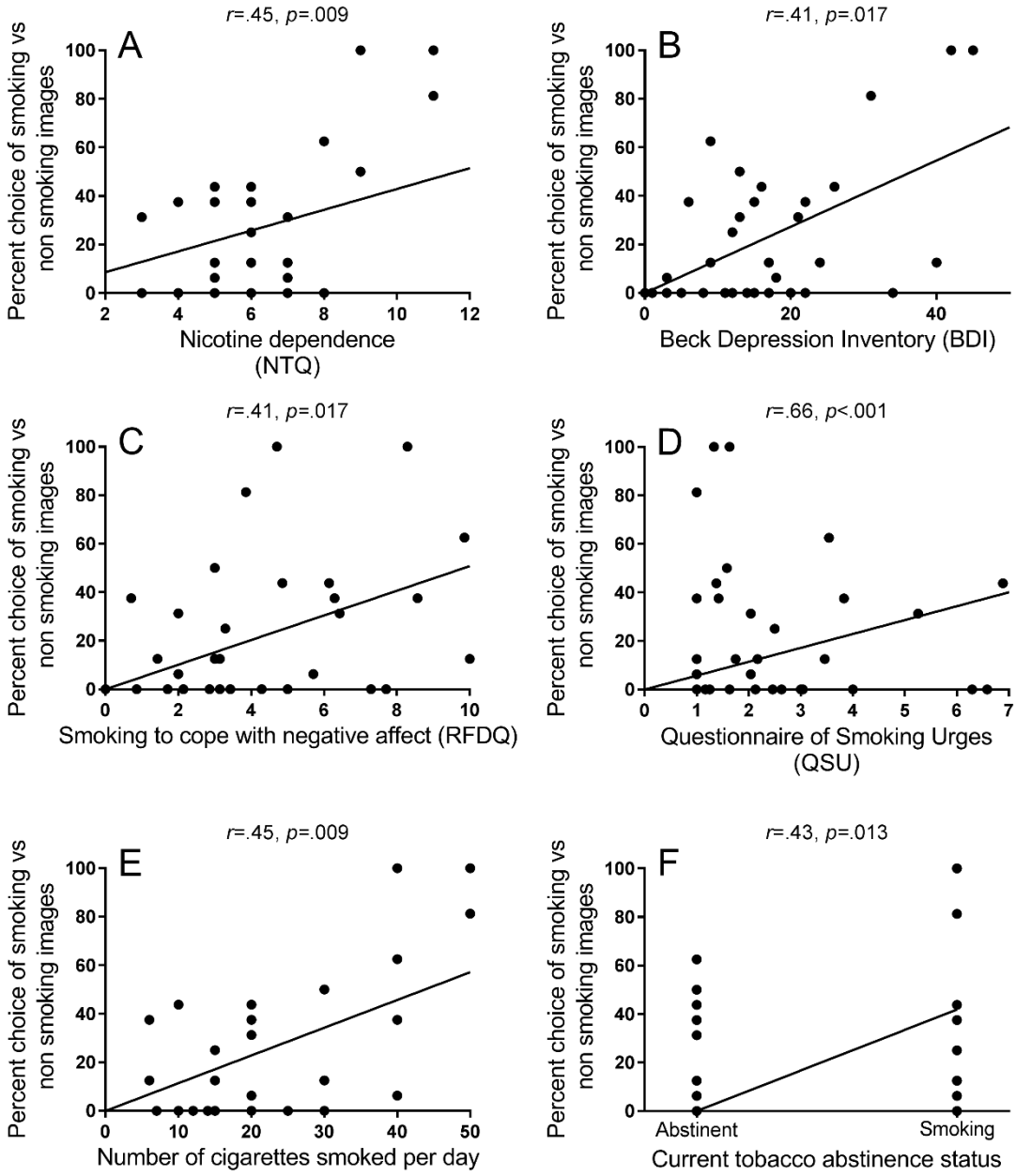
(63.6%) and high (18.2%) dependence. The proportion of participants in the BDI categories were minimal depression (45.5%), mild depression (21.2%), moderate depression (18.2%), and severe depression (15.2%).

5.5.2 Correlations

Table 5.1 shows the correlation matrix between percent choice of the smoking versus non-smoking pictures and risk factors measured in questionnaires. Percent tobacco choice was significantly correlated with gender, nicotine dependence (NTQ), craving to smoke measured in the QSU, depression (BDI), two RFDQ reasons for smoking subscales (negative coping and cued craving), cigarettes smoked per day (prior to any current quit attempt), and abstinence status. In order to control for multiple comparisons, we used a control of false discovery rate method (Benjamini and Hochberg 1995). When setting the false discovery rate at 5%, all significant correlations with percent choice of smoking images remained significant. Figure 5.1A-F shows the significant correlations between percent tobacco choice and key risk factors (the correlation involving RFDQ cued craving was not graphed because it was of secondary interest and did not replicate in Experiment 2). These data indicate that the concurrent choice task is sensitive to variation in the relative value of tobacco associated with a wide range of risk factors in treatment-engaged smokers.

	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean	SD	Range
1.Percent choice														22.54	29.35	0-100
2.Age	-.32													56.12	9.68	37-72
3.Gender	**-.47**	.05												45.5%		
4.NTQ total	**.45**	-.15	-.26											6.06	1.95	3-11
5.QSU total	**.66**	-.23	**-.35**	.13										2.48	1.68	1-6.88
6.BDI	**.41**	**-.35**	.01	.22	**.46**									16.82	11.47	0-45
7.RFDQ negative affect	**.41**	-.33	-.34	.32	.32	**.38**								4.06	2.83	0-10
8.RFDQ social pressure	.27	-.20	-.29	.14	**.54**	.31	**.41**							4.40	3.14	0-10
9.RFDQ cued craving	**.44**	-.02	-.31	.16	**.52**	**.38**	**.54**	**.44**						2.73	2.58	0-8
10.Previous quit attempts	-.15	-.18	**.43**	-.16	-.09	-.11	.16	-.08	-.04					3.84	4.41	0-20
11.Years smoked	-.09	**.63**	-.12	-.00	-.04	-.30	-.08	.12	.14	-.11				38.70	9.10	19-54
12.Age at smoking uptake	-.24	.34	.09	-.18	-.13	-.34	-.22	-.24	-.10	.16	-.22			15.27	3.79	8-25
13.Cigarettes smoked per day	**.45**	.01	**-.45**	**.50**	.10	.06	.14	-.08	.05	-.05	.13	-.02		21.97	12.23	6-50
14.Abstinence status	**.43**	-.12		.34	**.34**	**.57**	.19	.26	.29	.07	.13	-.26	.27	69.7%		

Table 5.1 – Correlation matrix between percent smoking versus non-smoking picture choice in the task and risk factors measured by questionnaires, with associated means, standard deviations and ranges. Note that cigarettes smoked per day was prior to any current quit attempt. For categorical variables (gender and abstinence status), the mean column shows percentage of males, and individuals who were abstinent, respectively. Correlations incorporating gender and abstinence status were rank biserial correlations. P values <.05 are highlighted in bold. NTQ= Nicotine Tolerance Questionnaire; QSU= Questionnaire of Smoking Urges; BDI= Beck Depression Inventory; RFDQ= Reasons for Drinking Questionnaire (adapted for smoking).



Figures 5.1A to 5.1F – Spearman's rank correlations between percent choice of smoking versus non-smoking pictures and key risk variables assessed by questionnaires. Associated test statistics are shown above each graph and in Table 5.1.

5.6 Experiment 2

5.6.1 Participants

Participant characteristics are shown in Table 5.2. The proportion of participants in the four AUDIT categories were: mild (0%), hazardous (2.1%), harmful (2.1%) and possible

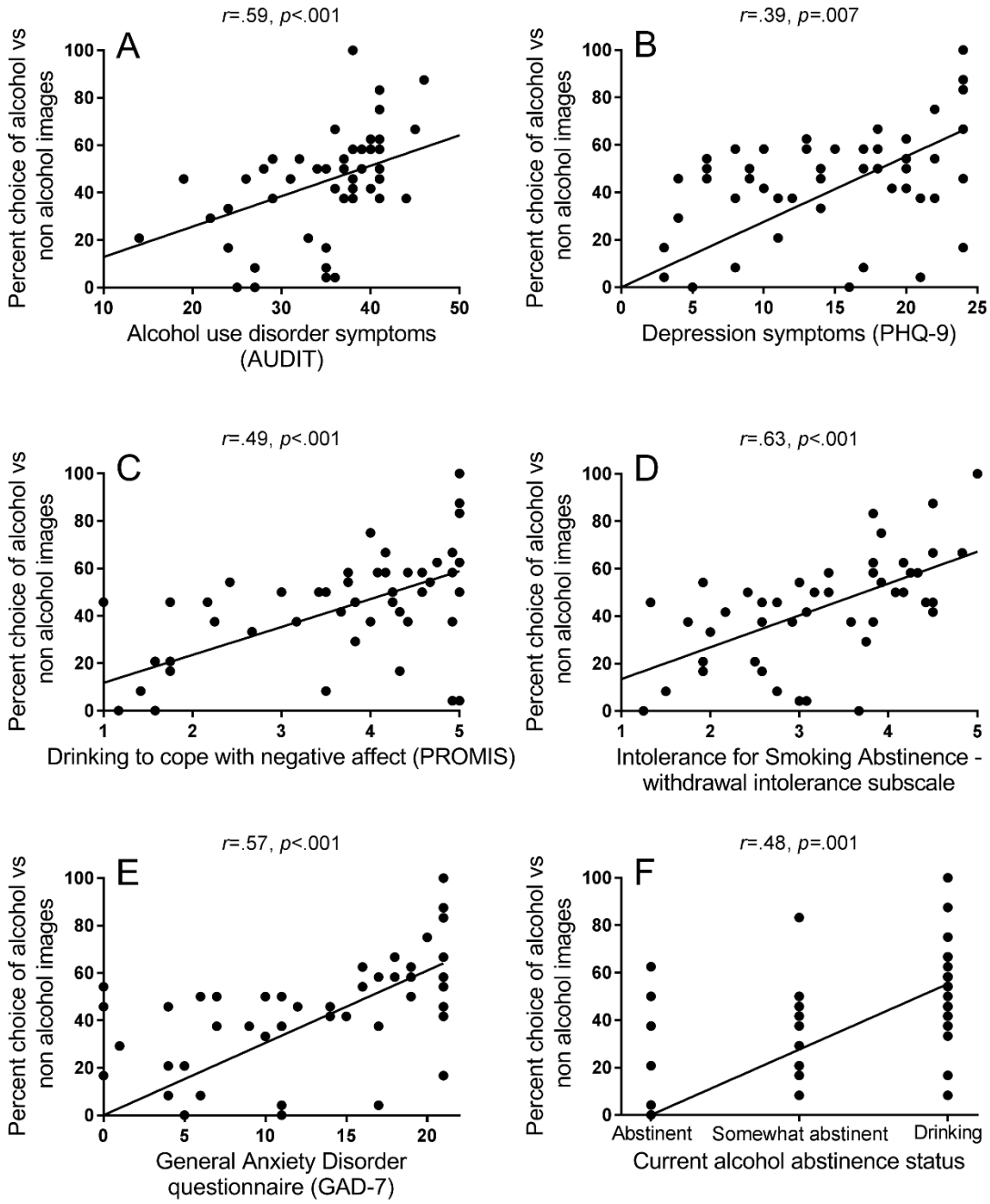
dependence (95.8%). The proportion of participants in the PHQ-9 categories were: no or minimal depression (8.3%), mild (18.8%), moderate (22.9%), moderately severe (18.8%), and severe (31.3%). The proportion of participants in the GAD-7 categories were: no or minimal anxiety (14.6%), mild (14.6%), moderate (20.8%), and severe (50%).

5.6.2 Correlations

Table 5.2 shows the correlation matrix between percent choice of alcohol versus food pictures and key questionnaire variables. Percent choice of alcohol images was significantly correlated with alcohol dependence (AUDIT), depression (PHQ-9), drinking to cope with negative affect (PROMIS), intolerance of withdrawal discomfort (IDQ), anxiety (GAD-7), and abstinence status (abstinent, somewhat abstinent, or drinking). As in Experiment 1, a false discovery rate method (Benjamini and Hochberg 1995) was used to control for multiple comparisons. When setting the false discovery rate at 5%, all significant correlations with percent choice of alcohol images remained significant. Figure 5.2A-F shows the significant correlations between percent alcohol choice and risk factors. These data indicate that the concurrent choice task is sensitive to variation in the relative value of alcohol associated with a wide range of risk factors in treatment-engaged drinkers.

	1	2	3	4	5	6	7	8	Mean	SD	Range
1.Percent choice									44.18	22.48	0-100
2.Age	-.16								44.25	14.06	19-69
3.Gender	.14	-.06							70.8%		
4.AUDIT	**.59**	-.27	.06						34.83	7.04	14-46
5.PHQ-9	**.39**	-.16	.03	**.50**					14.56	6.62	3-24
6.GAD-7	**.57**	-.28	.09	**.67**	**.79**				13.00	6.79	0-21
7.IDQ	**.63**	-.10	.03	**.51**	**.40**	**.52**			3.29	1.00	1.25-5
8.Drinking to cope with negative affect (PROMIS)	**.49**	-.22	.19	**.73**	**.58**	**.70**	**.58**		3.66	1.23	1-5
9.Abstinence status	**.48**	.17	-.18	.08	.06	.23	**.30**	.03	20%; 24.4%; 55.6%		

Table 5.2– Correlation matrix between percent alcohol versus non-alcohol picture choice in the task and risk factors measured by questionnaires, with associated means, standard deviations and ranges. For categorical/ordinal variables (gender and abstinence status), the mean column shows percentage of males, and individuals who were abstinent, somewhat abstinent, and drinking, respectively. Correlations incorporating gender were rank biserial correlations. P values <.05 are highlighted in bold. AUDIT= Alcohol Use Disorders Identification Test; PHQ-9= Patient Health Questionnaire – depression symptoms; GAD-7= General Anxiety Disorder Questionnaire; IDQ= Intolerance for Smoking Abstinence Questionnaire, withdrawal intolerance subscale (adapted for alcohol use); PROMIS= Patient-Reported Outcomes Measurement Information System, coping expectancies subscale.



Figures 5.2A to 5.2F – Spearman's rank correlations between percent choice of alcohol versus food pictures and key risk variables assessed by questionnaires. Associated test statistics are shown above each graph and in Table 5.2.

5.7 Discussion

In both experiments, preferential choice of the drug image over the alternative image was associated with questionnaire indices of drug dependence severity, in clinical samples of treatment-engaged smokers and drinkers, respectively. Specifically,

preferential tobacco choice was associated with Fagestrom Nicotine Tolerance Questionnaire scores, and preferential alcohol choice was associated with AUDIT scores. These findings validate the concurrent pictorial choice task as a proxy for dependence in clinical samples, confirming previous associations found in cocaine addicts (Moeller et al. 2013; Moeller et al. 2009), hazardous drinkers from the community (Hardy and Hogarth 2017) and treatment-enrolled smokers with cancer (Miele et al. 2018). Furthermore, this association corroborates similar findings with student drinkers (Hardy et al. 2017; Hogarth and Hardy 2018a; Hogarth and Hardy 2018b; Hogarth et al. 2018a) and smokers (Chase et al. 2013; Hogarth 2012; Hogarth and Chase 2011; 2012). Together, these data indicate that the choice task is a robust marker for drug dependence severity in both clinical and subclinical drug users, and fit the idea that dependence is driven by greater value ascribed to drugs relative to alternative rewards (Bentzley et al. 2014; Heyman 2013; Hursh and Silberberg 2008; MacKillop 2016).

Preferential drug choice was also associated with multiple risk factors that have been demonstrated in other studies to be prospective markers for both dependence formation and propensity to relapse. First, in both experiments, preferential drug choice was associated with depression symptom intensity and drug use to cope with negative affect, corroborating previous findings with community (Hardy and Hogarth 2017) and student drinkers (Hogarth and Hardy 2018b; Hogarth et al. 2018a). Importantly, both depression and coping motives have been shown to be prospective risk factors for dependence (Crum et al. 2008; Crum et al. 2013b) and relapse (Mathew et al. 2017; Samet et al. 2013). Second, a key novel finding of the current study was that preferential alcohol choice was associated with anxiety symptom intensity in treatment-enrolled drinkers in Experiment 2. Like depression, anxiety has also been established as a prospective risk factor for substance dependence and relapse (Charney et al. 2005; Kushner et al. 2005; Swendsen et al. 2010). Third, in Experiment 1, preferential tobacco picture choice was associated with craving and the RFDQ reasons for smoking cued craving subscale. In Experiment 2, preferential alcohol picture choice was associated with withdrawal intolerance. Both craving and withdrawal intolerance are prospective risk factors for relapse (Brandon et al. 2003; Brown et al. 2005; Killen and Fortmann 1997). Collectively, these data suggest that the concurrent pictorial drug

choice task is sensitive to the fundamental constitutional traits which predispose individuals to both dependence formation, and propensity to relapse, i.e. the ascription of greater relative value to the drug over alternative reinforcers (Bentzley et al. 2014; Heyman 2013; Hursh and Silberberg 2008; MacKillop 2016).

A key novel finding was that, in both experiments, preferential drug image choice was associated with current abstinence status, with currently abstinent individuals choosing the drug image less frequently than currently using individuals. One plausible explanation for these findings is that the abstinent group had greater abstinence intentions, or abstinence self-efficacy, potentially acquired from engagement with treatment services, leading them to deliberately avoid drug cues. This is potentially the same process responsible for abstinent former users showing reduced attentional bias to drug cues (Ehrman et al. 2002) and craving for drugs (Alessi et al. 2004). It is also important to note, however, the possibility of demand characteristics. Given that abstinence status was self-reported in both experiments, it is possible that individuals who reported that they were abstinent to maintain a positive self-presentation were also less likely to choose drug images on the pictorial choice task. This limitation could be overcome in future studies by the use of objective, biological markers of abstinence.

Finally, preferential tobacco picture choice in Experiment 1 was associated with number of cigarettes smoked per day (prior to any quit attempt). However, this same association was not found with treatment-engaged smokers with cancer (Miele et al. 2018), and has been found in only two (Hogarth 2012; Hogarth and Chase 2011) out of three (Hogarth and Chase 2012) studies with student smokers. Thus, there remains uncertainty about the replicability of this association which should be tested in future studies.

Individual correlation coefficients ranged from .39 - .66, i.e. medium to large effect sizes. After controlling for multiple correlations using the false discovery rate (FDR) method, all significant correlations remained significant. Even if a small proportion of correlations were false positives, this would not change the overall conclusion that the pictorial choice task (PCT) is an assay of relative drug value which is sensitive to multiple risk factors. Based on these findings it seems likely that the PCT measured a

common latent variable underlying all of the risk factors, namely, the value ascribed to the drug versus alternative reinforcers. The pictorial choice task (PCT) can therefore be considered as a valid methodological option for assaying relative drug value in humans. The PCT may have advantages over the economic demand task (MacKillop 2016) in being quicker to complete taking approximately 2-3 minutes to run and requiring no complex instructions, thus requiring minimal participant literacy, and obtaining a behavioural as opposed to self-report measure of drug value. The PCT may have advantages over human choice tasks where participants earn drug points (Hogarth and Chase 2011) or consume the drug (Bickel et al. 1995; Hart et al. 2000; Stoops et al. 2012) in that the PCT is technically simpler to implement, and ethical approval easier to obtain, especially for clinical samples who are attempting abstinence. This task may be used to screen clients who are at greatest risk and need additional therapeutic support, and could also be used as a convenient outcome measure to test experimental or therapeutic manipulations thought to modify drug-seeking behaviour.

In conclusion, two experiments validated the concurrent pictorial choice task as sensitive to multiple risk factors in treatment-engaged drug users. Preferential drug image choice was found to be significantly associated with dependence, depression, anxiety, drug use to cope with negative affect, craving, drug use frequency and current abstinence status. These findings suggest that the concurrent pictorial choice task is sensitive to the relative value ascribed to the drug, conjointly determined by a diverse range of risk factors.

Chapter 6. A novel concurrent pictorial choice model of mood-induced relapse in hazardous drinkers

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6.1 Abstract

This study tested whether a novel concurrent pictorial choice procedure, inspired by animal self-administration models, is sensitive to the motivational effect of negative mood induction on alcohol-seeking in hazardous drinkers. Forty eight hazardous drinkers (scoring ≥ 7 on the Alcohol Use Disorders Inventory) recruited from the community completed measures of alcohol dependence, depression and drinking coping motives. Baseline alcohol-seeking was measured by percent choice to enlarge alcohol versus food related thumbnail images in two-alternative forced-choice trials. Negative and positive mood was then induced in succession by means of self-referential affective statements and music, and percent alcohol choice was measured after each induction in the same way as baseline. Baseline alcohol choice correlated with alcohol dependence severity (r=.42, p=.003), drinking coping motives (in two questionnaires, r=.33, p=.02 and r=.46, p=.001) and depression symptoms (r=.31, p=.03). Alcohol choice was increased by negative mood over baseline (p<.001, η_p^2 = .280), and matched baseline following positive mood (p=.54, η_p^2=.008). The negative mood-induced increase in alcohol choice was not related to gender, alcohol dependence, drinking to cope or depression symptoms (ps≥.37). The concurrent pictorial choice measure is a sensitive index of the relative value of alcohol, and provides an accessible experimental model to study negative mood-induced relapse mechanisms in hazardous drinkers.

6.2 Introduction

Negative reinforcement models of addiction propose that negative states, such as withdrawal and negative affect, strongly motivate drug-seeking behaviour to remove or ameliorate these states (Koob, 2013). The significance of negative affect as a motivator of alcohol use is borne out by the finding that alcohol dependent individuals retrospectively attribute negative mood as their reason for relapsing more frequently than any other (Brown et al., 1990; Hodgins, el-Guebaly, & Armstrong, 1995; Marlatt, 1996; Strowig, 2000). Furthermore, experimental studies have shown that induction of acute negative mood reliably promotes alcohol-seeking behaviour, as indexed by increased subjective craving, preferential choice, willingness to spend, consumption and cognitive bias (Birch et al., 2004; Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Cyders et al., 2016; Kelly, Masterman, & Young, 2011; Litt, Cooney, Kadden, & Gaupp, 1990; Rousseau, Irons, & Correia, 2011; Rubonis et al., 1994; Willner, Field, Pitts, & Reeve, 1998; Zack, Poulos, Fragopoulos, & MacLeod, 2003; Zack, Poulos, Fragopoulos, Woodford, & MacLeod, 2006; Zack, Toneatto, & MacLeod, 1999). Critically, sensitivity to negative mood-induced alcohol craving predicts relapse in dependent drinkers even after controlling other relevant predictor variables (Brady et al., 2006; Cooney, et al., 1997; Higley et al., 2011; Sinha et al., 2011). Therefore, treatments that reduce negative-mood induced alcohol-seeking may promote abstinence after quitting.

Various negative mood induction procedures have been used to motivate alcohol-seeking behaviour including sad music (Birch, et al., 2004; Kelly, et al., 2011; Willner, et al., 1998), the presentation of negative words or phrases (Zack, et al., 2003; Zack, et al., 2006; Zack, et al., 1999), guided imagery where participants describe key negative-affect related drinking triggers (Cooney, et al., 1997; Rubonis, et al., 1994) or negative autobiographical memories (Cyders, et al., 2016; Litt, et al., 1990; Rousseau, et al., 2011) which are scripted for re-reading at test. The current study used a combination of self-referential negative statements (Velten, 1968), such as 'I don't think things are ever going to get better', plus musical mood induction (Martin, 1990) because this combination is more effective than either alone (Zhang, Yu, & Barrett, 2014), and this method is more time efficient than guided imagery.

Various methods have also been used to measure the increase in alcohol-seeking prompted by negative mood induction, including intra-nasal alcohol self-administration (Cyders, et al., 2016), free alcohol consumption (Cyders, et al., 2016; Magrys & Olmstead, 2015; McGrath, Jones, & Field, 2016; Pratt & Davidson, 2009; Zack, et al., 2006), economic demand/willingness to pay (Amlung & MacKillop, 2014; Owens, Ray, & MacKillop, 2014; Rousseau, et al., 2011) and willingness to work for alcohol (Willner & Jones, 1996), alcohol relief expectancies (Birch, et al., 2004), alcohol craving (Brady, et al., 2006; Cooney, et al., 1997; Field & Powell, 2007; Litt, et al., 1990; Pratt & Davidson, 2009; Rubonis, et al., 1994; Willner & Jones, 1996), and alcohol cognitive bias (Austin & Smith, 2008; Field & Powell, 2007; Field & Quigley, 2009; Grant, Stewart, & Birch, 2007; Kelly, et al., 2011; Potthast, Neuner, & Catani, 2015; Woud, Becker, Rinck, & Salemink, 2015; Zack, et al., 2003; Zack, et al., 2006; Zack, et al., 1999).

The key innovation of the current study was to test a novel concurrent pictorial choice procedure in which participants chose to enlarge alcohol versus food related thumbnail images in two-alternative forced-choice trials. This method was chosen because previous studies have shown that preferential choice to enlarge cocaine versus control images is associated with cocaine use frequency (Moeller et al., 2013; Moeller et al., 2009), and preference to enlarge tobacco over food images is increased by mood induction and withdrawal (Hogarth, Mathew, & Hitsman, 2017). Furthermore, related choice procedures have demonstrated the sensitivity of alcohol choice to taste aversion learning (Rose, Brown, Field, & Hogarth, 2013), and the sensitivity of tobacco choice to mood induction (Hogarth et al., 2015a), alternative reinforcer value (Stoops, Poole, Vansickel, & Rush, 2011), acute satiety (Hogarth & Chase, 2011), nicotine replacement pharmacotherapy (Hogarth, 2012) and tobacco dependence severity (Hogarth, 2012; Hogarth & Chase, 2011, 2012). Finally, in animals, two-alternative self-administration models have revealed the sensitivity of drug choice to a wide range of manipulations of drug value (Ahmed, 2010; Moeller & Stoops, 2015; Nader & Woolverton, 1991; Nader & Woolverton, 1992b; Panlilio, Hogarth, & Shoaib, 2015).

The current study tested whether a negative mood induction procedure combining self-referential negative statements and sad music would augment percent alcohol

choice in a concurrent pictorial choice procedure in hazardous drinkers. Forty eight hazardous drinkers completed questionnaires of alcohol dependence, drinking coping motives and depression symptoms. Baseline alcohol-seeking was measured by percent choice to enlarge alcohol versus food related thumbnail images in two-alternative forced choice trials. Negative and then positive moods were induced by affective statements and music, and concurrent pictorial alcohol choice was measured after each induction procedure. Subjective mood was measured to validate each induction procedure. The key prediction was that percent alcohol choice would increase following negative mood induction and decrease following positive mood induction, validating this method as a model of negative mood-induced relapse in hazardous drinkers. Secondary analysis examined whether baseline alcohol choice, and negative mood-induced alcohol choice differed between males and females (Cyders et al., 2016; Rubonis et al., 1994; Willner et al., 1998), or varied with drinking coping motives (e.g. (Field & Quigley, 2009) or depression symptoms (Hogarth, et al., 2017), as suggested by previous studies.

6.3 Method

6.3.1 Participants

Participants were 48 adults from the community who responded to online adverts. All participants answered yes when asked if they regularly drank more alcohol per week than specified by UK guidelines (21 units for men, 14 for women), and reported an Alcohol Use Disorders Inventory (AUDIT) total score above the hazardous threshold of ≥ 7 (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). Participants were recompensed with £15. Ethical approval was obtained from the University of Exeter Research Ethics Committee.

6.3.2 Questionnaires

Breath alcohol was recorded with an AlcoSense Lite before questionnaires were administered. Questionnaires were as follows. (1) the Alcohol Use Disorders Inventory Test (AUDIT: Babor, et al., 2001). The total score (range 0-40) was used to index alcohol use and associated problems. Questions one to three were used to quantify alcohol consumption: drinking days per week, drinks per drinking day and binge drinking

frequency, respectively. (2) The Reasons for Drinking Questionnaire (RFDQ: Zywiak, Connors, Maisto, & Westerberg, 1996) from which the negative coping subscale was examined. This subscale includes 7 items which ask participants to assess how important different reasons for drinking are for their own consumption, including sadness, anger, frustration, anxiety, tension, illness and relationship difficulties, measured on a 0-10 scale ranging from 'not at all important' to 'very important'. (3) The Drinking Motives Questionnaire Revised (DMQ-R: Cooper, 1994) from which the negative coping subscale was examined. This subscale contains 5 items which ask participants to assess how frequently their drinking is motived by each listed reason – including worries, depression/nervousness, bad mood, to build confidence and to forget problems – rated on a 1-5 scale ranging from 'almost never' to 'almost always'. (4) Beck's Depression Inventory IA was used to record depression symptoms (BDI: Beck, Steer, Ball, & Ranieri, 1996).

6.3.3 Baseline alcohol choice

Instructions stated: 'In this task you can choose to view images of alcohol and food using the left and right arrow keys. Press the space bar to begin'. As shown in Figure 6.1A, each trial presented a pair of thumbnail images, one alcohol and one food related randomly in the left and right position, which remained until the left or right arrow key was chosen. This enlarged the chosen image, which remained alone on screen for 2 seconds. Thirty two baseline trials randomly sampled from a set of 28 alcohol images (including beer, wine and spirits) and 28 food images (all typical UK dinners).

6.3.4 Negative mood induction

Instructions then requested careful attention to statements and sad music (Barber's Adagio for Strings) began playing through headphones (Morrison & O'Connor, 2008). There followed 16 trials in which 16 Velten self-referential negative statements (e.g. 'I don't think things are ever going to get better' – for a full list see Hogarth, et al., 2015a) were presented in random order for 10 seconds each.

6.3.5 Negative test phase

Instructions stated: 'You can now view alcohol and food pictures in the same way as before. Press the space bar to continue'. There were 64 test trials each containing a

negative statement randomly sampled from the set of 16 and presented for 3 seconds, before an alcohol/food image choice was made in identical fashion to baseline.

6.3.6 Positive mood induction

Instructions requested careful attention to statements, then happy music (Mozart's Eine Kleine Nachtmusik) began playing through headphones (Morrison & O'Connor, 2008). There followed 16 trials in which 16 positive statements (e.g. 'I feel cheerful and lively' – for a full list see Hogarth, et al., 2015a) were presented once each in random order for 10 seconds.

6.3.7 Positive test phase

Instructions stated: 'You can now view alcohol and food pictures in the same way as before. Press the space bar to continue'. There were 64 test trials, identical to the negative test phase, except that each trial contained a positive statement randomly sampled from the set of 16.

6.3.8 Subjective mood measures

Subjective mood was measured by the on-screen question 'How do you currently feel?', and a 9 point Likert scale ranging from 1='happy', 5='neutral', 9='sad'. This measure was obtained after each phase of the design as shown in Figure 6.1. The mood scores after the induction and test phases were averaged for negative and positive phases, to create three scores reflecting mood at baseline, in the negative induction/test phase, and in the positive induction/test phase.

6.3.9 Analytical plan

Subjective mood scores were entered into a mixed ANOVA with the within-subjects variable block (baseline, negative, positive) and the between-subjects variable gender (male, female) to validate the induction procedures. Percent choice of alcohol over food was also calculated from baseline, negative and positive trials (>50%=preference for alcohol, <50%=preference for food) and entered into a mixed ANOVA with the within-subjects variable block (baseline, negative, positive) and the between-subjects variable gender to determine whether alcohol choice was sensitive to mood induction. Pearson correlations were used to examine the association between baseline percent alcohol

choice, the negative mood-induced increase in alcohol choice (from baseline to negative block), and the questionnaire variables AUDIT, RFDQ and DMQ-R negative coping, and BDI.

6.4 Results

6.4.1 Participants

Table 6.1 shows the characteristics of participants, divided by gender. There were no significant differences between males and females in these measures. AUDIT questions one to three were used to characterise level of alcohol consumption. The sample means of 3.3 for AUDIT Q1, 2.1 for Q2 and 2.7 for Q3 indicate that the sample, on average, drank two or three times a week, drank five to six drinks on these occasions, and had a binge drinking session between monthly and weekly.

	Group		
	Males (n=22) M (SD, range)	Females (n=26) M (SD, range)	*p*
Age	28.8 (10.7, 19-63)	25.2 (10.0, 19-51)	.23
Breath alcohol (mg/l)	0 (0, 0-0)	0 (.1, 0-.3)	.36
AUDIT total score	18.4 (5.7, 8-33)	16.8 (4.9, 7-26)	.32
AUDIT Q1	3.5 (.6, 2-4)	3.2 (.5, 2-4)	.17
AUDIT Q2	2.2 (1.2, 0-4)	2.0 (.8, 1-3)	.43
AUDIT Q3	2.7 (.5, 2-3)	2.7 (.5, 2-3)	.84
RDFQ negative coping	3.4 (2.4, 0-7.1)	3.3 (2.3, 0-8.1)	.79
DMQ-R negative coping	3.0 (1.1, 1.2-4.6)	2.7 (.8, 1.0-4.2)	.24
BDI	11.7 (9.5, 0-35)	9.2 (6.8, 1-26)	.28

Table 6.1: Characteristics of the male and female group. Breath alcohol mg/l = milligrams per litre. AUDIT = Alcohol Use Disorders Inventory Test. AUDIT Q1-Q3 = drinking days per week, drinks per drinking day, and binge drinking frequency, respectively (see results for interpretation of these numbers). RFDQ = Reasons for Drinking Questionnaire. DMQ-R = Drinking Motives Questionnaire Revised. BDI = Beck's Depression Inventory.

6.4.2 Subjective mood

ANOVA with subjective mood data shown in Figure 6.1B produced a significant main effect of block, $F(2,92) = 37.61$, $p < .001$, $\eta_p^2 = .450$, no main effect of gender, $F(1,46) = .45$, $p = .51$, $\eta_p^2 = .010$, and no interaction between block and gender, $F(2,92) = .62$, $p = .54$, $\eta_p^2 = .013$. Pairwise comparison of the three blocks revealed a significant difference

between baseline and negative, $F(1,47) = 29.63$, $p < .001$, $\eta_p^2 = .387$, baseline and positive, $F(1,47) = 17.84$, $p < .001$, $\eta_p^2 = .275$, and negative and positive, $F(1,47) = 54.43$, $p < .001$, $\eta_p^2 = .537$. Finally, t-tests comparing each mood score against the 'neutral' value of 5 indicated that baseline was not significantly different, $t(47)=-.97$, $p=.34$, whereas mood in the negative block was significantly greater than 5 (i.e. towards the 'sad' end of the scale), $t(47)=4.49$, $p<.001$, and mood in the positive block was significantly less than 5 (i.e. towards the 'happy' end of the scale), $t(47)=-4.56$, $p<.001$. Thus, the mood induction procedures produced the expected shift in subjective mood state, and there were no differences in this effect between males and females.

6.4.3 Alcohol choice

ANOVA with the alcohol choice scores shown in Figure 6.1C produced a significant main effect of block, $F(2,92) = 10.84$, $p < .001$, $\eta_p^2 = .191$, no main effect of gender, $F(1,46) = 1.96$, $p = .17$, $\eta_p^2 = .041$, and no interaction between block and gender, $F(2,92) = 1.01$, $p = .37$, $\eta_p^2 = .021$. Pairwise comparison of the three blocks revealed a significant difference between baseline and negative, $F(1,47) = 18.26$, $p < .001$, $\eta_p^2 = .280$, negative and positive, $F(1,47) = 11.38$, $p = .001$, $\eta_p^2 = .195$, but not between baseline and positive, $F(1,47) = .38$, $p = .54$, $\eta_p^2 = .008$. Thus, negative mood induction increased alcohol choice relative to baseline, and positive mood induction returned alcohol choice to baseline.

To determine whether the changes in alcohol choice across blocks were driven by time order effects or mood induction, each block was segmented into quarters. Percent alcohol choice remained stable across quarters of the baseline block (44.5, 44.0, 40.6, and 43.5, respectively), increased step-wise and remained stable across quarters of the negative test (56.1, 52.6, 51.8, and 53.9, respectively), and then decreased step-wise and remained stable across quarters of the positive test (41.4, 42.1, 43.1, and 40.1, respectively). ANOVA on these data with the variables block (baseline, negative, positive) and quarter (4) yielded a main effect of block, $F(2,282) = 10.43$, $p < .001$, $\eta_p^2 = .182$, and no main effect of quarter, $F<1$, or block by quarter interaction, $F(6,282) = 1.06$, $p = .39$, $\eta_p^2 = .022$. Furthermore, the main effect of quarter was not significant in either baseline, $F<1$, negative, $F(3,141) = 1.76$, $p = .16$, $\eta_p^2 = .036$, or positive block, $F<1$. Overall, these findings suggest that changes in alcohol choice were driven by mood induction rather than time.

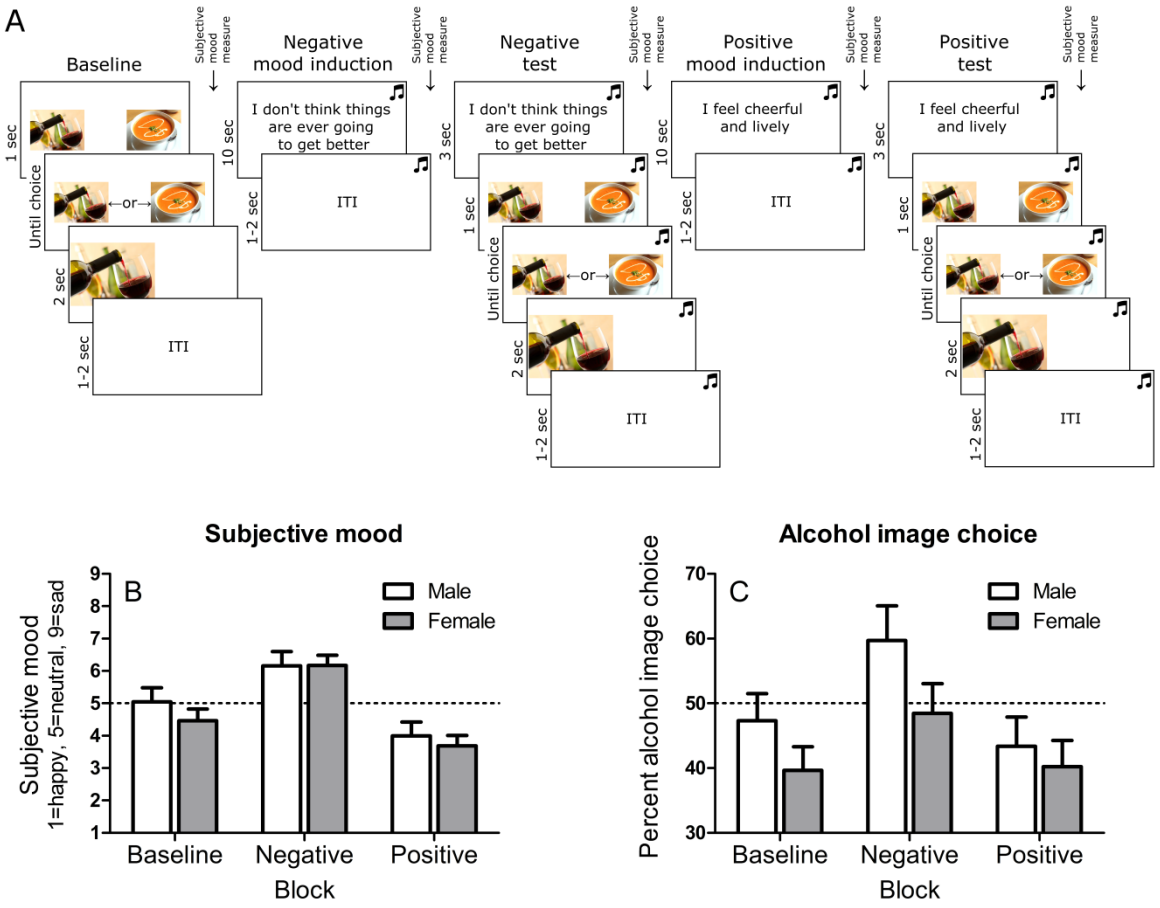

Figure 6.1: A: Procedure used to test the impact of negative and positive mood induction on alcohol choice. At baseline, alcohol choice was measured by preference to select for enlargement alcohol versus food related thumbnail images in two-alternative forced choice trials. Negative mood was then induced by depressive statements and music (Barber's Adagio for Strings) before alcohol choice was tested again in the same way. Positive mood was then induced by positive statements and music (Mozart's Eine Kleine Nachtmusik) before alcohol choice was tested again in the same way. Subjective mood was reported on a 1-9 scale from 1='happy', 5='neutral', 9='sad' between each successive stage of the procedure. The key question was whether negative mood would increase percent alcohol choice relative to baseline and the positive condition, validating this experimental model of mood-induced alcohol-seeking in hazardous drinkers. B: Subjective mood during the baseline, negative and positive mood induction blocks, separated by gender. Results indicate that negative mood increased sadness and positive mood induction increased happiness, relative to baseline, and there were no gender effects or interactions. C: Percent alcohol versus food choice in the baseline, negative and positive mood induction blocks separated by gender. Results indicated that negative mood induction increased alcohol choice relative to the baseline, positive mood induction returned alcohol choice to baseline, and there were no gender effects or interactions.

6.4.4 Correlations between alcohol choice and questionnaire scales

Table 6.2 shows the correlation coefficients between baseline alcohol choice, negative mood-induced alcohol choice (increase in alcohol choice from the baseline to negative block), questionnaire scales and subjective negative mood reactivity (increase in sadness from baseline to negative block). Baseline alcohol choice was significantly

correlated with AUDIT, RFDQ and DMQ-R negative coping scales, and BDI. Negative mood-induced alcohol choice did not correlate with any variable. Finally, neither percent alcohol choice measured in the positive mood induction block, nor the decreases in alcohol choice between positive versus negative blocks correlated significantly with any of the questionnaire measures, *r*s<.25, *p*s>.08 (not shown in Table 6.2).

	Negative mood-induced alcohol-seeking	AUDIT	RFDQ negative coping	DMQ-R negative coping	BDI	Subjective negative mood reactivity
Percent alcohol choice baseline	*r*=-.08, *p*=.55	***r*=.42, *p*=.003**	***r*=.33, *p*=.02**	***r*=.46, *p*=.001**	***r*=.31, *p*=.03**	*r*=.22, *p*=.12
Negative mood-induced alcohol-seeking		*r*=-.03 *p*=.84	*r*=.09 *p*=.53	*r*=.13 *p*=.37	*r*=.03 *p*=.85	*r*=.07 *p*=.62
AUDIT			*r*=.22 *p*=.14	***r*=.36 *p*=.01**	*r*=.26 *p*=.08	*r*=-.01 *p*=.95
RFDQ negative coping				***r*=.77 *p*<.001**	***r*=.67 *p*<.001**	*r*=-.09 *p*=.55
DMQ-R negative coping					***r*=. 60 *p*<.001**	*r*=-.07 *p*=.649
BDI						*r*=-.25 *p*=.09

Table 6.2: Correlation matrix between alcohol choice measures and questionnaires. Negative mood induced alcohol-seeking scores reflect the increase in percent alcohol choice between the baseline and negative conditions. AUDIT = Alcohol Use Disorders Inventory; RFDQ = Reasons for Drinking Questionnaire; DMQ-R = Drinking Motives Questionnaire Revised; BDI = Beck's Depression Inventory. Bold text highlights significant correlations.

6.5 Discussion

The first key finding of the study was that greater choice of alcohol versus food images in the baseline block correlated with AUDIT, drinking coping motives and depression symptoms. One interpretation of these relationships is that the concurrent pictorial choice procedure indexes the relative value of alcohol (Murphy, Correia, Colby, & Vuchinich, 2005), and that hazardous drinkers who report higher AUDIT, drinking coping motives or depression symptoms ascribe greater relative value to alcohol over alternative rewards. In support of this claim, two earlier studies have similarly found

that cocaine choice in the concurrent pictorial choice procedure was associated with cocaine use frequency (Moeller, et al., 2013; Moeller, et al., 2009), suggesting that the measure provides a valid index of drug value in different drug user groups. The second key finding was that the negative and positive mood induction procedures were effective in shifting subjective mood state towards sadness and happiness respectively, as anticipated. However, the most important finding was that alcohol choice increased following negative mood induction and retuned to baseline following positive mood induction, suggesting that the concurrent pictorial choice measure is sensitive to the motivational effect of negative mood induction on the relative value of alcohol. What is more, the effect of negative mood induction on alcohol choice relative to baseline was large ($\eta_p^2 = .280$). Smokers with diagnosed current major depression have shown an even larger effect ($\eta_p^2 = .782$) of negative mood induction on tobacco choice in the concurrent pictorial choice task (Hogarth, et al., 2017). Thus, the concurrent pictorial choice measure offers a sensitive, accessible and clinically useful method for studying negative mood-induced relapse processes in hazardous drinkers, and is considerably simpler than existing models designed for this purpose (Brady, et al., 2006; Cooney, et al., 1997; Higley, et al., 2011; Sinha, et al., 2011).

The negative mood-induced increase in alcohol choice was comparable in magnitude, and not statistically different, in males and females, suggesting that published mixed findings of this sort might be discounted (Cyders, et al., 2016; Rubonis, et al., 1994; Willner, et al., 1998). More troubling is that negative mood-induced alcohol choice did not correlate with drinking coping motives, in contrast to several studies which have reported this association. It is important to note, however, that all these studies used undergraduate student samples (Austin & Smith, 2008; Birch, et al., 2004; Field & Powell, 2007; Field & Quigley, 2009; Grant, et al., 2007a; Rousseau, et al., 2011; Woud, et al., 2015; Zack, et al., 2003), apart from one which used alcoholic males (Cooney, et al., 1997). One possible explanation is that the relationship between negative mood-induced alcohol choice and drinking coping motives is nonlinear, and approaches asymptote at higher levels of coping, making a correlation harder to detect in hazardous drinkers compared to students. Finally, negative mood-induced alcohol choice did not correlate with depression symptoms. This contradicts our previous finding that smokers with major depression (compared to smokers without) were more

sensitive to negative mood-induced tobacco choice in a procedure similar to the present (Hogarth, et al., 2017). Given the existing weak evidence that negative mood-induced alcohol choice increases with depression symptoms (Cooney, et al., 1997; Owens, et al., 2014), a study is needed to sample drinkers across the depression continuum to achieve sufficient power to determine if such an association does exist.

One limitation of the study was that negative and positive blocks were experienced in the same sequential order by all participants, rather than counterbalanced. This means that changes in alcohol choice could have been driven by mood induction procedures or by time variables such as sensitization or habituation to stimuli, or task disengagement. Additional analyses, however, revealed that alcohol choice changed as a step-function immediately following negative and positive mood induction, and did not change significantly across quarters within each block. This suggests that changes in alcohol choice were driven by the mood induction procedures rather than time variables. One uncertain interpretation remains, however. It is not clear whether positive mood induction actively returned alcohol choice to baseline, or whether the return to baseline was due to the termination of the negative mood induction procedure. However, the majority of mood induction studies are designed such that there is a gap between negative mood induction and the test of alcohol self-administration, consumption, demand or craving, indicating that the negative mood induction effect persists for some time. It seems likely, therefore, that the positive mood induction actively opposed negative mood induction to return alcohol choice to baseline rapidly. If this interpretation is correct, the current model could be used to test mood management interventions or antidepressant pharmacotherapy as protective agents against negative mood induced alcohol relapse (Hesse, 2009). However, further studies are needed in which positive, negative and neutral induction procedures are counterbalanced to determine whether positive mood induction can in fact oppose negative mood induction, and whether positive mood induction can reduce alcohol choice below baseline when tested in isolation.

There also remains uncertainty about whether the changes in alcohol choice were driven by the self-referential mood relevant statements, the music, or both. Previous studies have shown that sad music alone (Birch, et al., 2004; Kelly, et al., 2011; Willner,

et al., 1998) and negative statements alone (Zack, et al., 2003; Zack, et al., 2006; Zack, et al., 1999) can produce changes in alcohol-seeking and subjective mood. However, the specific musical pieces and textual statements employed in the current study (derived from Morrison & O'Connor, 2008) have not been tested in isolation, and therefore their independent effects on alcohol choice remains unclear. More generally, future studies should explore different induction procedures that evoke specific emotional states so as to better isolate the affective states that most effectively drive alcohol choice, so these might be modelled and targeted therapeutically.

Finally, the magnitude of the mood induction effects is worthy of note. Compared to baseline, negative mood induction increased subjective negative mood by an average of 1.4 points on a 1-9 scale, which is comparable to previous publications (e.g. Morrison & O'Connor, 2008) and suggests that the negative mood induction procedure was mild, conforming to ethical requirements. The negative mood induction procedure increased alcohol choice by an average of 10.4% on a 0-100% scale. Although this effect size was large, the numerical change observed may have been limited by the high value of food (baseline alcohol choice was 43% overall) and the possibility of a negative mood-induced increase in food choice in restrained eaters (Cardi, Leppanen, & Treasure, 2015). Consequently, the negative mood induction effect might be increased in future studies by using lower value non-food images as the alternative choice.

To conclude, this study found in hazardous drinkers that a novel concurrent pictorial choice measure was sensitive to individual differences in the relative value of alcohol, and to the motivational effect of negative mood induction. This concurrent pictorial choice measure offers a sensitive and accessible method for studying the mechanisms of negative mood-induced relapse processes in hazardous drinkers, and may be useful in the development of new targeted treatments.

Chapter 7. Negative mood-induced alcohol-seeking is greater in young adults who report depression symptoms, drinking to cope, and subjective reactivity

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7.1 Abstract

Acute negative mood powerfully motivates alcohol-seeking behaviour, but it remains unclear whether sensitivity to this effect is greater in drinkers who report depression symptoms, drinking to cope, and subjective reactivity. To examine these questions, 128 young adult alcohol drinkers (age 18-25) completed questionnaires of alcohol use disorder symptoms, depression symptoms and drinking to cope with negative affect. Baseline alcohol choice was measured by preference to enlarge alcohol versus food thumbnail images in two-alternative forced choice trials. Negative mood was then induced by depressive statements and music, before alcohol choice was tested again. Subjective reactivity was indexed by increased sadness pre to post mood induction. Baseline alcohol choice correlated with alcohol dependence symptoms (p=.001), and drinking coping motives (ps≤.01). Mood induction increased alcohol choice and subjective sadness overall (ps<.001). The mood-induced increase in alcohol choice was associated with depression symptoms (p=.007), drinking to cope (ps≤.03), and subjective reactivity (p=.007). The relationship between mood-induced alcohol choice and drinking to cope remained significant after covarying for other drinking motives. Furthermore, the three predictors (depression, drinking to cope and subjective reactivity) accounted for unique variance in mood-induced alcohol choice (ps≤.03), and collectively accounted for 18% of the variance (p<.001). These findings validate the pictorial alcohol choice task as sensitive to the relative value of alcohol and acute negative mood. The findings also accord with the core prediction of negative reinforcement theory that sensitivity to the motivational impact of negative mood on alcohol-seeking behaviour may be an important mechanism that links between depression and alcohol dependence.

7.2 Introduction

According to negative reinforcement theory, alcohol dependence, persistence and relapse are driven by adverse withdrawal, cognitive, emotional or psychiatric states powerfully motivating alcohol use in order to mitigate those states (e.g. Crum, Green, Storr, & et al., 2008; Hall et al., 2015; Mathew, Hogarth, Leventhal, Cook, & Hitsman, 2017). Perhaps the most direct evidence for negative reinforcement theory comes from experimental studies in which negative mood induction (including stress) is shown to motivate alcohol craving, choice, demand, consumption and cognitive bias (Amlung & MacKillop, 2014; Field & Quigley, 2009; Rousseau, Irons, & Correia, 2011; Zack, Poulos, Fragopoulos, Woodford, & MacLeod, 2006). Negative reinforcement theory also predicts that individuals who are vulnerable to alcohol dependence should be more sensitive to negative affective triggers for alcohol-seeking behaviour (Heilig, Egli, Crabbe, & Becker, 2010; Hussong, Jones, Stein, Baucom, & Boeding, 2011). Indirect support for this claim comes from the finding that sensitivity to negative mood-induced alcohol craving predicts relapse risk in alcoholics (Brady et al., 2006; Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Higley et al., 2011; Sinha et al., 2011). However, it is not clear whether sensitivity to mood-induced alcohol-seeking is associated with other markers of alcohol dependence vulnerability, especially in young adult drinkers. To test this core prediction of negative reinforcement theory, the current study examined whether sensitivity to mood-induced alcohol-seeking was greater in young adult drinkers who reported depression symptoms, drinking to cope, alcohol use disorder symptoms, and subjective reactivity to negative mood.

There is currently mixed evidence as to whether depression symptoms are associated with greater sensitivity to negative mood-induced alcohol-seeking behaviour. Two studies have shown that depression symptom intensity had a numerically stronger correlation with alcohol craving measured after negative mood induction than after neutral induction, weakly suggesting that depression is associated with greater sensitivity to a mood-induced increase in craving (Cooney et al., 1997; Owens, Ray, & MacKillop, 2015). In contrast, we recently found that depression symptoms were not associated with greater sensitivity to mood-induced alcohol-seeking in a sample of 48 hazardous drinkers recruited from the community who completed a procedure very

similar to the one used in the present study (Hardy & Hogarth, 2017). However, this null association contrasts with two smoking studies. In the first study, we found that smokers with current major depressive disorder were more sensitive to a negative mood-induced increase in tobacco-seeking than smokers without major depression, and this sensitivity also increased linearly with depression symptom intensity across the sample as a whole (Hogarth, Mathew, & Hitsman, 2017). This finding corroborated an earlier study in which depression symptom intensity in heavy daily smokers was associated with sensitivity to the effect of negative mood induction on tobacco consumption (Fucito & Juliano, 2009). Given these mixed findings, the primary aim of the current study was to re-examine the relationship between depression symptoms and sensitivity to negative mood-induced alcohol-seeking in a large sample of young adult drinkers, testing a core prediction of negative reinforcement theory.

Self-reported drinking to cope has been consistently associated with sensitivity to mood-induced alcohol-seeking in young adult drinkers (Austin & Smith, 2008; Birch et al., 2004; Field & Powell, 2007; Field & Quigley, 2009; Grant, Stewart, & Birch, 2007; Rousseau et al., 2011; Woud, Becker, Rinck, & Salemink, 2015; Zack, Poulos, Fragopoulos, & MacLeod, 2003). In the present study, therefore, we expect that drinking to cope will be associated with greater sensitivity to mood-induced alcohol-seeking. The additional question, however, is whether this association is sufficiently specific to coping motives that it can survive when other drinking motives (enhancement, conformity, social pressure and cued craving) are statistically controlled, as has been reported in two preliminary studies (Grant et al., 2007a; Woud et al., 2015). This finding would indicate that the relationship between self-reported drinking to cope and sensitivity to negative mood-induced alcohol-seeking is not mediated by other drinking motives.

Existing studies are inconsistent as to whether severity of alcohol use disorder symptoms is associated with mood-induced alcohol-seeking. Although four studies have reported such an association (Randall & Cox, 2001; Sinha et al., 2009; Zack et al., 2003; Zack, et al., 2006), seven studies have reported nonsignificant correlations (Austin & Smith, 2008; Cooney et al., 1997; Field & Powell, 2007; Field & Quigley, 2009; Hardy & Hogarth, 2017; Woud et al., 2015; Zack, Toneatto, & MacLeod, 1999) and six other

studies have not reported this correlation despite having the relevant data (Birch et al., 2004; Grant et al., 2007a; McGrath, Jones, & Field, 2016; Owens et al., 2015a; Potthast, Neuner, & Catani, 2015; Rousseau et al., 2011). Negative reinforcement theory predicts that alcohol dependence symptoms should be associated with mood-induced alcohol-seeking, if this is the underpinning mechanism. Therefore, the current study evaluated this association, to try and clarify the mixed findings.

There is also mixed evidence as to whether mood-induced alcohol-seeking is associated with subjective emotional reactivity to negative triggers. In relation to this association, there is weak evidence from three alcohol studies (Kelly, Masterman, & Young, 2011; Owens et al., 2015a; Sinha et al., 2009), strong evidence from one smoking study (Hogarth et al., 2015a), and nonsignificant correlations reported in two studies (Magrys & Olmstead, 2015; McGrath et al., 2016). Therefore, the current study evaluated the association between mood-induced alcohol-seeking and subjective mood reactivity, to address this mixed literature and the possible role of mood regulation skills in alcohol dependence (Berking et al., 2011). Overall, if the current study found that sensitivity to mood-induced alcohol-seeking is associated with markers for alcohol dependence in young adults (depression symptoms, drinking to cope, alcohol use disorder severity and subjective reactivity) these findings would provide initial support for the core prediction of negative reinforcement theory that sensitivity mood-induced alcohol-seeking plays a role in vulnerability to alcohol dependence.

7.3 Method

7.3.1 Participants and procedure

The study recruited 128 student drinkers (50% male) who reported drinking alcohol at least monthly. The study was approved by the University of Exeter Psychology Ethics Committee and participants gave informed written consent. Participants completed questionnaires of alcohol use disorder, depression symptoms, and drinking motives. Baseline alcohol-seeking was measured by preference to select for enlargement alcohol versus food related thumbnail images in two-alternative forced choice trials. This pictorial choice task was chosen because percent drug choice increases with dependence severity and drug use frequency suggesting it indexes the relative value of the drug (Hardy & Hogarth, 2017; Moeller et al., 2013; Moeller et al., 2009), and is

reliably increased by mood induction (Hardy & Hogarth, 2017; Hogarth et al., 2017). Negative mood was then induced by depressive statements and sad music, before alcohol-seeking was tested again in the same way. Subjective mood reactivity was indexed by the increase in sadness recorded pre and post mood induction. It was expected that mood induction would increase subjective sadness and alcohol-seeking overall. The question at stake was whether the mood-induced growth in alcohol-seeking would increase with depression symptoms, drinking coping motives, alcohol use disorder severity and subjective mood reactivity.

7.3.2 Questionnaires

The following questionnaires were completed. (1) The Alcohol Use Disorders Inventory Test (AUDIT: Babor, Higgins-Biddle, Saunders, & Monteiro, 2001), which is scored on a scale of 1-40, where scores ≥ 8 indicate hazardous drinking. (2) Depression symptoms were recorded using Beck Depression Inventory II (BDI: Beck, Steer, Ball, & Ranieri, 1996), where scores of 0-13=minimal, 14-19=mild, 20-28=moderate, and 29-63=severe symptom intensity. (3) The Reasons for Drinking Questionnaire (RFDQ: Zywiak, Connors, Maisto, & Westerberg, 1996). The negative coping subscale of the RFDQ includes 7 items which ask participants to assess how important different reasons for drinking are for their own consumption, including sadness, anger, frustration, anxiety, tension, illness and relationship difficulties, measured on a 0-10 scale ranging from 'not at all important' to 'very important'. The RFDQ measured two other subscales: social pressure and cued craving. (4) The Drinking Motives Questionnaire Revised (DMQ-R: Cooper, 1994). The negative coping subscale of the DMQ-R contains 5 items which ask participants to assess how frequently their drinking is motived by each listed reason, including worries, depression/nervousness, bad mood, to build confidence and to forget problems – rated on a 1-5 scale ranging from 'almost never' to 'almost always'. The DMQ-R measured three other subscales: social context, enhancement and conformity.

7.3.3 Mood induction effect on alcohol choice

Baseline alcohol choice (see Figure 7.1): Instructions stated: 'In this task you can choose to view images of alcohol and food using the left and right arrow keys. Press the space bar to begin'. Each trial presented a pair of thumbnail images, one alcohol and one

food related randomly in the left and right position, which remained until the left or right arrow key was chosen. This enlarged the chosen image, which remained alone on screen for 2 seconds. There were thirty two baseline trials. The thumbnails were randomly sampled with replacement from a set of 28 alcohol images (including beer, wine and spirits) and 28 food images (all typical UK dinners).

Mood induction: Participants first rated their current subjective mood on a scale from 1-9 ranging from 'Happy' to 'Sad' (baseline assessment). Instructions requested careful attention to statements then sad music (Barber's Adagio for Strings) began playing through headphones (Morrison & O'Connor, 2008). There followed 16 trials in which the 16 negative statements were presented once each, in random order, for 10 seconds. An example negative statement is 'I don't think things are ever going to get better' (for the full list see Hogarth et al., 2015a). After these trials, participants rated their subjective mood again (post-induction assessment).

Test: Instructions stated: 'You can now view alcohol and food pictures in the same way as before. Press the space bar to continue'. There were 64 test trials each containing a negative statement randomly sampled from the set of 16 and presented for 3 seconds, before an alcohol or food choice was made in the same way as at baseline. The sad music continued to play throughout. After these 64 test trials, participants once again rated their subjective mood (post-test assessment).

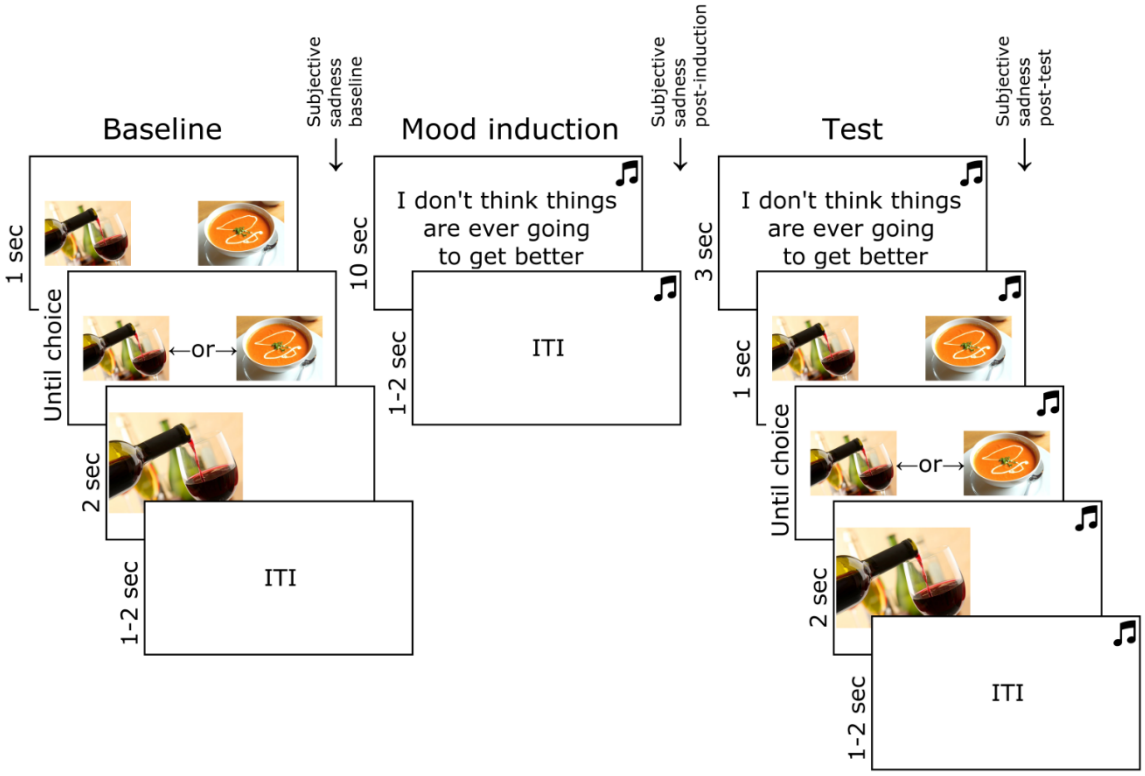

Figure 7.1: Procedure used to test the impact of negative mood induction on alcohol choice. At baseline, alcohol-seeking was measured by preference to select for enlargement alcohol versus food related thumbnail images in two-alternative forced choice trials. Negative mood was then induced by depressive statements and sad music (Barber's Adagio for Strings), before alcohol-seeking was tested again in the same way. Subjective reactivity was indexed by the increase in sadness pre and post mood induction. The key question was whether the increase in percent choice of alcohol versus food images from baseline to test (mood-induced alcohol-seeking) would be associated with depression symptoms, drinking to cope, alcohol use disorder symptoms, and subjective reactivity. ITI = intertrial interval.

7.3.4 Analytical plan

Percent choice of alcohol over food was calculated from baseline and test trials (>50%=preference for alcohol, <50%=preference for food). ANOVAs first tested the difference in alcohol choice and subjective sadness between the baseline and test blocks. Separate mixed general linear models (GLMs) were then conducted with percent alcohol choice as the dependent variable, the within-subjects variable block (baseline, test), and a continuous between-subjects variable in each model, either depression symptoms (BDI), RFDQ negative coping, DMQ-R negative coping, alcohol use disorder (AUDIT), or the increase in subjective sadness pre and post mood induction. A significant interaction in these GLMs would indicate that the change in

alcohol choice from baseline to test (mood-induced alcohol-seeking) varied as a function of the continuous variable, revealing individual differences in sensitivity to mood-induced alcohol-seeking. A main effect of the continuous variable would indicate that there was a correlation between overall alcohol choice and the continuous variable.

7.4 Results

7.4.1 Participants

Of the 128 participants recruited, 13 were excluded for being outlying (>1.5 times the inter quartile range) on either the dependent measures (percent alcohol choice at baseline [n=3], or test [n=0]), or the continuous between-subjects predictor variables (depression symptoms [n=4]; RFDQ negative coping [n=0]; DMQ-R negative coping [n=0]; alcohol use disorder [n=3]; change in subjective sadness after mood induction [n=3]). These exclusions were undertaken because GLMs can be adversely influenced by outliers (Draper & John, 1981). These exclusions did not change the key findings or conclusions of the study, and increase the reliability of the findings because they are cannot be attributed to outliers. The mean characteristics of the remaining 115 participants were: age=20.8 (SD =1.3, range=18-25), BDI=4.6 (3.6, 0-16), RFDQ negative coping=1.9 (1.7, 0-6.6), DMQ-R negative coping=1.9 (.71, 1-3.6), AUDIT=9.11 (4.8, 1-21). AUDIT questions one to three were used to define the level of alcohol consumption in the sample. The sample means of 2.3, 1.5 and 1.6, for these questions respectively, indicated that the sample, on average, drank somewhere between two to four times a month and two to three times a week, drank between three and six drinks on these drinking episodes, and had a binge drinking session (more than six drinks) approximately monthly. There were 58 males and 57 females.

7.4.2 Experimental task

7.4.2.1 Subjective sadness

Subjective sadness measured post-induction (M = 5.2, SEM = 0.17) and post-test (M = 5.35, SEM = 0.17) were not significantly different, $F(1,113) = 1.49$, $p = .22$, $\eta_p^2 = .013$, and were highly correlated (r=.78, p<.001), so were averaged for simplicity. Subjective sadness increased significantly from baseline (M = 3.62, SEM = 0.14) to the averaged

post-induction/test score (M = 5.3, SEM = 0.16), $F(1,113) = 122.68$, $p < .001$, $\eta_p^2 = .518$, indicating that the mood induction procedure was effective in generating the intended change in mood.

7.4.2.2 Main effect of mood induction on alcohol-seeking

As shown in Figure 7.2A, percent alcohol over food image choice increased significantly from baseline to test $F(1,113) = 29.55$, $p < .001$, $\eta_p^2 = .206$, demonstrating an effect of mood induction on alcohol-seeking in the sample as a whole. To determine whether the increase in alcohol choice from baseline to test was driven by mood induction or time related variables (e.g. habituation, sensitisation, task disengagement) these two blocks were segmented into quarters. Percent alcohol choice remained stable across quarters of the baseline block (22.3, 24.9, 24.0, 22.8, respectively) and then increased step-wise and remained stable across quarters of the test block (34.9, 34.3, 32.9, 31.4, respectively). ANOVA on these data with the variables block (baseline, test) and quarter (4) yielded a main effect of block, $F(1,342) = 29.55$, $p < .001$, $\eta_p^2 = .206$, and no main effect of quarter, $F(3,342) = 1.82$, $p = .14$, $\eta_p^2 = .016$, or block by quarter interaction, $F(3,342) = 1.54$, $p = .21$, $\eta_p^2 = .013$. These findings suggest that the step-wise increase in alcohol choice from baseline to test was driven by the mood induction procedure, rather than time related variables.

7.4.2.3 Individual sensitivity to mood-induced alcohol-seeking

Table 7.1 shows the bivariate correlation matrix between the alcohol-seeking measures and questionnaire scales. The general linear model (GLM) involving the Beck Depression Inventory (BDI) shown in Figure 7.2B revealed a main effect of BDI, $F(1,113) = 3.95$, $p < .05$, $\eta_p^2 = .034$, and a significant interaction between BDI and block (baseline, test), $F(1,113) = 7.61$, $p = .007$, $\eta_p^2 = .063$. The GLM with the Reasons for Drinking Questionnaire (RFDQ) negative coping subscale shown in Figure 7.2C revealed a significant main effect of RFDQ negative coping, $F(1,113) = 12.88$, $p < .001$, $\eta_p^2 = .102$, and a significant interaction between RFDQ negative coping and block, $F(1,113) = 4.68$, $p = .03$, $\eta_p^2 = .040$. Similarly, the GLM with the Drinking Motives Questionnaire Revised (DMQ-R) negative coping subscale shown in Figure 7.2D revealed a significant main effect of DMQ-R negative coping, $F(1,113) = 22.62$, $p < .001$, $\eta_p^2 = .167$, and a significant interaction between DMQ-R negative coping and block,

$F(1,113) = 7.60$, $p = .007$, $\eta_p^2 = .063$. By contrast, the GLM with the Alcohol Use Disorders Inventory Test (AUDIT) shown in Figure 7.2E showed a significant main effect of AUDIT, $F(1,113) = 11.93$, $p = .001$, $\eta_p^2 = .095$ but no interaction between AUDIT and block, $F(1,113) = 0.38$, $p = .54$, $\eta_p^2 = .003$. Finally, the GLM with mood reactivity (the increase in subjective sadness from baseline to the post-induction/test average) shown in Figure 7.2F revealed no main effect of mood reactivity, $F(1,113) = 2.43$, $p = .12$, $\eta_p^2 = .021$, but an interaction between mood reactivity and block, $F(1,113) = 7.55$, $p = .007$, $\eta_p^2 = .063$. In summary, these results indicate that mood-induced alcohol-seeking is associated with BDI, RFDQ and DMQ-R negative coping, and subjective mood reactivity, but not AUDIT.

	Percent alcohol choice test	Mood-induced alcohol-seeking	BDI	RFDQ negative coping	DMQ-R negative coping	AUDIT	Subjective reactivity
Percent alcohol choice baseline	***r*=.61 *p*<.001**	*r*=-.09 *p*=.31	*r*=.06 *p*=.54	***r*=.24 *p*=.01**	***r*=.31 *p*=.001**	***r*=.31 *p*=.001**	*r*=.02 *p*=.87
Percent alcohol choice test		***r*=.73 *p*<.001**	***r*=.24 *p*=.01**	***r*=.32 *p*<.001**	***r*=.41 *p*<.001**	***r*=.26 *p*=.005**	***r*=.21 *p*=.03**
Mood-induced alcohol-seeking			***r*=.25 *p*=.007**	***r*=.20 *p*=.03**	***r*=.25 *p*=.007**	*r*=.06 *p*=.538	***r*=.25 *p*=.007**
BDI				***r*=.35 *p*<.001**	***r*=.37 *p*<.001**	***r*=.23 *p*=.01**	*r*=-.10 *p*=.29
RFDQ negative coping					***r*=.71 *p*<.001**	***r*=.40 *p*<.001**	***r*=-.20 *p*=.03**
DMQ-R negative coping						***r*=.54 *p*<.001**	*r*=-.13 *p*=.16
AUDIT							*r*=.01 *p*=.89

Table 7.1: Correlation matrix between alcohol-seeking measures and questionnaires. Mood induced alcohol-seeking was the difference in percent alcohol choice between baseline and test conditions (positive values indicate a bigger mood induction effect). AUDIT = Alcohol Use Disorders Inventory; RFDQ = Reasons for Drinking Questionnaire; DMQ-R = Drinking Motives Questionnaire Revised; BDI = Beck's Depression Inventory. Bold text highlights the significant correlations.

7.4.3 Analyses of other drinking motives

Further analyses were undertaken to explore the role of other Reasons for Drinking Questionnaire (RFDQ) and Drinking Motives Questionnaire (DMQ-R) subscales. GLMs following an identical structure (outlined in the analytical plan) indicated that all other RFDQ and DMR-R subscales showed a significant main effect, demonstrating an association with overall percent alcohol choice (RFDQ social pressure, $F(1,113) = 17.54$, $p < .001$, $\eta_p^2 = .134$; RFDQ cued craving, $F(1,113) = 10.25$, $p = .002$, $\eta_p^2 = .083$; DMQ-R social context, $F(1,113) = 11.54$, $p < .001$, $\eta_p^2 = .093$; DMQ-R enhancement, $F(1,113) = 27.04$, $p < .001$, $\eta_p^2 = .193$) apart from DMQ-R conformity, $F(1,113) = 1.38$, $p = .24$, $\eta_p^2 = .012$. More importantly, none of these RFDQ and DMQ-R subscales showed a significant interaction with block, indicating no evidence of an association with mood-induced alcohol-seeking (RFDQ social pressure, $F(1,113) = 0.24$, $p = .62$ $\eta_p^2 = .002$; RFDQ cued craving, $F(1,113) = 0.02$, $p = .88$, $\eta_p^2 = .000$; DMQ-R social context, $F(1,113) = 0.72$, p

= .39, η_p^2 = .006; DMQ-R enhancement, $F(1,113) = 0.34$, $p = .56$ η_p^2 = .003; DMQ-R conformity, $F(1,113) = 0.01$, $p = .94$, η_p^2 = .000). Finally, RFDQ negative coping continued to interact significantly with block (Figure 7.2C) when the other two RFDQ subscales were included in the GLM, $F(1,111) = 9.68$, $p = .002$, η_p^2 = .080. Furthermore, the DMQ-R negative coping continued to interact significantly with block (Figure 2D) when the other three DMQ-R subscales were included in the GLM, $F(1,110) = 10.43$, $p = .002$, η_p^2 = .087, demonstrating that mood-induced alcohol-seeking was selectively associated with negative coping motives.

7.4.4 Analysis of gender and age

Further analyses were undertaken to explore gender and age variables. An ANOVA incorporating gender (2) and block (2) revealed no main effect of gender, $F(1,113) = 0.07$, $p = .79$, η_p^2 = .001, or interaction between gender and block, $F(1,110) = 0.38$, $p = .54$, η_p^2 = .003. Similarly, a GLM incorporating age and block (2) revealed no effect of age, $F(1,113) = 0.20$, $p = .66$, η_p^2 = .002, or interaction between age and block, $F(1,113) = 0.02$, $p = .88$, η_p^2 = .000. These results indicate no evidence of relationships between mood-induced alcohol-seeking and gender or age.

7.4.5 Multiple regression: predicting mood-induced alcohol-seeking

A multiple regression model was undertaken to determine the proportion of variance in mood-induced alcohol-seeking accounted for by the predictors, as well as the independence of the predictors. The Reasons for Drinking Questionnaire (RFDQ) and Drinking Motives Questionnaire (DMQ-R) negative coping scores were highly correlated, r=.71, p<.001, and so were converted to z scores to normalize their distribution, and averaged to create a single index. The dependent variable was mood-induced alcohol-seeking, i.e. the increase in alcohol choice from baseline to test. The three predictor variables entered into the model were the Beck Depression Inventory (BDI), the combined RFDQ/DMQ-R negative coping score, and mood reactivity (i.e. the increase in subjective sadness from baseline to the post-induction/test average score). These predictors explained a significant proportion (18%) of variance in mood-induced alcohol-seeking, $F(3,111) = 7.97$, $p < .001$, $R^2 = .18$. Furthermore, all three predictor variables accounted for unique variance: BDI, $\beta = .20$, $t(114) = 2.17$, $p = .03$, combined

negative coping, β = .21, $t(114)$ = 2.26, p = .03, and subjective mood reactivity, β = .31, $t(114)$ = 3.54, p = .001.

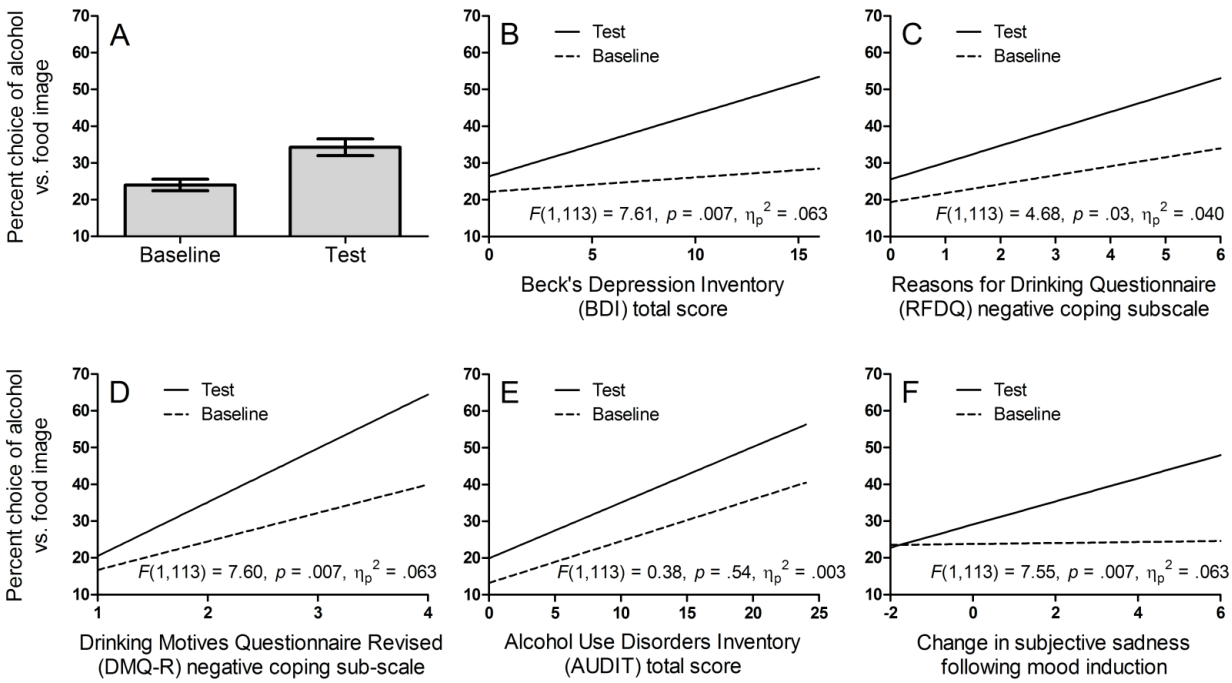

Figure 7.2 A: Average percent choice of alcohol versus food images in the baseline and test block (following negative mood induction). B-F: Regression slopes relating percent choice of alcohol versus food images at baseline and test with five continuous between-subjects variables: (B) Beck Depression Inventory (BDI) depression symptoms (C) the Reasons for Drinking Questionnaire (RFDQ) negative coping subscale, (D) Drinking Motives Questionnaire Revised (DMQ-R) negative coping subscale, (E) alcohol use disorder AUDIT scores, and (F) the change in subjective sadness from baseline to the post-induction/test average (subjective reactivity). The statistical insets report the interaction between the within-subjects variable block (baseline, test) and the continuous between-subjects variable. Block interacted significantly with depression symptoms (BDI) coping motives (RFDQ and DMQ-R) and subjective reactivity (but not alcohol use disorder), demonstrating greater sensitivity to mood-induced alcohol-seeking with these individuals.

7.5 Discussion

The most novel and theoretically pertinent finding of the study was that depression symptoms were associated with greater sensitivity to negative mood-induced alcohol-seeking. As noted in the introduction, two previous alcohol studies provided weak evidence for this association (Cooney et al., 1997; Owens et al., 2015a), and one study failed to detect this association in a sample of 48 hazardous community drinkers who completed the same task as the present (Hardy & Hogarth, 2017) – perhaps due to low

power or narrow variance in depression scores. In contrast, a correlation between depression and sensitivity to negative mood-induced tobacco-seeking was found in a small sample of smokers preselected to have high and low depression symptoms (Hogarth et al., 2017), corroborating Fucito & Juliano (2009). Therefore, the current study is the first to demonstrate that depression is associated with sensitivity to mood-induced alcohol-seeking, just as depression is associated with mood-induced tobacco-seeking, consistent with a core prediction of negative reinforcement theory. Given the relatively young sample, this finding provides evidence for a negative reinforcement mechanism that could drive vulnerability to future alcohol dependence in individuals reporting depression symptoms.

The association between coping motives and mood-induced alcohol-seeking has been demonstrated in a number of previous studies, in young adult drinkers (Austin & Smith, 2008; Birch et al., 2004; Field & Powell, 2007; Field & Quigley, 2009; Grant et al., 2007a; Rousseau et al., 2011; Woud et al., 2015; Zack et al., 2003) and alcoholic men (Cooney et al., 1997). Although we failed to find this association with hazardous community drinkers (Hardy & Hogarth, 2017), perhaps due to low power or restricted variance in drinking to cope scores. The unique contribution of the current study was to demonstrate that the relationship between drinking to cope and mood-induced alcohol-seeking could not be attributed to other drinking motives, supporting earlier preliminary findings (Grant et al., 2007a; Woud et al., 2015). In addition, we found that drinking to cope and depression symptoms accounted for unique variance in the mood-induced alcohol-seeking, suggesting no (cross-sectional) mediation effects, perhaps contradicting the view that coping motives are the proximal determinants of behaviour (Cooper, Frone, Russell, & Mudar, 1995). However, the true status of any mediation pathways between depression symptoms, drinking to cope, and mood-induced alcohol-seeking can only be resolved by a more highly powered study.

The relationship between subjective reactivity and mood-induced alcohol-seeking supports prior weak evidence for this relationship from three alcohol studies (Kelly et al., 2011; Owens et al., 2015a; Sinha et al., 2009), and strong evidence from one smoking study (Hogarth et al., 2015a), and contradicts two null findings (Magrys & Olmstead, 2015; McGrath et al., 2016). Despite subjective reactivity being associated with mood-

induced alcohol choice, there is a question as to whether this measure is a clinically meaningful marker, because it did not correlate positively with depression symptoms, coping motives or alcohol use disorder severity. Given this, it seems unlikely that subjective reactivity reflects the sort of mood-regulation skills that are thought to confer risk for alcohol dependence (Berking et al., 2011).

The most troubling finding, from the perspective of negative reinforcement theory, was that alcohol use disorder severity indexed by the AUDIT was not associated with sensitivity to negative mood-induced alcohol-seeking. This null association is actually backed by the weight of published evidence, with seven studies reporting a similar null association (Austin & Smith, 2008; Cooney et al., 1997; Field & Powell, 2007; Field & Quigley, 2009; Hardy & Hogarth, 2017; Woud et al., 2015; Zack et al., 1999), and only four studies reporting a significant association (Randall & Cox, 2001; Sinha et al., 2009; Zack et al., 2003; Zack et al., 2006). From these data, one could reject the core tenet of negative reinforcement theory, and conclude that negative mood-induced alcohol-seeking does not underpin alcohol dependence. Alternatively, one could dismiss these null associations on the assumption that questionnaires of alcohol dependence (such as the AUDIT) are not optimised to identify young adult drinkers who are most at risk of developing alcohol dependence in the future, because they largely assess drinking frequency, rather than perceived loss of control over drinking (Pilkonis et al., 2016). Indeed, within the current sample, the mean variance of AUDIT items reflecting drinking frequency (questions 1-3) was .57; substantially larger than the (constrained) mean variance of .19 for items reflecting alcohol problems (questions 4-10). It is possible that drinking frequency in young adults might be driven by various factors including friendship networks (Kuntsche et al., 2014), whereas perceived loss of control over drinking might be more closely associated with sensitivity to mood-induced alcohol-seeking. A better test of negative reinforcement theory, therefore, would be to examine whether negative mood-induced alcohol-seeking is associated with a questionnaire that specifically indexes perceived loss of control over drinking in young adults, rather than drinking frequency (Pilkonis et al., 2016).

Baseline alcohol choice appeared to index individual differences in the relative value of alcohol. Baseline alcohol choice correlated with alcohol use disorder (AUDIT) scores

and drinking to cope with negative affect indexed by two questionnaires, corroborating a previous study with hazardous community drinkers (Hardy & Hogarth, 2017). Two related cocaine studies using a pictorial cocaine choice procedure have found that cocaine choice is associated with cocaine use frequency (Moeller et al., 2013; Moeller et al., 2009). Furthermore, similar choice procedures in which smokers choose between points exchangeable for tobacco versus food have demonstrated that tobacco choice correlates with cigarettes smoked per day, smoking days per week, craving and dependence (Chase, MacKillop, & Hogarth, 2013; Hogarth, 2012; Hogarth & Chase, 2011, 2012). These findings suggest that percent drug choice in these procedures indexes the relative value of the drug, which underpins consumption frequency and dependence severity. We might therefore have greater confidence that the effect of negative mood induction on alcohol choice models the motivational processes driving alcohol consumption and dependence in the natural environment.

It is noteworthy that depression symptoms and negative coping motives were not associated with greater subjective reactivity to mood induction. The null association between depression symptoms and subjective mood reactivity is consistent with our previous study (Hardy & Hogarth, 2017) and substantial literature (Bylsma, Morris, & Rottenberg, 2008; Falkenberg, Kohn, Schoepker, & Habel, 2012). The implication is that increased sensitivity to mood-induced alcohol-seeking in young adult drinkers who report depression symptoms and coping motives is not mediated by heightened subjective reactivity to negative mood triggers. Rather, we propose that negative mood induction more effectively motivated alcohol-seeking in individuals with high depression/coping scores because these individuals have had more experience of the greater reward value of alcohol in the negative mood state, which allows the negative mood state to more effectively promote goal-directed alcohol-seeking, through incentive learning (Hogarth et al., 2015a; Hutcheson, Everitt, Robbins, & Dickinson, 2001; Mathew et al., 2017).

One limitation of the study was that the negative mood induction condition was not compared against a control condition (as has been done in other studies: Hogarth et al., 2015a). The current design was selected to maximise the ability to detect individual differences in sensitivity to negative mood-induced alcohol-seeking by running all

participants in that condition. The weakness however is that the increase in alcohol choice from baseline to test could be interpreted as being driven by mood induction or by time related variables such as sensitization or habituation to stimuli, or task disengagement. Additional analyses, however, revealed that alcohol choice increased as a step-function immediately following negative mood induction, and did not change significantly across quarters within each block. This suggests that the increase in alcohol choice at test was driven by the mood induction procedure rather than time related variables.

To conclude, this study found that sensitivity to negative mood-induced alcohol-seeking was greater in young adults who reported depression symptoms, drinking to cope, and subjective reactivity to mood induction. These findings accord with the core prediction of negative reinforcement theory that certain vulnerable individuals are more sensitive to the motivational impact of negative states on alcohol-seeking behaviour. This sensitivity arguably underpins the risk of alcohol dependence in vulnerable individuals, but longitudinal and causal studies are needed to confirm this prediction.

Chapter 8. Depressive statements prime goal-directed alcohol-seeking in individuals who report drinking to cope with negative affect

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8.1 Abstract

Background Most variants of negative reinforcement theory predict that acute depressed mood can promote alcohol-seeking behaviour, but the precise mechanisms underpinning this effect remain contested. One possibility is that mood-induced alcohol-seeking is due to the formation of a stimulus-response (S-R) association, enabling depressed mood to elicit alcohol-seeking automatically. A second possibility is that depressed mood undergoes incentive learning, enabling it to enhance the expected value of alcohol and thus promote goal-directed alcohol-seeking. **Objectives** These two explanations were distinguished using a human outcome-revaluation procedure. **Methods** One hundred and twenty eight alcohol drinkers completed questionnaires of alcohol use disorder, drinking to cope with negative affect and depression symptoms. Participants then learned that two responses earned alcohol and food points respectively (baseline) in two-alternative forced-choice trials. At test, participants rated the valence of randomly sampled negative and positive mood statements and, after each statement, chose between the alcohol- or food-seeking response in extinction. **Results** The percentage of alcohol- vs. food-seeking responses was increased significantly in trials containing negative statements compared to baseline and positive statement trials, in individuals who reported drinking to cope with negative affect (p=.004), but there was no such interaction with indices of alcohol use disorder (p=.87) or depression symptoms (p=.58). **Conclusions**: Individuals who drink to cope with negative affect are more sensitive to the motivational impact of acute depressed mood statements priming goal-directed alcohol-seeking. Negative copers' vulnerability to alcohol dependence may be better explained by excessive affective incentive learning than by S-R habit formation.

8.2 Introduction

The core tenet of negative reinforcement theory is that alcohol dependence is caused by withdrawal, emotional or psychiatric states (such as agitation, depression, anxiety etc.) powerfully motivating alcohol use in order to mitigate these states (Baker et al. 2004; Cox and Klinger 1988; Eissenberg 2004; Hall et al. 2015; Kassel et al. 2003; Khantzian 1997; Koob and Volkow 2010; Marlatt 1996; Mathew et al. 2017; Sinha 2001; Solomon and Corbit 1973; Wikler 1984). However, the exact mechanisms by which adverse states trigger alcohol-seeking remain unclear. Several negative reinforcement accounts claim that negative affect triggers alcohol-seeking automatically, i.e. without forethought for the consequences (Baker et al. 2004; Everitt and Robbins 2016; Koob and Volkow 2010; Schwabe et al. 2011). This claimed automatic status of alcohol-seeking arguably explains why drinking persists despite significant harms or intentions to quit. These theoretical papers articulate two variants of the automatic account. According to one variant, alcohol's ability to mitigate adverse states means that alcohol is experienced as having a greater reward value in those states. The greater reward value of alcohol reinforces a strong direct association (connection) between the adverse state stimuli (S) and the alcohol-seeking motor response (R). These S-R links enable the adverse states to elicit the alcohol-seeking response automatically, unconsciously, habitually or compulsively, i.e. without forethought for the wider harmful consequences of alcohol use or current intentions to quit. The second variant of the automatic account differs in that it presumes that adverse states (e.g. anxiety) acutely reduce cognitive capacity, favouring automatic control over alcohol-seeking by S-R links which have previously formed between *external* alcohol related stimuli and the alcohol-seeking response. By promoting automatic control over alcohol-seeking by external alcohol cues, adverse states reduce the influence of expected harms and intentions to quit on behaviour, and so promote dependence and relapse.

Other negative reinforcement theories, by contrast, claim that adverse affective states motivate alcohol-seeking by retrieving explicit coping motives – beliefs that alcohol can help mitigate adverse states (Cox and Klinger 1988; Kassel et al. 2003; Khantzian 1997; Marlatt 1996; Mathew et al. 2017; Sinha 2001). Such motivational negative reinforcement models may be specified in more mechanistic detail by being integrated

with incentive learning theory (Dickinson and Balleine 2010; Hogarth et al. 2015a; Hutcheson et al. 2001). According to this combined account, individuals who report drinking to cope with negative affective states are reporting their direct experience of alcohol having a greater reward value because of its ability to acutely mitigate those states. This incentive learning experience enables negative affective states to raise the expected value of alcohol (in the same way that hunger raises the expected value of food because food is more rewarding when hungry). The greater expected reward value of alcohol in the negative affective state is combined with instrumental knowledge of the responses that produce alcohol in the current environmental context (Hardy et al. 2017), thus promoting goal-directed (intentional) instrumental choice to obtain alcohol. In short, individuals who report drinking to cope with negative affect are vulnerable to alcohol dependence and relapse (Beseler et al. 2008; Crum et al. 2013a; Crum et al. 2013b; Lazareck et al. 2012; Menary et al. 2011; Merrill et al. 2014; Robinson et al. 2011; Windle and Windle 2015) because negative affective states act as powerful motivators of goal-directed alcohol-seeking which overrule expected harms and intentions to quit (just as intense hunger might overrule weight loss intentions).

A key source of evidence supporting this particular incentive learning model is the finding that individuals who report drinking to cope with adverse affective states are more sensitive to the motivational impact of experimentally induced negative mood or stress on alcohol-seeking behaviour, as indexed by craving, consumption, preferential choice or cognitive bias (Austin and Smith 2008; Birch et al. 2004; Brady et al. 2006; Cooney et al. 1997; Field and Powell 2007; Field and Quigley 2009; Grant et al. 2007a; Rousseau et al. 2011; Woud et al. 2015; Zack et al. 2003); but for null results see, (Field and Powell 2007; Thomas et al. 2014). The strong interpretation of these findings is that coping motives play a causal role in enabling mood induction to promote alcohol-seeking, rather than automatic S-R processes. However, because coping motives are only correlated with mood-induced alcohol-seeking, they could be merely epiphenomenal, while an S-R process is actually responsible for the effect. Existing studies cannot discriminate these two positions.

The outcome-revaluation procedure has provided a more decisive method for determining whether drug-seeking behaviour is controlled by incentive learning or S-R

mechanisms, in both animals (Corbit et al. 2012; Dickinson et al. 2002; Hutcheson et al. 2001; Miles et al. 2003) and humans (Hogarth 2012; Hogarth and Chase 2011; Hogarth et al. 2013). The rationale of this method can be illustrated with one key study. Hutcheson et al. (2001) found that heroin withdrawal could augment a novel heroin-seeking response in an extinction test, but only in rats that had previously experienced heroin in the withdrawal state. This effect can be explained by incentive learning but not by S-R theory. Arguably, rats learn that heroin has greater reward value in the withdrawal state (incentive learning), enabling this state to raise the expected value of heroin, which integrates with instrumental knowledge of the novel heroin-seeking response, enabling goal-directed selection of that response. By contrast, S-R mechanisms cannot explain this effect for two reasons. First, the heroin-seeking response was never reinforced in the withdrawal state, so an S-R association could not form between withdrawal and the response. The other S-R variant is also not viable because if withdrawal impaired cognition promoting control over heroin-seeking by S-R links between external cues and the response, then withdrawal should have promoted heroin-seeking in rats that had not previously experienced heroin in that state (had no incentive learning experience). However, this effect was not found. Thus, the outcome-revaluation procedure provides a compelling test of whether the impact of negative affective states on drug-seeking behaviour is driven by incentive learning rather than S-R mechanisms.

The current study utilised a human outcome-revaluation procedure to test whether acute depressed mood statements would prime goal-directed alcohol-seeking to a greater extent in individuals who report drinking to cope with negative affect. One hundred and twenty eight alcohol drinkers first completed questionnaires of alcohol use disorder, drinking to cope with negative affect and depression symptoms. Participants then learned at baseline that two responses earned alcohol and food points respectively in a set of two-alternative forced choice trials. At test, participants rated the valence of randomly sampled negative affective statements (e.g. 'I don't think things are ever going to get better') and positive statements (e.g. 'I feel enthusiastic and confident now'), and following each statement, chose between the alcohol- and food-seeking response in extinction (i.e. no alcohol or food points were earned). It was expected that negative mood statements would increase the percentage of alcohol-

versus food-seeking choices compared to positive statements and baseline to a greater extent in individuals who report drinking to cope with negative affect. This finding would support a merger of motivational negative reinforcement theory (Cox and Klinger 1988; Kassel et al. 2003; Khantzian 1997; Marlatt 1996; Mathew et al. 2017; Sinha 2001) and incentive learning theory (Dickinson et al. 2002; Hogarth 2012; Hogarth and Chase 2011; Hutcheson et al. 2001). That is, the finding would suggest that explicit beliefs concerning the greater reward value of alcohol in the negative affective state are the causal mechanism driving the intentional choice to drink, rather than an automatic S-R mechanism. This theoretical distinction has important implications for alcohol treatment strategy, suggesting that for drinkers who report negative coping motives, the most effective treatment should be forms of cognitive behaviour therapy (CBT) that directly target negative coping motives (Anker et al. 2016; Bradizza et al. 2017; Kushner et al. 2013; Stasiewicz et al. 2013), whereas mood management (Monti et al. 1990; Monti and Rohsenow 1999; Pettinati et al. 2013), and attempts to counter-train implicit learning processes (Gladwin et al. 2015) are likely to be comparatively less effective in this group.

8.3 Method

8.3.1 Participants

The study recruited 128 drinkers (50% male) who reported drinking alcohol at least monthly. The study was approved by the University of Exeter Psychology Ethics Committee.

8.3.2 Questionnaires

Questionnaires were the Alcohol Use Disorders Inventory Test (AUDIT: Babor et al. 2001) and the Reasons for Drinking Questionnaire (RFDQ: Zywiak et al. 1996) from which the negative coping subscale was examined. This subscale includes 7 items which ask participants to assess how important different reasons for drinking are for them, including sadness, anger, frustration, anxiety, tension, illness and relationship difficulties, measured on a 0-10 scale ranging from 'not at all important' to 'very important'. Depression symptoms were recorded using Beck's Depression Inventory IA (Beck et al. 1996a).

8.3.3 Mood induction effect on alcohol choice

Baseline alcohol versus food choice (see Figure 8.1): Participants were presented with two 275ml bottles of Beck's beer and two 45g Cadbury's Dairy Milk chocolate bars on the desk and instructed: 'In this task, you can earn points for beer and chocolate to take with you at the end. In each trial, choose the UP or DOWN arrow key to earn these rewards. Your points will be drawn from a lottery at the end of the experiment. You may win the 2 beers, the 2 chocolate bars, all 4 or none at all. The more points you earn for each reward, the better your chances of winning more of that reward'. This was a deception – all participants received a small Freddo chocolate bar at the end of the experiment. Trials began with a question mark, whereupon an up or down key press produced the alcohol or chocolate outcome, comprising an image of the reinforcer plus corresponding text 'You win a [beer/chocolate] point' for 1 second. The response-outcome contingencies were counterbalanced between subjects. After 32 baseline trials, contingency knowledge was tested with two questions in random order: 'Which arrow key earned [beer/chocolate] the UP or DOWN key?'

Mood statements: Participants were instructed to carefully consider negative and positive mood statements, listed in Table 8.1 (Hogarth et al. 2015a; Velten 1968; Westermann et al. 1996). In each trial, either a negative or positive statement was presented for 4 seconds, before participants rated how sad to happy this made them feel on a 9 point scale. Across 8 trials, the presented statement was randomly selected from the set of 32, comprising 16 negative and 16 positive statements (see Table 8.1).

Test: Participants were instructed: 'In this part of the task, please continue to consider the mood statements. Also, the UP and DOWN arrow keys will win beer and chocolate points in the same way as earlier in the task. You will be told how many points you have earned at the end. Press the space bar to begin'. In each test a mood statement was presented for 4 seconds, before participants rated how sad-happy it made them feel. Upon presentation of the question mark, the alcohol- or food-seeking response was made. No outcomes were presented at the test stage, so any effect of mood statements on choice must be mediated by goal-directed knowledge of the response-outcome contingencies acquired in training. Across 64 test trials, there were two cycles

of 32, each containing 16 negative and 16 positive statements selected in random order. Retention of contingency knowledge over the test phase was tested as before.

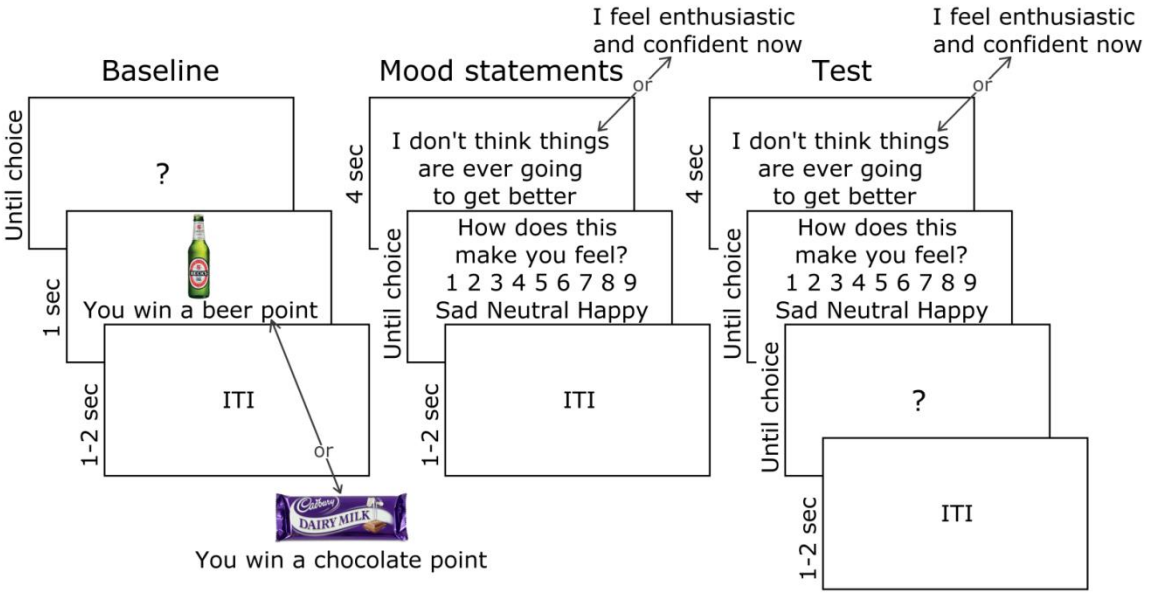

Figure 8.1: Outcome-revaluation procedure used to test the impact of negative and positive mood statements on goal-directed alcohol-seeking. At baseline, participants learned that up and down keyboard responses earned beer and chocolate points respectively. Participants then rated how sad or happy randomly sampled negative and positive mood statements made them feel (see Table 8.1 for a list of statements). At test, participants continued to rate the valence of negative and positive statements, but after each statement, made a free choice between the beer- or chocolate-seeking response trained at baseline, but without feedback of whether beer or chocolate points were earned (i.e. in extinction). Negative mood statements were expected to increase the percentage of beer- over chocolate-seeking responses, compared to positive statements and baseline, in individuals who reported drinking to cope with negative affect. This would demonstrate greater sensitivity to the motivational effect of negative mood statements on goal-directed alcohol-seeking.

Negative mood statements	Positive mood statements
• I feel a little down today	• I feel cheerful and lively
• My work is harder than I expected	• On the whole, I have very little difficulty in thinking clearly
• Sometimes I feel so guilty that I can't sleep	• I'm pleased that most people are so friendly to me
• I wish I could be myself, but nobody likes me when I am	• I can make friends extremely easily
• Today is one of those days when everything I do is wrong	• I feel enthusiastic and confident now
• I doubt that I'll ever make a contribution in the world	• There should be a lot of good times coming along
• I feel like my life is in a rut that I'm never going to get out	• I'm able to do things accurately and efficiently
• My mistakes haunt me, I've made too many	• I know that I can achieve the goals I set
• Life is such a heavy burden	• I have a sense of power and vigour
• I'm tired of trying	• I'm feeling amazingly good today
• Even when I give my best effort, it just doesn't seem to be good enough	• I feel highly perceptive and refreshed
• I don't think things are ever going to get better	• I can concentrate hard on anything I do
• I feel worthless	• My thinking is clear and rapid
• What's the point of trying	• Life is so much fun; it seems to offer so many sources of fulfilment
• I feel cheated by life	• Life is firmly in my control
• Every time I turn around, something else has gone wrong	• I'm really feeling sharp now

Table 8.1: Negative and positive mood statements used in the study. At the beginning of each test trial, one statement was presented (randomly sampled from the entire set of 32), and rated for how sad-happy it makes the participant feel, before a choice was made between the alcohol- or food-seeking response in extinction.

8.3.4 Analytical plan

Percent alcohol- versus food-seeking choice was calculated from baseline trials and test trials with negative and positive statements (>50%=preference for alcohol, <50%=preference for food). An ANOVA first tested the difference between these three

conditions. Separate general linear models (GLMs) were conducted with percent alcohol choice as the dependent variable, condition (3) as the within-subjects variable and a single, continuous between-subjects variable in each model: alcohol use disorder (AUDIT), negative coping motives (RFDQ) and depression symptoms (BDI). A significant interaction indicated that the difference in alcohol choice between conditions varied with the continuous variable. A main effect of the continuous variable indicated that there was a simple correlation between overall alcohol choice and the continuous variable. Interactions were followed up by GLMs contrasting the three conditions.

8.4 Results

8.4.1 Participants

Of the 128 participants recruited, five failed to accurately report the response-outcome contingencies after baseline or test and so were excluded, as is standard in this paradigm (e.g. Hogarth et al. 2015a). The mean characteristics of the 123 participants who were analysed were: age=20.9 (SD =1.7, range=18-32), AUDIT=10.2 (5.1, 1-25), RFDQ negative coping score=1.7 (1.5, 0-5.9), BDI=5.7 (5.4, 0-26). There were 61 males and 62 females.

8.4.2 Experimental task

Negative and positive statements were rated as having significantly different valence. The negative mood statements were rated as making participants feel sad (M = 2.71, SEM = 0.09) whereas the positive statements were rated as making participants feel happy (M = 7.36, SEM = 0.09), $F(1,122) = 1036.42$, $p < .001$, $\eta_p^2 = .895$. There was no overall difference in alcohol choice measured between the baseline, test-negative and test-positive conditions, $F(1,122) = 1.14$, $p = .32$, $\eta_p^2 = .009$, as shown in Figure 8.1A.

Table 8.2 shows the correlation matrix between the questionnaire scales, baseline alcohol versus food choice and the mood-induced increase in alcohol choice (the difference between test-negative and test-positive conditions). The GLM with AUDIT shown in Figure 8.2B showed a significant main effect of AUDIT, $F(1,121) = 9.52$, $p = .003$, $\eta_p^2 = .073$ but no interaction between AUDIT and condition, $F(2,242) = 0.14$, $p = .87$, $\eta_p^2 = .001$. By contrast, the GLM with RFDQ negative coping shown in Figure 8.2C

revealed a significant a main effect of RFDQ negative coping, $F(1,121) = 8.93$, $p = .003$, $\eta_p^2 = .069$, and significant interaction between RFDQ negative coping and condition, $F(2,242) = 5.54$, $p = .004$, $\eta_p^2 = .044$. Specific contrasts indicated that this interaction between RFDQ negative coping and condition was significant when the GLM included baseline and test-negative conditions, $F(1,121) = 7.33$, $p = .008$, $\eta_p^2 = .057$, and when it included test-negative and test-positive conditions, $F(1,121) = 7.44$, $p < .007$, $\eta_p^2 = .058$, but not when it included baseline and test-positive conditions, $F(1,121) = 0.82$, $p = .37$, $\eta_p^2 = .007$. Finally, the GLM with BDI shown in Figure 2D revealed a main effect of BDI, $F(1,121) = 6.50$, $p = .01$, $\eta_p^2 = .051$, but no interaction between BDI and condition, $F(2,242) = 0.55$, $p = .58$, $\eta_p^2 = .005$. In summary, these results indicate AUDIT, RFDQ negative coping and BDI all have a simple correlation with baseline and overall alcohol choice, but only RFDQ negative coping is associated with greater sensitivity to the motivational impact of negative mood statements on alcohol-seeking at test.

Secondary analyses were undertaken to explore the role of other variables. A GLM incorporating the second RFDQ subscale, social pressure, and condition (baseline, test-negative, test-positive) revealed no main effect of subscale, $F(1,121) = 3.62$, $p = .06$, $\eta_p^2 = .029$, or interaction, $F(2,242) = 2.68$, $p = .07$, $\eta_p^2 = .022$. Similarly, a GLM incorporating the remaining RFDQ subscale, cued craving, and condition (3) revealed a significant main effect of subscale, $F(1,121) = 7.93$, $p = .006$, $\eta_p^2 = .062$, but no interaction, $F(2,242) = .42$, $p = .66$, $\eta_p^2 = .003$. Importantly, the interaction between RFDQ negative coping and condition (3) remained significant when the other two RFDQ subscales were both included (controlled) in the GLM, $F(2,238) = 6.83$, $p = .001$, $\eta_p^2 = .054$. Similarly, the interaction between RFDQ negative coping and condition (3) remained significant when BDI and AUDIT were both included (controlled) in the model, $F(2,238) = 6.39$, $p = .002$, $\eta_p^2 = .051$. Turning to the gender variable, an ANOVA incorporating gender (2) and condition (3) indicated that males chose more alcohol overall (M=34.8, SEM=3.3) than females (M=24.8, SEM=3.3), $F(1,121) = 4.58$, $p = .03$, $\eta_p^2 = .037$, but there was no interaction between gender and condition, $F(2,242) = .75$, $p = .47$, $\eta_p^2 = .006$. A GLM incorporating age and condition (3) revealed no effect of age, $F(1,121) = 2.33$, $p = .13$, $\eta_p^2 = .019$, or interaction, $F(2,242) = .19$, $p = .83$, $\eta_p^2 = .002$. A GLM incorporating the difference in valence rating between negative and positive statements and condition (3) revealed no effect of valence rating, $F(1,121) = .37$, $p = .54$, $\eta_p^2 = .003$, or interaction,

$F(2,242) = 1.13$, $p = .32$, $\eta_p^2 = .009$. These results indicate that the relationship between RFDQ negative coping and greater sensitivity to mood-induced alcohol-seeking cannot be explained by other variables measured in the study.

	Experiment 1			
	BDI	RFDQ Negative Coping	Baseline Alcohol-seeking	Mood induced alcohol-seeking
AUDIT	*r*=.25 *p*=.005	*r*=.43 *p*<.001	*r*=.24 *p*=.007	*r*=-.00 *p*=.967
BDI		*r*=.43 *p*<.001	*r*=.19 *p*=.038	*r*=.05 *p*=.553
RFDQ Negative Coping			*r*=.22 *p*=.015	*r*=.24 *p*=.007
Baseline alcohol choice				*r*=.07 *p*=.461

Table 8.2: Correlation matrix between questionnaire and alcohol-seeking measures. AUDIT = Alcohol Use Disorders Inventory; RFDQ = Reasons for Drinking Questionnaire; BDI = Beck's Depression Inventory. Baseline alcohol-seeking was the percent choice of alcohol over food at baseline. Mood induced alcohol-seeking was the difference in percent alcohol choice between the test-negative and test-positive conditions.

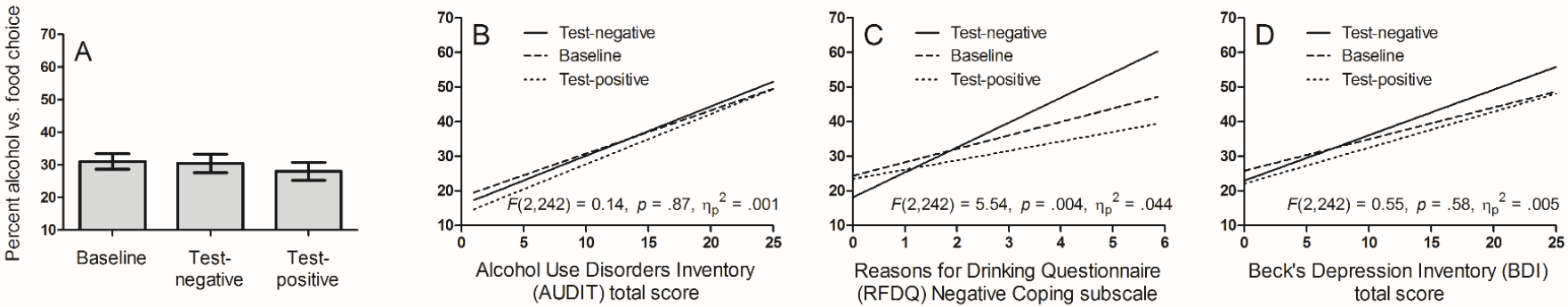

Figure 8.2 *A: Average percent choice of the alcohol- over food-seeking response in baseline, test-negative and test-positive trials. B-D: Regression slopes relating the percent choice of alcohol- over food-seeking responses in baseline, test-negative and test-positive trials with three continuous between-subjects variables: (B) alcohol use disorder AUDIT scores, (C) the Reasons for Drinking Questionnaire negative coping subscale, and (D) Beck's Depression Inventory. The statistical insets report the interaction between the within-subjects variable condition (3) and the continuous between-subjects variable AUDIT, RFDQ or BDI. The significant interaction involving RFDQ negative coping (Figure C) indicates that individuals who reported drinking to cope with negative affect were more sensitive to the motivational impact of negative mood statements on goal-directed alcohol-seeking.*

8.5 Discussion

The main finding of the current study was that individuals who reported drinking to cope with negative affect were more sensitive to the motivational impact of negative mood statements promoting goal-directed alcohol- versus food-seeking in an outcome-revaluation procedure. This finding advances previous studies which have also found that coping motives predict sensitivity to mood or stress-induced alcohol-seeking, as indexed by craving, consumption, preferential choice or cognitive bias (Austin and Smith 2008; Birch et al. 2004; Brady et al. 2006; Cooney et al. 1997; Field and Powell 2007; Field and Quigley 2009; Grant et al. 2007a; Rousseau et al. 2011; Woud et al. 2015; Zack et al. 2003) and disconfirms two null results (Field and Powell 2007; Thomas et al. 2014). The novel contribution of the current study was to demonstrate that mood-induced alcohol-seeking can be driven by incentive learning rather than S-R habit processes. Previous studies could not distinguish these accounts. According to the incentive learning account, individuals who reported negative coping motives have learned that alcohol is more rewarding in negative affect states, enabling negative statements to raise the expected value of alcohol, which is integrated with instrumental knowledge of which response produces alcohol, promoting goal-directed choice of that response. This finding supports a merger of motivational negative reinforcement theories (Cox and Klinger 1988; Kassel et al. 2003; Khantzian 1997; Marlatt 1996; Mathew et al. 2017; Sinha 2001) and incentive learning theory (Dickinson et al. 2002; Hogarth 2012; Hogarth and Chase 2011; Hutcheson et al. 2001), in which explicit beliefs concerning the greater reward value of alcohol in the negative affective state are the causal mechanism driving the intentional choice to drink, rather than an automatic S-R mechanism, in individuals who report negative drinking coping motives.

The putative causal role played by negative coping motives and accompanying sensitivity to mood-induced alcohol-seeking in alcohol dependence and relapse has been supported by a range of studies. In longitudinal studies, self-reported coping motives are a prospective marker for subsequent alcohol dependence (Beseler et al. 2008; Crum et al. 2013a; Crum et al. 2013b; Lazareck et al. 2012; Menary et al. 2011; Merrill et al. 2014; Robinson et al. 2011; Windle and Windle 2015). For instance, Crum et al. (2013b) found that, for individuals who reported drinking to cope with negative

affect at baseline, there was a 3.1 times increase in risk of new-onset alcohol dependence and a 3.4 times increased risk of persistent alcohol dependence at follow up. Second, in cross sectional studies, a wide range of psychiatric symptoms are associated with more severe alcohol dependence, and this relationship is consistently mediated by self-reported drinking to cope with negative affect, suggesting coping motives are the proximal driver of alcohol dependence (Asberg and Renk 2012; Dvorak et al. 2014; Fossos et al. 2011; Gonzalez et al. 2011; Grayson and Nolen-Hoeksema 2005; Holahan et al. 2001; Kaysen et al. 2007; McDevitt-Murphy et al. 2015; Mooney et al. 2008; O'Hare and Sherrer 2011; Øverup et al. 2015; Peirce et al. 1994; Reardon et al. 2002; Schuck and Widom 2001; Schuckit et al. 2006; Simpson et al. 2014; Stewart et al. 2001; Topper et al. 2011; Ullman et al. 2005; Yeater et al. 2010; Young-Wolff et al. 2009). Third, retrospective interview studies have found that alcoholics typically attribute more than 50% of relapse episodes to negative affect, interpersonal conflict or physical ailments, suggesting that reactivity to negative triggers drives relapse (Brown et al. 1990; Hodgins et al. 1995; Hore 1971; Marlatt 1996). Finally, greater increases in alcohol craving following experimental negative mood induction predicts vulnerability to alcohol relapse even when other relevant predictors are controlled (Brady et al. 2006; Cooney et al. 1997; Higley et al. 2011; Sinha et al. 2011, also for cocaine relapse see Back et al. 2010; Sinha et al. 2006). For example, Sinha et al. (2011) found that only 0.02% of high stress-induced craving responders remained abstinent from alcohol at 80 day follow-up, whereas 35% of low stress-induced craving responders survived. These studies are consistent with the claim that explicit beliefs that alcohol has a greater reward value in a negative affect state (incentive learning) plays a causal role in driving alcohol-seeking behaviour.

By contrast, the main finding cannot be explained by S-R accounts of how depressed mood promotes alcohol-seeking (Baker et al. 2004; Everitt and Robbins 2016; Koob and Volkow 2010; Schwabe et al. 2011). Negative mood statements could not have formed a stronger S-R association with the alcohol- versus food-seeking response because testing was conducted in extinction and, therefore, neither response was reinforced in the presence of negative mood statements. Similarly, external contextual cues were commonly present when both responses were made during baseline training, and so would have formed equivalent S-R links with the alcohol- and food-seeking responses.

Consequently, negative statements could not have promoted alcohol-seeking through either a stronger S-R link to that response, or by facilitating S-R links between external cues and the alcohol-seeking response. Finally, S-R theory could only explain the correlation between coping motives and mood-induced alcohol-seeking by suggesting that coping motives are epiphenomenal rather than causal, which contradicts substantial data demonstrating the importance of coping motives in alcohol dependence noted above.

There are implications for treatment strategy in the concluding that negative mood-induced alcohol-seeking in those who drink to cope is driven by incentive learning rather than more automatic S-R mechanisms. First, if the belief that alcohol has a higher value in negative affect states plays a causal role in driving alcohol-seeking in individuals who drink to cope, then CBT which targets coping motives should be most effective in this group. Support for this claim comes from the finding that versions of CBT that target negative coping motives are more effective than treatment as usual (Bradizza et al. 2017; Chaney et al. 1978; Jones et al. 1982; Kushner et al. 2013; Monti et al. 1990; Stasiewicz et al. 2013; Watt et al. 2006), and this therapeutic effect is greater in individuals who report negative coping motives (Anker et al. 2016). Second, brief interventions which target coping motives have also produced promising therapeutic outcomes. For example, Conrod et al. (2013) selected high risk adolescents who were high in anxiety, hopelessness, impulsivity or sensation seeking and trained them to identify individualised drinking triggers and adaptive coping strategies. This intervention reduced the odds of drinking during the trial by 29% compared to no treatment, suggesting that targeting coping motives in high risk individuals may function as an effective preventative strategy. Similarly, Blevins and Stephens (2016) found that in undergraduates drinkers, a single session focusing on negative drinking coping motives and alternative coping strategies (in contrast to normative alcohol education) reduced self-reported drinking problems at 2-months follow up, which was mediated by reductions in drinking coping motives (see also Banes et al. 2014). Finally, trait adaptive coping skills have been shown to protect drinkers who reported drinking to cope, from stress induced priming of alcohol consumption (Merrill and Thomas 2013), and to be associated with reduced negative coping motives and alcohol use problems (Bravo et al. 2016b; Fernandez et al. 2010; Littlefield et al. 2010; Murphy and

Mackillop 2012; Pearson et al. 2015; Roos et al. 2015; Tull et al. 2015). The implication of these studies is that CBT which targets negative coping motives is potentially the optimal treatment strategy for individuals who drink to cope with negative affect, consistent with the incentive learning account. By contrast, mood management (Monti et al. 1990; Monti and Rohsenow 1999; Pettinati et al. 2013), and attempts to counter-train implicit learning processes (Gladwin et al. 2015) should be comparatively less effective because they do not tackle the beliefs that drive alcohol-seeking this group.

One important issue for the incentive learning account is whether the motivational impact of adverse states on goal-directed drug-seeking is powerful enough to override the catastrophic costs of drug use and intentions to quit – the hallmark of dependence. Two studies suggest that this is possible. First, Hutcheson et al. (2001) showed that heroin withdrawal could promote goal-directed heroin-seeking. Given that alcohol withdrawal constitutes severe and diverse symptoms, including seizures, delirium tremens, anxiety, depression and sleep disturbance (Heilig et al. 2010) it is plausible that these states (or anticipation of them) would exert a sufficiently powerful motivating effect on goal-directed alcohol-seeking to override costs and intentions to quit. Second, we recently demonstrated using a similar outcome-revaluation procedure to that in the present study, that negative mood induction increased goal-directed tobacco-seeking even in smokers who were tobacco sated, and who would otherwise reduce their tobacco-seeking when mood induction was absent (Hogarth et al. 2015a). The implication is that negative mood acted as a powerful motivational state which was capable of fully overriding satiety, and might therefore plausibly be able to override expected harms and intentions to quit.

Mood-induced alcohol-seeking did not vary with either AUDIT or BDI scores, despite these scores correlating with RFDQ negative coping (these correlations have also been reported in other studies: (Armeli et al. 2010; Bolton et al. 2009; Bravo et al. 2016a; Cooper et al. 1995; Gonzalez et al. 2009; Gonzalez et al. 2011; Grant et al. 2009; Holahan et al. 2004; Peirce et al. 1994; Rafnsson et al. 2006; Turner et al. 1997). Furthermore, the relationship between mood-induced alcohol-seeking and RFDQ negative coping remained significant even when AUDIT and BDI scores were controlled, consistent with the view that coping motives are the proximal determinant of the mood induction

effect (Cooper et al. 1995; Hufford et al. 2003; Marlatt 1985; Shiffman 2005; Witkiewitz et al. 2007; Zack et al. 1999). In contrast, some studies have found that sensitivity to mood-induced alcohol-seeking increased with alcohol dependence and depression symptoms. Specifically, three studies found that mood-induced alcohol-seeking was greater in more dependent drinkers (Sinha et al. 2009; Zack et al. 2003; Zack et al. 2006), but several others have either reported nonsignificant associations (Austin and Smith 2008; Cooney et al. 1997; Field and Powell 2007; Field and Quigley 2009; Woud et al. 2015; Zack et al. 1999) or have not reported the analysis despite having the relevant data (Birch et al. 2004; Grant et al. 2007a; McGrath et al. 2016; Owens et al. 2014; Potthast et al. 2015; Rousseau et al. 2011). With respect to depression symptoms, two studies have shown that the correlation between depression symptoms and alcohol craving was numerically greater in a negative mood than a neutral induction condition, providing weak evidence that depression is associated with greater sensitivity to mood-induced alcohol-seeking (Cooney et al. 1997; Owens et al. 2014). More compellingly, we recently demonstrated that negative mood-induced tobacco-seeking was greater in smokers with current major depressive disorder than those without (Hogarth et al. 2017), corroborating an earlier smoking study reporting a similar effect across subclinical depression symptoms (Fucito and Juliano 2009). In the current study, the failure to find that mood-induced alcohol-seeking was associated with AUDIT and BDI scores was presumably due to the student sample containing too few individuals at the more severe end of these spectrums.

To conclude, this study found that individuals who reported drinking to cope with negative affect were more sensitive to the motivational impact of depressive statements on goal-directed alcohol-seeking behaviour in an outcome-revaluation procedure. This effect can be explained by incentive learning, where the negative mood state raises the expected value of alcohol promoting goal-directed alcohol-seeking, but not by S-R habit theory. We have drawn upon wider literature to argue that the development of alcohol dependence, vulnerability to relapse, and the persistence of alcohol use despite substantial costs and intention to quit may be better explained by excessive affective incentive learning than by propensity to habitual or automatic control over alcohol-seeking behaviour.

Chapter 9. Pictorial smoking choice predicts nicotine dependence and associated risk factors in recently-hospitalised smokers, but shows no evidence of modulation by negative mood in an intermixed mood induction procedure

9.1 Abstract

This study tested whether a concurrent pictorial choice procedure is sensitive to the motivational effect of negative mood induction on tobacco choice in recently-hospitalised, treatment-seeking smokers. Thirty three recently-hospitalised smokers, recruited from the inpatient smoking cessation service, completed measures of nicotine dependence, depression and smoking coping motives, and reported their abstinence status (smoking vs. quit). Baseline smoking picture choice was measured by percent choice to enlarge smoking versus face thumbnail images in two-alternative forced-choice trials. Negative and positive mood was then induced in an intermixed procedure by means of self-referential positive and negative affective statements, and percent smoking choice was measured in these two conditions. Baseline percent smoking choice correlated with nicotine dependence severity (r=.45, p=.009), symptoms of depression (r=.41, p=.017), smoking coping motives (r=.41, p=.017), urge to smoke (r=.66, p<.001), cigarettes smoked per day (r=.45, p=.009), and abstinence status (r=.43, p=.013). Smoking choice was not significantly increased by negative affective statements compared to baseline or positive affective statements (p=.242, η_p^2 = .04). While the concurrent pictorial choice measure is a sensitive index of the relative value of smoking, there was no evidence for the efficacy of the mood induction procedure in altering smoking motivation in this sample.

9.2 Introduction

The research presented so far has shown, firstly, that our concurrent choice procedure provides a behavioural assay of baseline alcohol motivation, and effectively tracks raised alcohol value following negative mood induction. It has also shown that the extent of this raised alcohol choice is greater in individuals who are depressed and who drink to cope. If this effect contributes to dependence formation and maintenance, we might expect to observe it in other drug-using populations, particularly those with a high incidence of depression and coping motives. The overall aim of the present experiment was therefore to replicate our previous findings in a high-risk population of recently-hospitalised smokers, who have a high incidence of depression and smoking to cope. The first aim was to validate a pictorial concurrent choice measure of smoking motivation in this population. The second aim was to determine whether an intermixed mood induction procedure could modulate smoking motivation, as measured via this pictorial concurrent choice procedure, and the third aim was to determine whether the magnitude of this mood induction effect varied as a function of symptoms of depression and smoking to cope with negative affect. This translation of the pictorial choice task from alcohol to smoking would also provide important evidence of the task's generalisability and therefore overall utility in addiction research.

In this study we have chosen to use a population of smokers who have been recently hospitalised. Compared with the general population, individuals with chronic, long-term illnesses such as chronic obstructive pulmonary disease are more likely to have symptoms of depression (Katon 2003; Walker et al. 2018), smoke (Jamison et al. 1991; Wilson 2006; Zvolensky et al. 2010), and smoke to cope with negative affect (Ditre and Brandon 2008). They are therefore at higher risk of negative affect driven relapse to smoking in circumstances in which continued smoking is likely to have deleterious effects on their health (Au et al. 2009; Godtfredsen and Prescott 2011; Xu et al. 1992): they are a 'critical to treat' population (Strang et al. 2013). Given this evidence, we might expect to find a large effect of negative mood induction on motivation to smoke in this population. Indeed, Hogarth et al. (2017) found that another high risk group, smokers with current major depression, showed a significantly greater increase in

tobacco picture choice in response to negative mood induction compared to non-depressed smokers. Observation of this effect would therefore provide direct translation from Hogarth and Hardy (2018b) and Hogarth et al. (2018a), and provide insight into potential interventions to limit negative affect driven relapse in the present population. The question is whether the task will effectively modulate smoking motivation in this population, who may have difficulties concentrating and/or engaging with the task (Clarke et al. 1991; Halford and Brown 2018). This would indicate the utility of this measure in this population.

The first aim of the present study was to validate our pictorial choice measure as a proxy for baseline smoking motivation, and to confirm its sensitivity to multiple risk factors which raise the value of smoking. Findings and discussion relating to this aim has been covered in Chapter 5.

The second aim was to replicate our previous finding that drug motivation can be augmented by means of negative mood induction, in a particularly high-risk population of smokers (Hardy and Hogarth 2017). In the general population, negative mood induction increases craving to smoke (Brandon et al. 1996; Perkins et al. 2013; Vinci et al. 2012), smoking behaviour (Conklin and Perkins 2005; Payne et al. 1991) and responding to earn cigarettes in computer based choice tasks (Willner and Jones 1996). Similarly, depressed smokers report greater desire to smoke and show greater responding to earn cigarettes in computer based choice tasks (Audrain-McGovern et al. 2014; Leventhal et al. 2014; Spring et al. 2003). We would therefore expect to observe a significant increase in smoking motivation under conditions of negative affect in our sample.

The final aim was to determine whether the extent of this negative affect driven smoking motivation was increased by self-reported depression and smoking to cope with negative affect. This would be consistent with Hogarth and Hardy (2018b); Hogarth et al. (2018a); Hogarth et al. (2017), which found that depression symptoms increased sensitivity to the effect of negative mood on both alcohol- and tobacco-seeking. Observation of this mechanism across drug types would bolster our claim that it contributes to dependence formation and maintenance. It would also allow

identification of individuals who may be at high risk for negative affect driven smoking relapse.

Participants were 33 smokers who had been recently hospitalised, recruited from the Royal Devon and Exeter smoking cessation service. Participants first completed a battery of questionnaires to record their level of depression, nicotine dependence, and reasons for smoking. A pictorial concurrent choice procedure, in which participants chose on each trial between smoking images and alternate, pleasant images of faces, was used as a behavioural measure of smoking motivation. Participants then experienced an intermixed mood induction procedure, with both negative and positive Velten mood statements (Hogarth and Hardy 2018b), and made an image choice following each statement This method is preferable to the block design used in Hardy and Hogarth (2017) as it eliminates time as a confounding variable. We would expect negative statements to significantly increase smoking pictorial choice, as in Hardy and Hogarth (2017), and for the magnitude of this mood induction effect to vary as a function of depression symptoms and smoking to cope with negative affect, replicating Hogarth and Hardy (2018b); Hogarth et al. (2018a); Hogarth et al. (2017).

9.3 Method

9.3.1 Participants

Participants were 33 treatment-enrolled smokers, recruited from the Royal Devon and Exeter (RD&E) hospital smoking cessation service. Participants had been admitted to hospital for a range of chronic and acute illnesses, including myocardial infarction, chronic obstructive pulmonary disease, and stroke. While in hospital they all received a short smoking cessation intervention, delivered by a stop smoking advisor. Testing took place either on the RD&E site in the Clinical Research Facility (CRF) or at the participant's home. Participants were recompensed with £15. This study was granted NHS Research Ethics Committee (REC) and Health Research Authority (HRA) approval.

Although this sample was reduced from 64 on the basis of recruitment rate, the final sample size remains powerful at >99% to detect a mood induction effect (η_p^2=0.28).

These calculations were made on the basis of previous evidence with hazardous drinkers (Hardy and Hogarth 2017).

9.3.2 Questionnaires

Participants reported age and gender (male = 1, female = 2). Questionnaires were as follows: (1) The Fagestrom Nicotine Tolerance Questionnaire (NTQ) to measure nicotine dependence (Fagerström 1978). The NTQ is composed of six items, and total mean scores have category labels of low dependence (1-2), low to moderate dependence (3-4), moderate dependence (5-7), and high dependence (8+). (2) The Questionnaire of Smoking Urges (QSU) to measure craving (Tiffany and Drobes 1991). The QSU comprises two factors: one measuring desire and intention to smoke, and the second measuring anticipated relief from negative affect when smoking. For the purposes of this study, we used a total QSU measure comprising an average of these two factors. (3) The Beck Depression Inventory (BDI-II), with the suicide item 9 removed, to measure current symptoms of depression (Beck et al. 1996b). This scale comprises 20 items, and total sum scores have category labels of minimal depression (0-13), mild depression (14-19), moderate depression (20-28), and severe depression (29-63). (4) The Reasons for Drinking Questionnaire (RFDQ), adapted for smoking (Westerberg et al. 1996). The RFDQ has three subscales reflecting smoking to cope with negative affect, social pressure, and cued craving. We adapted the RFDQ because the drinking to cope subscale in the original version correlated with percent alcohol picture choice in two earlier studies (Hardy and Hogarth 2017; Hogarth et al. 2018a), and adaptation required only replacement of the words 'drink, 'drinking' and 'alcohol' with 'smoke', 'smoking' and 'cigarettes' respectively. Participants also completed information on smoking history including self-reported current abstinence status ("Are you currently smoking or have you quit?": abstinent=0, smoking=1), number of previous quit attempts, number of cigarettes smoked per day prior to any current quit attempt, years smoked, and age initiated.

9.3.3 Baseline smoking choice

On-screen instructions stated: 'In this task, you can view different faces by choosing the LEFT or RIGHT thumbnail to enlarge. Press the space bar to begin'. On each trial, participants were presented with two greyscale thumbnail images, both of which

showed a close up of person's face (sometimes including shoulders). In each trial, the person in one thumbnail was smoking, while the alternate person in the other thumbnail was not smoking, randomly in the left or right location. Pictures of people smoking were used because they have been shown to be more rewarding than other types of smoking pictures (Mucha et al. 2008). However, because faces are themselves rewarding (Aharon et al. 2001), the alternative pictures also contained faces to control this factor. Thus, participants made choices between two rewarding face pictures, in one of which the person was smoking. Participants pressed the left or right arrow key to select one thumbnail, which enlarged in position for 2 seconds, and caused the other thumbnail to vanish, before a random inter-trial interval of between 1 and 2 seconds prior to the next trial. There were a total of 16 baseline choice trials. Each trial sampled the smoking image from a set of 12 and the non-smoking image from a set of 12, randomly with replacement. Each image set was half male and half female. Different people featured in the smoking and non-smoking image sets. Percent choice of the smoking versus non-smoking image was the dependent variable.

9.3.4 Test phase

In the practice phase, participants were instructed 'Please read the following emotion statements to yourself and try to imagine yourself moving into that state as you read them.' They were presented with four Velten mood statements, in a random order, two of which were positive and two negative (for example, 'Nobody understands me or even tries to', and 'This might turn out to have been one of my good days') each for seven seconds, with a random inter-trial interval of between 1 and 2 seconds prior to the next statement.

Participants then experienced a test block of 32 trials, in which a Velten mood statement randomly selected from 32 (see Table 9.1) was presented for seven seconds, after which participants were presented with a choice between smoking and face images as at baseline. Half of statements were positively valenced (test positive trials - e.g. 'I'm pleased that most people are so friendly'), and half negatively valenced (test negative trials - e.g. 'I'm tired of trying').

9.3.5 Mood repair procedure

Participants were instructed: 'You will now be shown a series of statements that represent a particular type of mood. Read each of the statements to yourself and focus your attention on it. Your success at coming to experience this mood will largely depend on your willingness to accept and respond to the idea in each statement and to allow each statement to act upon you. Attempt to respond to the feeling suggested by each statement. Then try to think of yourself as moving into that state'. Participants were then presented with eight positive Velten mood statements (e.g. 'I feel cheerful and lively'), each for three seconds, prior to a random intertrial interval of between 1 and 2 seconds.

9.3.6 Subjective mood measures

Subjective mood was measured by the on-screen question 'How happy or sad do you feel?' and a 9 point Likert scale with 1 = happy, 9 = sad, and 5 = neutral mood. This measure was obtained after the baseline, test, and mood repair phases.

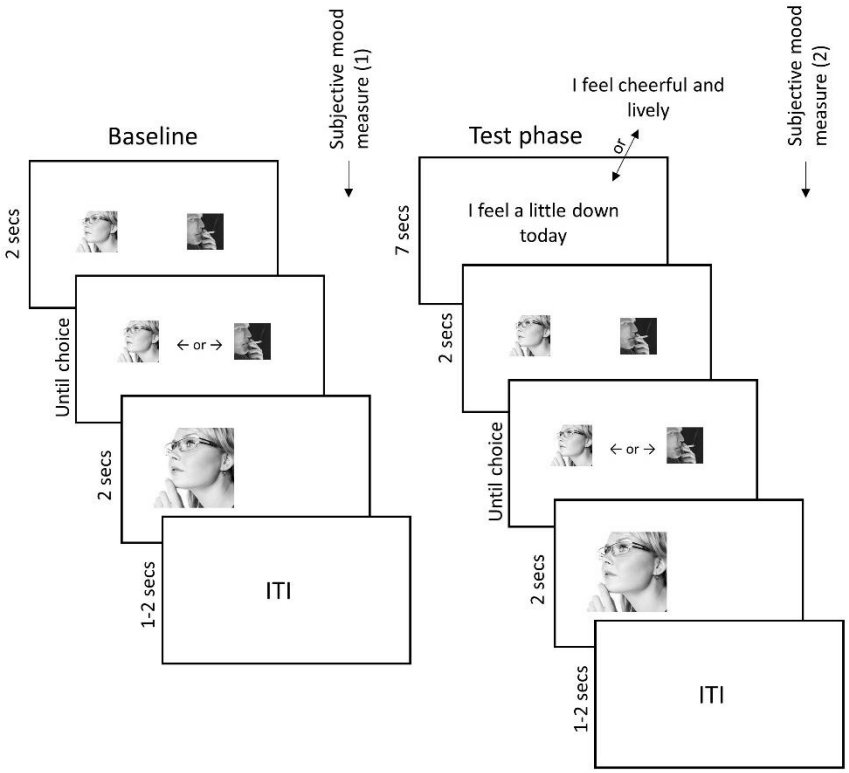

Figure 9.1 – Procedure used to test the impact of an intermixed mood induction procedure on smoking image choice. At baseline, smoking choice was measured by preference to select for enlargement smoking versus non-smoking related thumbnail images in two-alternative forced choice trials. In the test phase, smoking choice was measured following presentation of negative and positive mood statements. The mood repair phase is not shown. Subjective mood was reported on a nine point scale with 1 = happy, 9 = sad, and 5 = neutral mood between each stage of the procedure. The key question was whether the negative mood statements in the test phase would increase percent smoking choice relative to baseline and the positive mood statements at test, validating this model of negative affect driven smoking in recently hospitalised smokers.

Positive mood statements	Negative mood statements
Practice statements	
This might turn out to have been one of my good days	Nobody understands me or even tries to
I've certainly got energy and self-confidence to spare	I'm completely alone
Test statements	
I feel cheerful and lively	I feel a little down today
On the whole, I have very little difficulty in thinking clearly	My work is harder than I expected
I'm pleased that most people are so friendly to me	Sometimes I feel so guilty that I can't sleep
I can make friends extremely easily	I wish I could be myself, but nobody likes me when I am
I feel enthusiastic and confident now	Today is one of those days when everything I do is wrong
There should be a lot of good times coming along	I doubt that I'll ever make a contribution in the world
I'm able to do things accurately and efficiently	I feel like my life is in a rut that I'm never going to get out
I know that I can achieve the goals I set	My mistakes haunt me, I've made too many
I have a sense of power and vigour	Life is such a heavy burden
I'm feeling amazingly good today	I'm tired of trying
I feel highly perceptive and refreshed	Even when I give my best effort, it just doesn't seem to be good enough
I can concentrate hard on anything I do	I don't think things are ever going to get better
My thinking is clear and rapid	I feel worthless
Life is so much fun; it seems to offer so many sources of fulfilment	What's the point of trying
Life is firmly in my control	I feel cheated by life
I'm really feeling sharp now	Every time I turn around, something else has gone wrong
Mood repair statements	
I feel cheerful and lively	
On the whole, I have very little difficulty in thinking clearly	
I'm pleased that most people are so friendly to me	
I can make friends extremely easily	
I feel enthusiastic and confident now	
There should be a lot of good times coming along	
I'm able to do things accurately and efficiently	
I know that I can achieve the goals I set	

Table 9.1 – Positive and negative Velten mood statements used in the test and mood repair phases of the experiment.

9.4 Results

9.4.1 Participants

The proportion of participants in the four NTQ categories were low dependence (0%), low to moderate (18.2%), moderate (63.6%) and high dependence (18.2%). The proportion of participants in the BDI categories were minimal depression (45.5%), mild depression (21.2%), moderate depression (18.2%), and severe depression (15.2%).

9.4.2 Correlation between baseline smoking choice and key questionnaire variables

These findings are addressed in Chapter 5.

9.4.3 Subjective mood

A within-subjects ANOVA with subjective mood data shown in Figure 9.2B found no significant difference in mood rating between baseline, post-test and post mood repair measurements ($F(2,62) = 1.07$, $p=.348$, $\eta_p^2=.03$). Pairwise comparisons indicated no significant difference between baseline and post-test ($F(1,32)=2.15$, $p=.152$, $\eta_p^2=.06$), baseline and post repair ($F(1,32)=0.44$, $p=.514$, $\eta_p^2=.01$), or post-test and post-repair measures ($F(1,31)=0.63$, $p=.432$, $\eta_p^2=.02$). Therefore, there was no evidence of a shift in subjective mood between baseline, test, and mood repair phases. Since the test phase was intermixed negative and positive mood statements, there was no expectation that mood should significantly deteriorate following this phase.

9.4.4 Smoking choice

A within-subjects ANOVA with the smoking choice scores shown in Figure 9.2A showed no significant difference in percent smoking image choice between the three trial types (baseline, test negative and test positive) ($F(2,64) = 1.45$, $p=.242$, $\eta_p^2= .04$). Pairwise comparisons indicated no significant difference between baseline and positive ($F(1,32)= 0.45$, $p=.505$, $\eta_p^2=.01$), baseline and negative ($F(1,32)=0.91$, $p=.346$, $\eta_p^2=.03$) or negative and positive conditions ($F(1,32)= 3.02$, $p=.092$, $\eta_p^2=.09$). Therefore, there is no evidence that negative mood statement trials were associated with a significant increase in percent smoking choice compared to baseline or positive trials, and no evidence for the efficacy of the induction procedure in altering smoking motivation. Spearman's rank order correlations were used to test the relationship between change

in percent choice of smoking images between positive and negative test trials and risk factors assessed by baseline questionnaires. No significant correlation was found between the change in smoking choice between positive and negative test trials and dependence (NTQ: $r(33)= -.03$, $p=.880$), depression (BDI: $r(33)= -.14$, $p=.428$) or smoking to cope with negative affect (RFDQ negative affect: $r(33)= -.14$, $p=.440$).

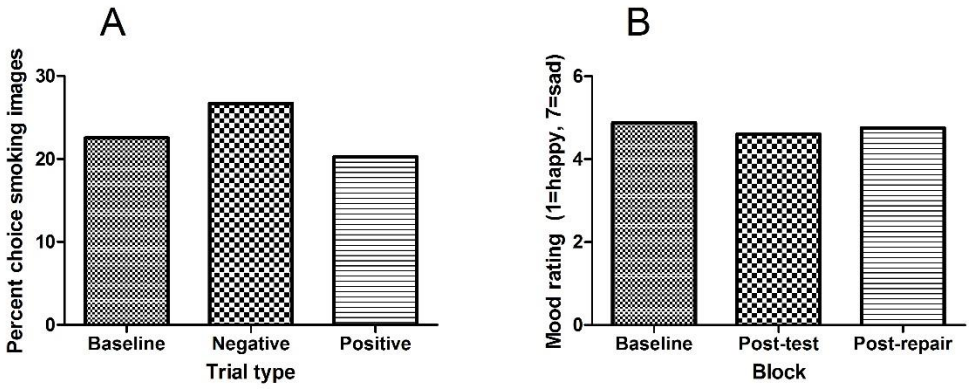

Figure 9.2 – A: Percent choice of smoking images, divided by trial type (baseline, test negative, test positive). B: Self-reported mood rating, divided by measurement time point (baseline, post-test, and post-repair).

9.5 Discussion

The first aim of the present study was to validate a pictorial concurrent choice measure of smoking motivation in a population of recently hospitalised smokers. The second aim was to determine whether an intermixed mood induction procedure could modulate smoking motivation, as measured via this concurrent choice procedure, and whether the magnitude of this mood induction effect varied as a function of symptoms of depression and smoking to cope with negative affect. The first aim of the present study is addressed in Chapter 5.

In relation to the second aim, we found no evidence that the intermixed mood induction procedure was effective in modulating smoking motivation: negative statement trials were not associated with a significantly higher smoking choice compared to positive statement trials or baseline, although the contrast between positive and negative statement trials approached significance. It is therefore important to be mindful of the possibility of a type II error in this analysis. This null finding is surprising since we predicted that the present sample of recently hospitalised smokers

should be at particularly high risk of negative affect driven smoking motivation (Ditre and Brandon 2008; Hogarth et al. 2017), and therefore we expected a large divergence in smoking image choice between positive and negative trials[1].

This failure to find a mood induction effect on smoking choice is even more surprising given that our previous study (Hogarth and Hardy 2018b) found that an identical intermixed procedure modulated alcohol choice in student drinkers who reported high negative coping motives. One reason why we may have failed to find a mood induction effect in the present sample is that the intermixed task may have proved overly demanding and/or required a higher level of engagement in the task than a block design: unlike block designs, the intermixed design requires concentration on each statement individually in order to be effective. The present population may have failed to engage with the procedure as a result of executive dysfunction or inattention, either secondary to depression (more than half of participants presented with mild or more severe symptoms of depression on the BDI-II) (Wang et al. 2006) or as a result of concurrent pain or other troubling physical symptoms (Eccleston and Crombez 1999; Kewman et al. 1991). These factors also more generally limit engagement with psychological therapies and/or smoking cessation services in this population (Halford and Brown 2018).

However, it is also likely that, by incorporating both negative and positive self-statements, an intermixed procedure will necessarily produce a smaller increase in negative affect and associated drug choice than a block design (i.e. a smaller effect size). This may be because intermixed positive stimuli work to undo the negative affect induced by negative stimuli (Fredrickson and Levenson 1998; Fredrickson et al. 2000; Smith et al. 2006). In line with this, we found in a previous study that, following negative mood induction, positive mood statements returned alcohol choice to baseline

[1] It is important to note that a different analytical approach to that used in the present study (for example, a planned one-tailed contrast between positive and negative test trials) may have revealed a significant effect of our intermixed procedure. Such an effect would be consistent with Hogarth and Hardy (2018b), and other experiments which have shown that negative mood induction increases craving to smoke (Brandon et al. 1996; Perkins et al. 2013; Vinci et al. 2012), smoking behaviour (Conklin and Perkins 2005; Payne et al. 1991) and willingness to work for cigarettes (Willner and Jones 1996).

in a sample of hazardous drinkers (Hardy and Hogarth 2017). This hypothesised smaller effect size means that we cannot be sure that our failure to detect an effect in the present study was not the result of insufficient power, since our power calculations were based on a block design procedure.

While our intermixed mood induction design appears to have been ineffective in manipulating smoking choice on a trial-by-trial basis, it is theoretically preferable to a block design since it means that any increase in smoking choice is not confounded with time. When baseline smoking choice is fairly low, as might be expected in a population where a proportion of participants are abstinent, any subsequent increase in smoking choice during a block negative mood induction phase may be attributable to regression to the mean and/or fatigue effects, such that participants begin to choose randomly between the two keys (producing 50% smoking choice and an increase from baseline). Fatigue effects were of particular concern in the present sample compared to a healthy population. We might therefore conclude that, while an intermixed mood induction design is preferable in excluding time as a confounding variable, it may not be suitable for smaller samples (due to its likely smaller effect size) and/or clinical populations in which poor engagement and concentration may limit its efficacy.

In terms of the final aim of the study, we found no evidence that individuals with depression or who smoked to cope with negative affect were more sensitive to the motivational effect of negative mood on tobacco choice (i.e. there was no significant correlation between change in smoking choice between negative and positive test trials, and symptoms of depression on the Beck Depression Inventory or drinking to cope on the Reasons for Drinking negative affect subscale). This is in contrast to Hogarth et al. (2017), which found that depressed smokers showed a significantly greater increase in smoking motivation in response to negative mood induction compared to non-depressed smokers, and Hogarth et al. (2018a) which found that negative affect driven alcohol motivation was greater in students who reported more depression symptoms and who drank to cope with negative affect. This failure to replicate may be attributable to our failure to find a significant mood induction effect, but also may be a function of reduced power (the present sample was reduced from 64 to 33 on the basis of difficulty of recruitment).

Overall, this experiment fulfilled its first aim in terms of demonstrating that a smoking pictorial concurrent choice task is able to index nicotine dependence and associated risk factors for dependence in a high-risk sample of recently hospitalised smokers. We were unable to demonstrate that this task was sensitive to modulation of the value of smoking by means of an intermixed mood induction procedure. This raises questions as to the suitability of such a procedure for clinical populations. Finally, we also failed to find a significant interactive effect of symptoms of depression or drinking to cope on negative affect driven smoking, although this was likely due to our failure to find a significant mood induction effect. Although ideally we would address these methodological concerns by re-testing this paradigm with a block design mood induction, time constraints meant that this was not possible.

Chapter 10. A natural walk intervention in hazardous drinkers shows no evidence of limiting negative affect driven alcohol choice in two experiments

10.1 Abstract

This study tested in two experiments whether a brief nature-based walking intervention would protect from negative affect driven alcohol motivation in a sample of hazardous drinkers (Experiment 1, N=48; Experiment 2, N=44). In both experiments, participants completed self-report measures of alcohol dependence, depression, reasons for drinking, distress tolerance, and subjective mood. Alcohol motivation was assessed at baseline using a pictorial choice procedure. In Experiment 1, the intervention comprised a structured 1 mile walk around the University of Exeter gardens. In Experiment 2, the intervention comprised a session of moderate pace walking on a treadmill, with concurrent exposure to a 4k video of natural surroundings and a Seasonal Affective Disorder (SAD) light. Control participants spent an equivalent period of time sitting quietly in the experimental room. In both experiments, participants experienced a Velten mood induction procedure (in Experiment 1 this was an intermixed procedure with positive and negative affective statements, and in Experiment 2 this was a block design with only negative affective statements), and alcohol choice was re-measured. In Experiment 1 we failed to find a significant increase in alcohol choice in negative compared to positive trials (p=.417, η_p^2=.01). In Experiment 2, there was no evidence that an increase in alcohol choice in response to the negative affective statements was significantly reduced by the intervention (interaction: p=.381, η_p^2=.02). Overall, these two experiments provide no evidence that a brief nature-based walking intervention can protect from negative affect driven alcohol motivation.

10.2 Introduction

In the previous chapters, it has been demonstrated that induced negative affect augments motivation to drink, and that the magnitude of this effect is greater in individuals with symptoms of depression and who drink to cope with negative affect. This subgroup may be particularly vulnerable to negative affect driven relapse. The aim of the following three chapters is to test three novel interventions in their ability to limit the effect of negative mood on alcohol motivation. Initial proof of concept in a general hazardous or dependent drinking population would provide preliminary evidence to justify future trials of the intervention in groups at high risk of negative affect driven relapse.

The aim of the first two experiments was to test a structured natural walk intervention. This intervention fits our criteria in terms of being brief and inexpensive to implement. It is also evidence-based: our intervention incorporates three components which have been shown to be associated with protection from negative mood induction in terms of resultant negative affect with short term exposure: exercise, light, and natural surroundings. Previous evidence has not tested whether these acute effects on mood translate into reduced alcohol motivation. The purpose of the present two studies was to test this.

In terms of exercise, there is evidence that acute interventions protect from stress induction, both in terms of self-reported negative affect (Bernstein and McNally 2017a; b; Edwards et al. 2017; Mata et al. 2013, although see Edwards et al. 2018 for a null finding), and physiological measures of stress such as blood pressure (Rejeski et al. 1992). Acute exercise has also been shown to protect against pharmacologically-induced negative affect (Head et al. 1996). These protective effects have been observed particularly in individuals who lack adaptive emotion regulation strategies: Bernstein and McNally (2017a) found that a session of 25 minutes of cycling diminished negative affect following a stressor in high ruminating individuals, while Bernstein and McNally (2017b) found that 30 minutes of jogging hastened recovery from negative mood induction in individuals who struggled to generate regulatory strategies prior to mood induction. These findings suggest that acute exercise may protect against

induced negative affect, particularly amongst individuals who otherwise struggle to regulate emotion adaptively.

The effects of light exposure have largely been tested in laboratory studies using 10,000 lux full spectrum (white light) boxes. Clinically depressed samples have shown improvements in mood after light exposure of 20 minutes (Virk et al. 2009) and one hour (Reeves et al. 2012). Studies have also shown acute improvements in mood in mildly seasonal (aan het Rot et al. 2008b) and non-depressed (Goel and Etwaroo 2006) groups of participants after acute light exposure. Only one study has investigated light therapy as a protective agent against negative mood induction (aan het Rot et al. 2008a). In this, participants undertook acute phenylalanine/tyrosine depletion (APTD) to worsen mood. Exposure to bright light compared to dim light protected against the effects of APTD on mood, but was insufficiently powerful to protect against a subsequent autobiographical negative mood induction. Therefore acute light exposure reliably raises mood and shows some promise in protecting from negative mood induction, although this intervention may only be effective in conjunction with other protective components.

Finally, participants show faster recovery from an acute stressor in terms of physiological measures of stress when they view nature concurrently through a window (Kahn et al. 2008) or on a screen (Gladwell et al. 2012; Laumann et al. 2003; Parsons et al. 1998; Ulrich et al. 1991). Notably, a study by Jiang et al. (2016) found a positive linear relationship between the density of trees in videoed street scenes observed by participants (2-62%) and recovery from a social stressor. Exposure to auditory nature stimuli has also been shown to quicken recovery from both negative affect (Benfield et al. 2014) and parasympathetic activation, as measured via skin conductance (Alvarsson et al. 2010). Acute exposure to nature therefore appears to enhance recovery from stress-driven physiological changes, although evidence for a direct effect on recovery from negative mood induction is sparser.

There are a number of mechanisms by which an intervention combining exercise, light and nature might limit negative affect and associated alcohol choice. Exercise might limit rumination (Brand et al. 2018), distract from negative affect (Van Dillen and Koole 2007), and/or improve executive functioning (Chang et al. 2012; Kubesch et al. 2003).

Bright light may stimulate serotonin synthesis (aan het Rot et al. 2008a; Lambert et al. 2002). Exposure to nature may reduce rumination (Bratman et al. 2015) and limit stimulation of the sympathetic nervous system (Li et al. 2011). Any observed beneficial effect of our intervention could be driven by any single mechanism, or a combination thereof.

We undertook two experiments to test whether sensitivity to negative mood driven alcohol motivation in heavy drinkers recruited from the community could be reduced by exposure to these three factors - nature, light, and exercise. In Experiment 1, the intervention was a brief structured walk in natural surroundings. In Experiment 2, the intervention was lab-based, with participants walking on a treadmill, with additional exposure to bright light and natural surroundings via video. Participants in these experiments were individuals who reported regularly drinking more alcohol than is recommended by UK guidelines (14 units) (Experiment 1, N=48; Experiment 2, N=44). In both experiments, participants completed self-report measures of alcohol dependence, depression, reasons for drinking, distress tolerance, and subjective mood. Alcohol motivation was assessed at baseline in all participants by a pictorial choice procedure, identical to Hardy and Hogarth (2017). In each trial, participants chose one of two thumbnail images to view enlarged, where one image was alcohol related, and the other image food related. Participants then experienced either the intervention or spent the equivalent time relaxing in the experimental room. In Experiment 1, the intervention comprised a structured 1 mile walk around the university gardens. In Experiment 2, the intervention comprised a session of moderate pace walking on a treadmill, with exposure to a 4k video of natural surroundings and a medical grade Seasonal Affective Disorder (SAD) light. In both experiments, participants then experienced a Velten mood induction procedure (in Experiment 1 this was an intermixed procedure with positive and negative affective statements, and in Experiment 2 this was a block design with only negative affective statements), and subsequent alcohol choice was re-measured.

We predicted, firstly, that negative mood statements (whether in the intermixed or block mood induction procedure) should augment pictorial alcohol choice in the control group, consistent with Hardy and Hogarth (2017). However, we expected that

this effect of negative mood induction on alcohol choice would be reduced or abolished in the intervention group. This would indicate the potential efficacy of a natural brief walk intervention on negative affect driven alcohol motivation in heavy drinkers. A secondary prediction was that we should find a significant association between pictorial alcohol choice at baseline and alcohol dependence, and other related risk factors including depression and drinking to cope. This would be consistent with our findings in Chapter 5 and Hardy and Hogarth (2017).

Experiment 1

10.3 Methods

10.3.1 Participants

Participants were 48 drinkers (30 male) from the community who responded to online adverts. All participants answered yes when asked if they regularly consumed more alcohol per week than recommended by UK guidelines (14 units). All participants were screened to ensure that they were able to complete a short walk including steps. Participants were recompensed with £15. Ethical approval was obtained from the University of Exeter Psychology Ethics Committee.

This sample size is >99% powerful to detect a mood induction effect (η_p^2=0.28). While the effect size of any potential protective effect of the walking procedure is uncertain, small effect sizes are unlikely to be clinically meaningful, and therefore failing to detect such an effect is not of major concern. Our sample is >90% powerful to detect a therapeutic effect of medium effect size (Cohen's *f*= 0.25) in a repeated measures, within-between interaction.

10.3.2 Procedure

10.3.2.1 Baseline measures

Questionnaires were as follows: 1) the Alcohol Use Disorders Inventory Test (AUDIT: Babor et al. 2001) to index alcohol use and associated problems. 2) the Beck Depression Inventory (BDI-II: Beck et al. 1996b) to measure depression. 3) the Reasons for Drinking

Questionnaire (RFDQ: Westerberg et al. 1996) to measure coping motives. 4) the Distress Tolerance Scale (DTS: Simons and Gaher 2005) to measure tolerance for distress. 5) the Positive and Negative Affect Schedule (PANAS: Watson et al. 1988) to measure affect.

10.3.2.2 Baseline alcohol choice

On-screen instructions stated: 'In this task you can choose to view images of alcohol and food using the left and right arrow keys. Press the space bar to begin'. An alcohol pictorial choice task, identical to that in Hardy and Hogarth (2017) was used to measure alcohol motivation. A block of 16 choice trials established participants' baseline preference for alcohol images.

10.3.2.3 Intervention

Participants were assigned to experimental or control groups alternately in a yoked procedure. During the intervention phase, all participants were asked to wear a Fitbit fitness tracker. The purpose of this was to verify completion of the walk in the experimental group, and to evaluate covariation between exercise intensity (indexed by heart rate) and protection against negative mood induced alcohol choice.

Participants in the experimental group undertook a 1 mile walk, with an elevation of 120 feet, on footpaths around the gardens of the University of Exeter. The walking group were given a booklet with the route (see Figure 10.1), and instructed: 'Now we are going to ask you to walk a route around the campus for approximately 20 minutes. Please follow the directions in the booklet provided. We ask you to wear the Fitbit throughout this period so we can measure your heart rate.' The fitness tracker was switched on outside the building, and participants were left to complete the route. The fitness tracker was switched off on their return.

The control group sat quietly in the experimental room for the period of time taken by the previous participant to complete the walk. The control group were instructed: 'Now we are going to leave you to relax in this room for approximately [yoked time of previous walking participant] minutes. Please just try and sit quietly. We ask you to wear the Fitbit throughout this period so we can measure your heart rate'. The fitness tracker was started, and participants were left in the experimental room for the stated

period of time. The fitness tracker was turned off following completion of this time period.

Figure 10.1 – Images of the walking procedure.

10.3.2.4 Post-intervention measures

To measure any change in affect following the intervention phase, all participants then completed the Positive and Negative Affect Scale (PANAS). Participants in the experimental group completed the Perceived Restorativeness Scale (Hartig et al. 1997) to measure their experience of the walk as restorative, and rated the intensity of the walk on a ten-point Likert scale.

10.3.2.5 Post-intervention concurrent alcohol choice

A second pictorial choice measure identical to baseline (16 trials) was taken to assess any change in alcohol motivation associated with the intervention phase.

10.3.2.6 Test alcohol choice

In the practise phase of this block, participants were presented with the instructions "Please read the following emotion statements to yourself and try to imagine yourself moving into that state as you read them". In each trial, participants were presented with one statement randomly selected from a list of four (two positive, two negative –

identical to the practice statements presented in Table 9.1). Each statement was presented for 7 seconds. Participants experienced four trials of this type.

Participants then completed a modified form of the concurrent choice task, in which an affective statement was presented for 7 seconds, before a choice between an alcohol and food picture whilst the affective statement remained on the screen. Participants experienced 32 trials randomly selecting between 16 sad and 16 happy statements (identical to the test statements in Table 9.1).

10.3.2.7 Mood repair procedure

Participants completed a positive mood induction procedure to ensure mood was positive prior to leaving the experiment. They were presented with 8 randomly-selected positive statements, each for 3 seconds (identical to those in Table 9.1).

10.3.2.8 Subjective mood measure

Subjective mood was measured with the onscreen question: 'How happy or sad do you feel?' with a scale from 1 (happy) to 9 (sad) with 5 representing neutral mood. This measure was obtained at 4 time points: after baseline alcohol choice, intervention, post-intervention alcohol choice, and test blocks (as shown in Figure 10.2).

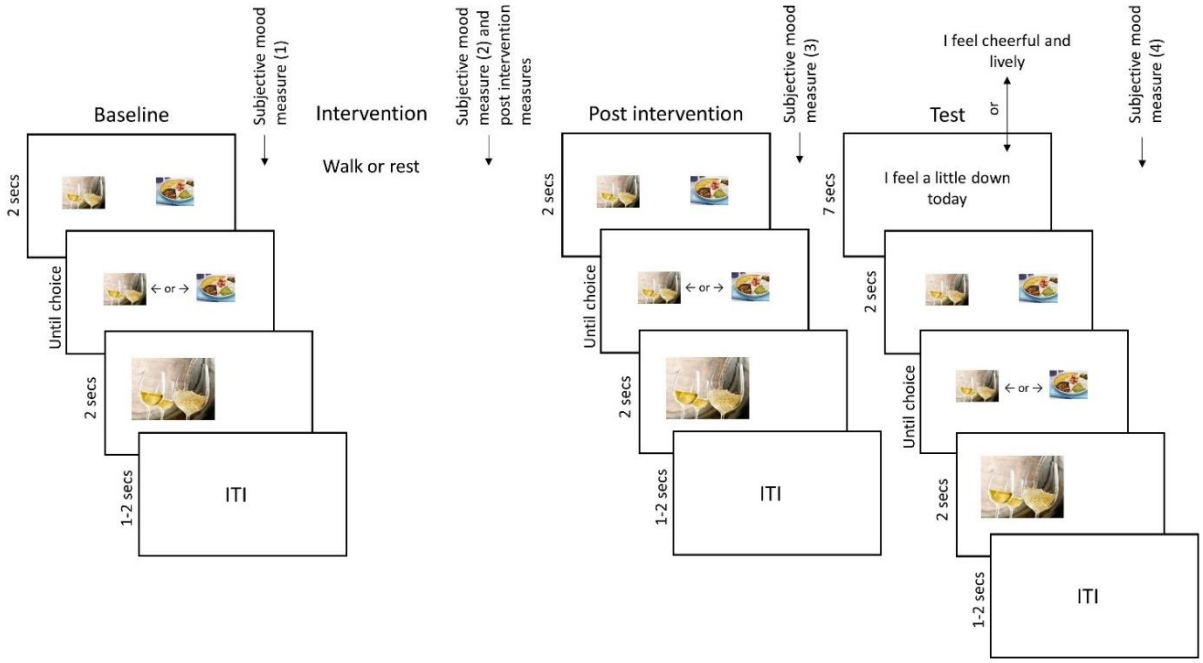

Figure 10.2 – Procedure used to test the impact of a natural walk procedure on alcohol image choice under conditions of negative mood. At baseline, alcohol choice was measured by preference to select for enlargement alcohol versus food thumbnail images in two-alternative forced choice trials. In the intervention phase, experimental participants completed a one mile walk in natural surroundings, while control participants sat quietly in the experimental room for an equivalent period of time. A second measure of alcohol choice was taken post-intervention. At test, participants received an intermixed mood induction procedure where a negative or positive affective statement was presented prior to each alcohol choice. The mood repair phase is not shown. The key question was whether the negative statements would increase percent alcohol choice relative to positive statements, and whether this was mitigated by the walk procedure.

10.4 Results

10.4.1 Participants

Participant characteristics, divided by group, are shown in Table 10.1. There was no significant difference between groups in any of the baseline measures taken. The proportion of participants in the four AUDIT categories were: mild (6%), hazardous (33%), harmful (19%) and possible alcohol dependence (42%). The proportion of participants in the BDI categories were: minimal depression (58.3%), mild depression (16.7%), moderate depression (25%), and severe depression (0%).

	Group		
	1 (experimental) M (SD, range)	**2 (control) M (SD, range)**	***p***
Age	32.83 (14.13, 19-63)	30.67 (12.42, 18-53)	.575
AUDIT	18.25 (7.77, 4-36)	17.83 (6.67, 5-31)	.843
BDI	11.54 (8.04, 0-28)	12.42 (8.88, 0-27)	.722
RFDQ negative affect	3.52 (2.37, 0-8)	2.96 (2.48, 0-8.14)	.424
RFDQ social pressure	5.94 (2.29, 1-9.33)	6.53 (2.06, 2.33-9.67)	.359
RFDQ cued craving	3.73 (2.14, 0-8.80)	3.26 (1.75, 0.80-7.40)	.412
DTS	39.38 (13.34, 21-73)	36.33 (14.28, 15-66)	.450
Baseline percent alcohol choice	45.31 (24.74, 6.25-87.50)	40.10 (19.67, 0-75)	.424

Table 10.1 - Key demographic variables and questionnaire measures divided by group, and associated p values for between-subjects ANOVAs comparing groups.

10.4.2 Intervention

During the intervention, data extracted from the fitness tracker showed that participants in the experimental group walked a mean distance of 0.99 miles (*SD*=0.06, range 0.92-1.13), completed a mean of 2235 steps (*SD*=303.50, range 1862-3024), burned 115 calories (*SD*=21.96, range 89-168), and had a mean heart rate of 103 bpm (*SD*=14.30, range 85-143). In contrast, the resting control group burned 28.79 calories (*SD*=12.95, range 17-61), and had a mean heart rate of 70 bpm (*SD*=14.02, range 56-111).

10.4.3 PANAS mood rating – positive affect

A mixed measures ANOVA with the positive affect PANAS scores shown in Figure 10.3D found no significant main effect of block (baseline to post-intervention) on positive affect ($F(1,46)= 3.07$, $p=.086$, $\eta_p^2=.06$), or main effect of group ($F(1,46)= 0.34$, $p=.565$, $\eta_p^2=.01$). There was, however, a significant interaction between group (experimental or control) and change in positive affect baseline to post-intervention ($F(1,46) = 27.63$, $p<.001$, $\eta_p^2=.38$). Pairwise comparisons indicated a significant increase in positive affect in the experimental group ($F(1,23)= 5.58$, $p=.027$, $\eta_p^2=.20$), and a significant decrease in positive affect in the control group ($F(1,23)= 27.28$, $p<.001$, $\eta_p^2=.54$).

10.4.4 PANAS mood rating – negative affect

A mixed measures ANOVA with the negative affect PANAS scores shown in Figure 10.3E found no significant main effect of block (baseline to post-intervention) on negative affect ($F(1,46)= 3.87$, $p=.055$, $\eta_p^2=.08$). There was also no significant interaction between group and change in negative affect baseline to post-intervention ($F(1,46)= 3.32$, $p=.075$, $\eta_p^2=.07$) (although this approached significance and may therefore represent a type II error), or main effect of group ($F(1,46)= 0.23$, $p=.635$, $\eta_p^2=.01$).

10.4.5 Subjective mood measure – baseline to post-intervention

A mixed measures ANOVA with subjective mood scores ('How happy or sad do you feel?') shown in Figure 10.3F found no significant main effect of block (baseline to post-intervention) on the subjective mood measure ($F(1,46)=0.45$, $p=.506$, $\eta_p^2=.01$). There was also no significant interaction between this measure baseline to post-intervention and group (experimental/control) ($F(1,46) = 0.20$, $p=.657$, $\eta_p^2=.004$), or main effect of group ($F(1,46)= 1.79$, $p=.188$, $\eta_p^2=.04$).

10.4.6 Subjective mood measure – pre-test to post-test

An identical mixed measures ANOVA with subjective mood scores shown in Figure 10.3F found a significant main effect of block (pre-test to post-test) on the subjective mood measure ($F(1, 46)=4.78$, $p=.034$, $\eta_p^2=.09$): participants showed a significant increase in sadness pre to post-test. There was also a significant interaction between this measure pre to post-test and group ($F(1,46) = 9.37$, $p=.004$, $\eta_p^2=.17$), and an unexpected main effect of group ($F(1,46)=4.32$, $p=.043$, $\eta_p^2=.09$), with greater subjective sadness in the control group. Pairwise comparisons indicated no significant change in the subjective mood measure pre to post-test in the experimental group ($F(1,23)= 0.35$, $p=.560$, $\eta_p^2=.02$) but a significant worsening of mood in the control group ($F(1,23)= 15.15$, $p=.001$, $\eta_p^2=.40$). Since the test phase was intermixed positive and negative statements, there was no expectation that mood should significantly deteriorate following this phase.

10.4.7 Alcohol choice

A mixed measures ANOVA with the alcohol choice scores shown in Figure 10.3G found no significant main effect of block (baseline to post-intervention) on alcohol choice ($F(1,46)<0.01$, $p=.951$, $\eta_p^2<.001$), interaction between block and group

($F(1,46)=0.19$, $p=.667$, $\eta_p^2=.004$), or main effect of group ($F(1,46)= 0.90$, $p=.349$. $\eta_p^2=.02$). There was also no significant main effect of trial type (test positive, test negative) on alcohol choice in the test phase ($F(1,46)=0.67$, $p=.417$, $\eta_p^2=.01$), no significant interaction between trial type and group ($F(1,46)=0.10$, $p=.750$, $\eta_p^2=.002$), and no main effect of group ($F(1,46)= 1.15$, $p=.289$, $\eta_p^2=.02$). The negative and positive trial types therefore did not manipulate alcohol choice as predicted.

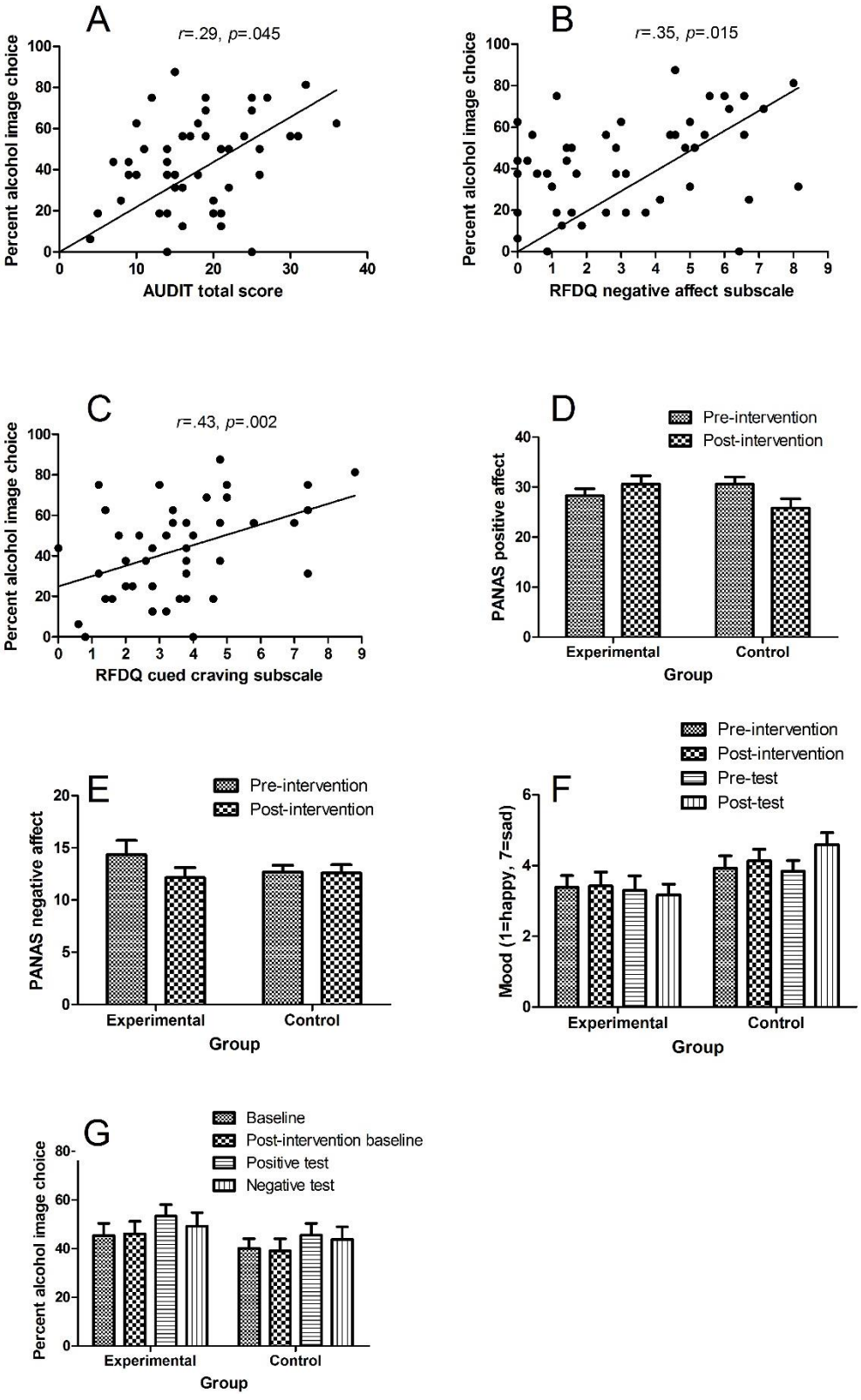

Figure 10.3: A to C – Spearman's rank correlations between percent choice of alcohol images and key questionnaire variables. Associated test statistics are shown above each graph. AUDIT = Alcohol Use Disorders Identification Test; RFDQ = Reasons for Drinking Questionnaire. Figure D - PANAS positive affect mood rating pre and post-intervention, divided by group. Figure E - PANAS negative affect mood rating pre and post-intervention, divided by group. Figure F - Subjective mood rating pre intervention, post-intervention, pre-test and post-test, divided by group. Figure G - Percent alcohol choice during baseline, post-intervention baseline, and test phases (positive and negative), divided by group.

10.4.8 Correlation between baseline alcohol choice and key questionnaire variables

Spearman's rank order correlations were used to test the relationship between percent choice of alcohol versus food images at baseline and risk factors assessed by baseline questionnaires. Table 10.2 shows the correlation matrix. Percent choice of alcohol images at baseline was significantly positively associated with alcohol dependence (AUDIT), drinking to cope with negative affect (RFDQ negative affect), and cued craving (RFDQ cued craving) (see Figure 10.3) but there was no significant association with depression (BDI) or distress tolerance (DTS). When a control of false discovery rate method (FDR) was applied at 5%, only the correlation between percent alcohol choice and RFDQ cued craving survived (Benjamini and Hochberg 1995).

	1	2	3	4	5	6	7	8	Mean	SD	Range
1. Baseline percent alcohol choice									42.71	22.27	0-87.50
2. Age	.04								31.75	13.21	18-63
3. Gender	.12	.02							62.5%		
4. AUDIT total	**.29**	.05	.08						18.04	7.17	4-36
5. BDI	.21	**.34**	.13	**.45**					11.98	8.39	0-28
6. RFDQ negative affect	**.35**	.24	.22	**.60**	**.62**				3.24	2.42	0-8.14
7. RFDQ social pressure	.13	-.12	.03	**.45**	.07	.28			6.24	2.18	1-9.67
8. RFDQ cued craving	**.43**	-.03	.09	**.66**	**.44**	**.60**	**.55**		3.49	1.95	0-8.80
9. DTS	.05	.15	.22	.23	**.54**	**.53**	-.01	**.33**	37.85	13.76	15-73

Table 10.2 – Correlation matrix between baseline percent alcohol versus food picture choice in the task and risk factors measured by questionnaires, with associated means, standard deviations and ranges. For gender, the mean column shows percentage of males. Correlations with gender were rank biserial correlations. P values <.05 are highlighted in bold. AUDIT= Alcohol Use Disorder Identification Test; BDI= Beck Depression Inventory; RFDQ= Reasons for Drinking Questionnaire; DTS= Distress Tolerance Questionnaire.

10.5 Discussion

The purpose of the present study was to determine whether a brief structured walk in natural surroundings could protect from negative mood induction in terms of resultant mood change and alcohol choice. The first finding was that the test phase was associated with a significant worsening of mood in the control group, but there was no such effect in the experimental group. Since the test phase comprised intermixed positive and negative statements, we did not necessarily expect a change in mood in either group. One interpretation of this finding is that the experimental intervention protected against a task-induced boredom/fatigue effect.

The second finding was that we failed to find a significant mood induction effect on percent alcohol choice using an intermixed procedure: there was no significant difference in percent alcohol choice between positive and negative affective statement conditions. This means that we were unable to test the key prediction of this study: that the walk intervention would reduce negative-affect driven alcohol choice. This failure to find a mood induction effect is inconsistent with our previous study, (Hogarth and Hardy 2018b), which showed that an identical intermixed mood induction procedure was effective in modifying alcohol choice in student drinkers with high coping motives. However, this finding is consistent with Chapter 9, in which an intermixed mood induction procedure failed to significantly manipulate smoking motivation in recently-hospitalised smokers. As in that study, we might postulate that the present null finding arose from the increased attentional requirements of an intermixed procedure, or a smaller effect size than the present study was designed to detect. Unfortunately, since these studies ran concurrently we were unable to modify our design in light of the null finding in Chapter 9.

These findings do, however, suggest that a block design mood induction procedure would be more appropriate in the present population since it has previously been shown to be effective (Hardy and Hogarth 2017). It would also be sensible to use a more comprehensive measure of mood (such as the Positive and Negative Affect Scale - Watson et al. 1988), to account for any systematic differences in emotions evoked between the two groups. These limitations were addressed in Experiment 2.

An interesting additional finding was a significant interaction between change in positive affect baseline to post-intervention and group, with the walking experimental group showing a significant increase in positive affect, and the control group a significant decrease. This is consistent with a number of studies which have shown that short periods of exercise (Ekkekakis et al. 2000; Liao et al. 2015; Mata et al. 2013; Reed and Ones 2006), light exposure (aan het Rot et al. 2008b; Goel and Etwaroo 2006; Reeves et al. 2012; Virk et al. 2009), and exposure to nature (Barton and Pretty 2010) increase positive affect. The present finding indicates that approximately 15-20 minutes of low intensity exercise in a natural environment can raise positive affect acutely in hazardous drinkers. Ultimately, however, we found no evidence that our intervention protected from enhanced alcohol motivation under conditions of negative affect.

Finally, we found significant positive correlations between baseline percent choice of alcohol images and alcohol dependence (AUDIT), drinking to cope with negative affect (RFDQ negative affect) and cued craving for alcohol (RFDQ cued craving). This is consistent with a number of previous studies which have shown that choice of drug images over alternative pleasant images significantly predicts current drug use and dependence (e.g. Hardy and Hogarth 2017; Moeller et al. 2013; Moeller et al. 2009), and associated risk factors including depression and drinking to cope (Hardy and Hogarth 2017; Hardy et al. 2018b). However, only RFDQ cued craving survived correction for multiple comparisons (using the false discovery rate method), and so these findings should be treated with caution.

Experiment 2

10.6 Introduction

The purpose of Experiment 2 was to address three key limitations in Experiment 1 – firstly, to use a block design mood induction procedure, secondly, to supplement our single item measure with a more comprehensive measure of mood and, finally, to control the walking intervention more precisely across participants by using an indoor lab procedure. An indoor procedure also means that exposure to the intervention can continue throughout the test phase, maximising any potential therapeutic effect.

In this experiment, participants were randomised into experimental (intervention) and control groups, in contrast to the yoked procedure in Experiment 1. All participants completed an initial baseline measure of alcohol motivation, using an identical pictorial choice task to Experiment 1. Participants in the experimental group completed a ten minute walk on a treadmill, and were exposed to a video of natural surroundings and a 10,000 lux Seasonal Affective Disorder light, while control participants sat quietly for the equivalent time period. The video was displayed on a 4k 65 inch LED television, since studies have shown that larger screen sizes increase the restorative effects of artificially displayed natural scenes (de Kort et al. 2006). The three components of the intervention (walking, light, and video) continued throughout the remainder of the experiment for experimental participants. All participants experienced a test phase during which they were initially primed with a number of negative affective statements such as 'I feel a little down today', and alcohol choice then measured following each subsequent statement. Mood in this study was measured by means of a two item subjective mood measure ('how happy/sad do you currently feel') and the PANAS. It was expected that the negative affective statements would increase alcohol choice over baseline (replicating previous effects), but that this effect should be reduced or abolished by the intervention, indicating a protective effect.

10.7 Methods

10.7.1 Participants

Participants were 44 drinkers (27 male) from the community who responded to online adverts. All participants answered yes when asked if they regularly consumed more alcohol per week than recommended by UK guidelines (14 units). All participants were screened to ensure that they were able to complete a short walk on a treadmill. Participants were recompensed with £15. Ethical approval was obtained from the University of Exeter Psychology Ethics Committee. Participants were randomised into the two groups (experimental/control).

As in Experiment 1, our sample size is 99% powerful to detect a mood induction effect (η_p^2=0.28), and ~90% powerful to detect a medium effect size (Cohen's *f* =0.25) in a repeated measures, within-between interaction.

10.7.2 Procedure

10.7.2.1 Baseline measures

Participants completed a battery of questionnaires to record their level of alcohol dependence (AUDIT), depression (BDI-II), motivation for drinking (RFDQ), distress tolerance (DTS), and positive and negative affect (PANAS) - identical to Experiment 1.

10.7.2.2 Baseline alcohol choice

Participants completed 16 trials of the concurrent choice task (identical to Experiment 1) to establish baseline preference for alcohol images.

10.7.2.3 Walk intervention

Participants were randomly assigned to either the experimental or control group. As in Experiment 1, all participants were asked to wear a Fitbit fitness tracker to measure heart rate. Experimental participants were instructed: 'Now we are going to ask you to walk on a treadmill for 10 minutes. Once 10 minutes has elapsed, you will continue with the experiment on the computer in front of you whilst walking. We ask you to wear the Fitbit throughout this period so we can measure your heart rate'. The fitness tracker was switched on, and participants undertook a 10 minute walk on the treadmill at 1.7mph. During the walk a 4k video of natural surroundings was presented on screen and participants listened on headphones to the associated audio. A medical grade 10,000 lux SAD light was switched on at the start of this phase. Experimental participants continued to be exposed to the nature video and light, and continued to walk on the treadmill, until the end of the concurrent choice test phase. At this point the fitness tracker was also switched off.

The control group were instructed: 'Now we are going to leave you to relax in this room for 10 minutes. Please just try and sit quietly. We ask you to wear the Fitbit throughout this period so we can measure your heart rate'. The fitness tracker was started, and participants were left in the experimental room for 10 minutes before continuing with the procedure. Participants in the control group remained seated

throughout. As in the experimental group, the fitness tracker was switched off at the end of the concurrent choice test phase.

10.7.2.4 Post-intervention alcohol choice

A second concurrent choice measure identical to baseline (16 trials) was taken to assess any change in alcohol motivation.

10.7.2.5 Test phase – concurrent choice

In the test phase, participants were instructed: "Please read the following emotion statements to yourself and try to imagine yourself moving into that state as you read them". In each trial in the practise phase, participants were presented with one negative affective statement randomly selected from a list of 16 (see Table 9.1) for 10 seconds, prior to an ITI of 1-2 seconds. Participants experienced 16 trials of this type.

Participants then completed a modified form of the concurrent choice task, in which a negative affective statement was presented for four seconds, prior to a choice between an alcohol and food image (identical to baseline) whilst the affective statement remained present on the screen. Participants experienced 32 trials randomly selecting from the 16 sad statements. At the end of this phase, the treadmill, light and screen were turned off for the experimental group, and participants were seated. The fitness tracker was switched off in all participants.

10.7.2.6 Post-test measures

To measure any change in affect following the procedure, participants completed the PANAS. Participants in the experimental group rated the intensity of the walk on a 10-point Likert scale.

10.7.2.7 Positive mood repair

All participants completed a positive mood induction procedure: they were presented with 8 randomly selected positive statements, each for 2 seconds prior to an ITI of 1-2 seconds (see Table 9.1).

10.7.2.8 Subjective mood measures

Subjective mood was measured by two onscreen questions in the format 'How [happy/sad] do you feel?' with a scale from 1 (not at all) to 7 (very much). The two questions were presented sequentially and randomly selected from 'happy' and 'sad'. This measure was obtained after baseline alcohol choice, intervention, post-intervention alcohol choice, and test blocks (as shown in Figure 10.4).

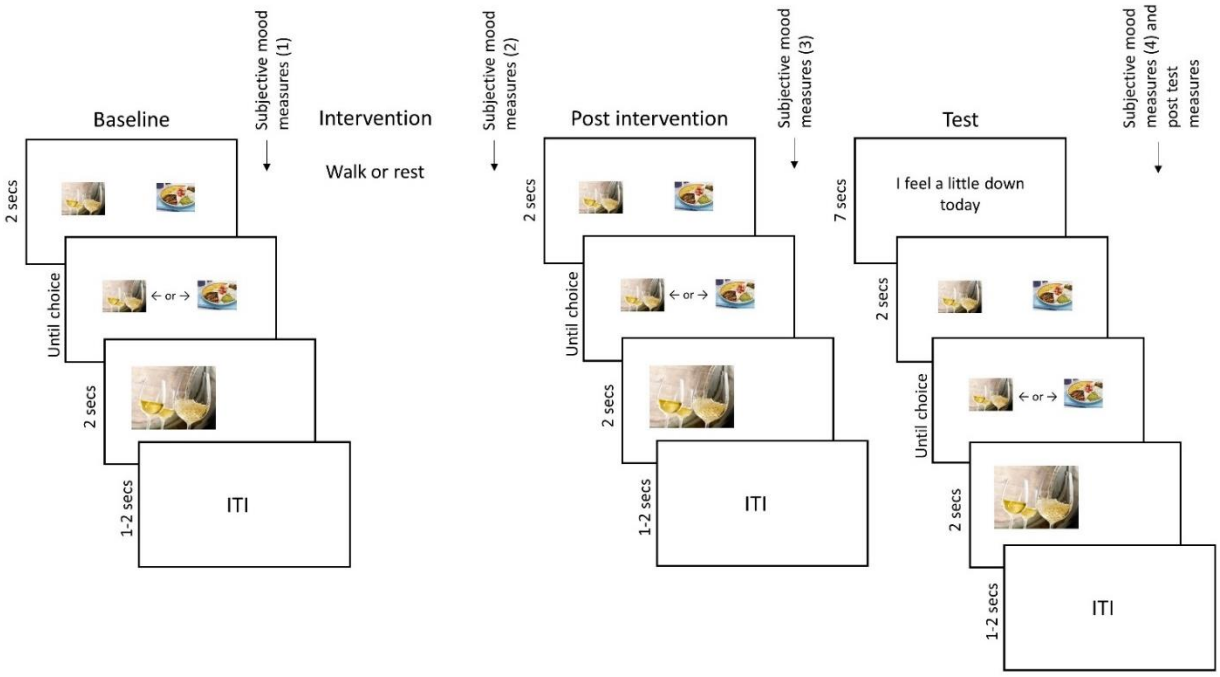

Figure 10.4 - Procedure used to test the impact of an indoor walk procedure on alcohol image choice under conditions of negative mood. At baseline, alcohol choice was measured by preference to select for enlargement alcohol versus food thumbnail images in two-alternative forced choice trials. In the intervention phase, experimental participants completed a 10 minute walk on a treadmill, with a 4k video of natural surroundings and 10,000 lux SAD light, while control participants sat in the experimental room for the equivalent period of time. Exposure to the three elements of the intervention (the walk, video, and light) continued in the experimental group until the end of the test phase. A second measure of alcohol choice was taken post-intervention. At test, participants received a block mood induction procedure where a negative self-statement was presented prior to each alcohol choice. The mood repair phase is not shown. The key question was whether the negative statements would increase percent alcohol choice relative to baseline measures, and whether this effect would be mitigated by the walk procedure.

10.8 Results

10.8.1 Participants

Participant characteristics, divided by group, are shown in table 10.3. There was no significant difference between groups in any of the baseline measures taken. The proportion of participants in the four AUDIT categories were: mild (14%), hazardous

(43%), harmful (18%) and possible alcohol dependence (25%). The proportion of participants in the BDI categories were minimal depression (68.2%), mild depression (11.4%), moderate depression (15.9%), and severe depression (4.5%).

10.8.2 Intervention

From the start of the intervention until the end of the test phase, data extracted from the fitness tracker showed that participants in the experimental group recorded a mean heart rate of 84 bpm (*SD*=14.31, range= 63-109) and burned 73 calories (*SD*=16.14, range= 40-100). In contrast, the control group recorded a mean heart rate of 69 bpm (*SD*=9.75, range= 56-92) and burned 23 calories (*SD*=2.77, range=20-32).

	Group		
	1 (experimental) **M (SD, range)**	**2 (control)** **M (SD, range)**	***p***
Age	40.09 (13.68, 19-58)	38.00 (15.88, 20-61)	.642
AUDIT	16.91 (6.70, 6-29)	13.36 (6.37, 5-30)	.079
BDI	13.32 (8.55, 2-33)	9.64 (8.21, 2-28)	.153
RFDQ negative affect	3.81 (2.30, 0-7.86)	2.51 (2.01, 0.14-7.29)	.054
RFDQ social pressure	5.26 (2.16, 0.67-9.00)	4.97 (2.73, 0-9.33)	.700
RFDQ cued craving	3.67 (1.98, 0-7)	2.97 (1.58, 0.40-6.80)	.202
DTS	42.86 (11.70, 19-68)	39.36 (14.65, 17-62)	.386
Percent choice baseline	44.60 (21.85, 0-81.25)	39.77 (21.61, 0-75)	.465

Table 10.3 - Key demographic variables and questionnaire measures divided by group, and associated p values for between-subjects ANOVAs comparing groups.

10.8.3 PANAS mood rating – positive affect

A mixed measures ANOVA with the positive affect PANAS scores shown in Figure 10.5B found a significant main effect of block (baseline to post-test) on PANAS positive affect ($F(1,42)= 8.81$, $p=.005$, $\eta_p^2=.17$): positive affect decreased between baseline and post-test measures. This was expected given that all participants experienced a negative mood induction during the test phase. There was, however, no significant interaction between this change in positive affect and group ($F(1,42) = 2.20$, $p=.145$, $\eta_p^2=.05$) or main effect of group ($F(1,42)=0.28$, $p=.597$, $\eta_p^2=.01$). Pairwise comparisons

indicated no significant change in positive affect in the experimental group ($F(1,21)= 1.03$, $p=.322$, $\eta_p^2=.05$), but a significant reduction in positive affect in the control group ($F(1,21)= 10.65$, $p=.004$, $\eta_p^2=.34$).

10.8.4 PANAS mood rating – negative affect

A mixed measures ANOVA with the negative affect PANAS scores shown in Figure 10.5C found no significant main effect of block (baseline to post-test) on PANAS negative affect ($F(1,42)= 2.47$, $p=.124$, $\eta_p^2=.06$). There was also no significant interaction between group and change in negative affect baseline to post-test ($F(1,42) = 0.51$, $p=.479$, $\eta_p^2=.01$), or main effect of group ($F(1,42)= 0.79$, $p=.380$, $\eta_p^2=.02$).

10.8.5 Happiness subjective mood measure – baseline to post-intervention

A mixed measures ANOVA with the happiness subjective mood scores shown in Figure 10.5D found a significant main effect of block (baseline to post-intervention) ($F(1,42)=5.30$, $p=.026$, $\eta_p^2=.11$): happiness increased significantly baseline to post-intervention across the sample. There was no significant interaction between this measure baseline to post-intervention and group ($F(1,42) = 1.14$, $p=.107$, $\eta_p^2=.06$), or main effect of group ($F(1,42)= 0.73$, $p=.398$, $\eta_p^2=.02$). Pairwise comparisons indicated a significant increase in happiness in the experimental group ($F(1,21)= 5.86$, $p=.025$, $\eta_p^2=.22$), but no such effect in the control group ($F(1,21)= 0.32$, $p=.576$, $\eta_p^2=.02$).

10.8.6 Sadness subjective mood measure – baseline to post-intervention

An identical mixed measures ANOVA with the sadness subjective mood scores shown in Figure 10.5E found no significant main effect of block (baseline to post-intervention) ($F(1,42)=3.28$, $p=.077$, $\eta_p^2=.07$). There was also no significant interaction between this measure baseline to post-intervention and group ($F(1,42)=3.28$, $p=.077$, $\eta_p^2=.07$) (although this approached significance and may therefore represent a type II error), or main effect of group ($F(1,42)= 0.46$, $p=.501$, $\eta_p^2=.01$).

10.8.7 Happiness subjective mood measure – pre-test to post-test

A mixed measures ANOVA with the happiness subjective mood scores shown in Figure 10.5D found a significant main effect of block (pre to post-test) on the happiness subjective mood measure ($F(1, 42)=17.34$, $p<.001$, $\eta_p^2=.29$): happiness decreased

significantly pre to post-test. There was no significant interaction between change in this measure and group ($F(1,42) = 0.35$, $p=.555$, $\eta_p^2=.008$), or main effect of group ($F(1,42)=0.05$, $p=.819$, $\eta_p^2=.001$). Pairwise comparisons indicated a significant reduction in happiness in both experimental ($F(1,21)= 16.26$, $p=.001$, $\eta_p^2=.44$) and control groups ($F(1,21)= 4.89$, $p=.038$, $\eta_p^2=.19$).

10.8.8 Sadness subjective mood measure – pre-test to post-test

An identical mixed measures ANOVA with the sadness subjective mood scores shown in Figure 10.5E found a significant main effect of block (pre to post-test) on the sadness subjective mood measure ($F(1,42)=19.94$, $p<.001$, $\eta_p^2=.32$): sadness increased significantly pre to post-test. There was no significant interaction between this measure and group ($F(1,42) = 0.72$, $p=.400$, $\eta_p^2=.02$), or main effect of group ($F(1,42)=0.01$, $p=.920$, $\eta_p^2<.001$). Pairwise comparisons indicated a significant increase in sadness in both the experimental ($F(1,21)= 6.29$, $p=.020$, $\eta_p^2=.23$) and control groups ($F(1,21)= 14.70$, $p=.001$, $\eta_p^2=.41$).

10.8.9 Alcohol choice

A mixed measures ANOVA with the alcohol choice scores shown in Figure 10.5F found no significant main effect of block (baseline, post-intervention) on alcohol choice ($F(1,42)=0.14$, $p=.707$, $\eta_p^2=.003$), interaction between block and group ($F(1,42)=0.05$, $p=.821$, $\eta_p^2=.001$), or main effect of group ($F(1,42)= 0.61$, $p=.438$, $\eta_p^2=.01$). On this basis, the two measures were averaged to form a single combined baseline measure.

A second ANOVA with the combined baseline and test alcohol choice scores found a significant main effect of block (combined baseline versus test) on alcohol choice ($F(1,42)= 19.60$, $p<.001$, $\eta_p^2=.32$), but no main effect of group ($F(1,42)= 0.17$, $p=.680$, $\eta_p^2=.004$). The test block was associated with a significant increase in alcohol choice compared to baseline. There was, however, no significant interaction between block and group: $F(1,42)=0.78$, $p=.381$, $\eta_p^2=.02$, providing no evidence of a differential change in alcohol choice between groups. Pairwise comparisons indicated a significant increase in alcohol choice between combined baseline and test for both experimental ($F(1,21)= 9.26$, $p=.006$, $\eta_p^2=.31$) and control groups ($F(1,21)= 10.67$, $p=.004$, $\eta_p^2=.34$). The test phase significantly increased alcohol choice in both groups.

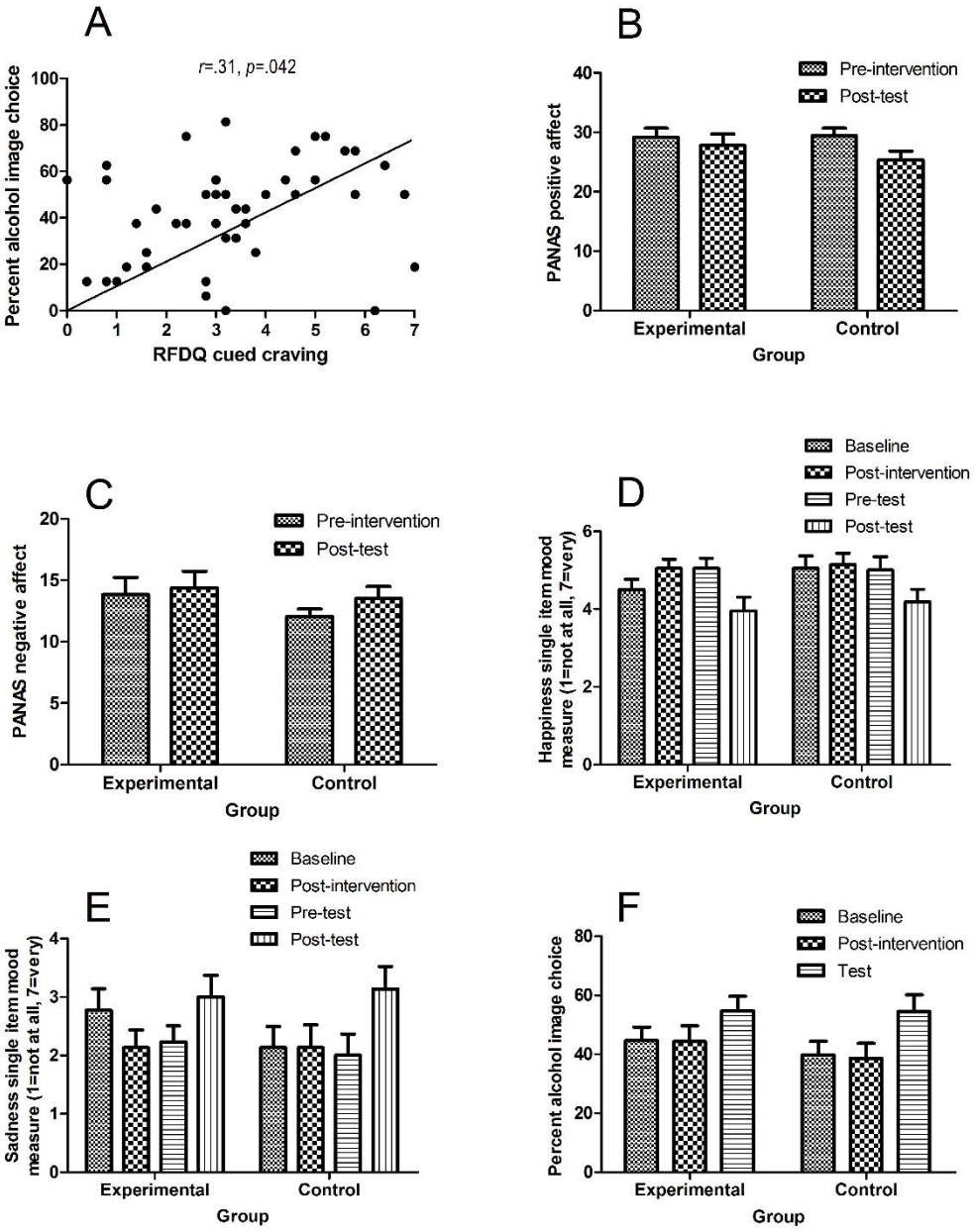

Figure 10.5 – A: Spearman's rank correlation between baseline percent choice of alcohol images and Reasons for Drinking Questionnaire cued craving scale. B: PANAS positive affect mood rating pre intervention and post-test, divided by group. C: PANAS negative affect mood rating pre intervention and post-test, divided by group. D: Happiness subjective mood rating at baseline, post-intervention, pre-test and post-test, divided by group. E: Sadness subjective mood rating at baseline, post-intervention, pre-test and post-test, divided by group. F: Percent alcohol choice during baseline, post-intervention, and test phases, divided by group.

10.8.10 Correlations between baseline alcohol choice and key questionnaire variables

As in Experiment 1, Spearman's rank order correlations were used to test the relationship between baseline percent alcohol choice and risk factors assessed by baseline questionnaires. Table 10.4 shows the correlation matrix. Baseline percent alcohol choice was significantly correlated with age and the RFDQ cued craving

subscale (see Figure 10.5A). No significant correlations were found between percent choice and alcohol dependence (AUDIT), depression (BDI-II), drinking to cope (RFDQ negative affect), or distress tolerance (DTS). When a control of false discovery rate method (FDR) was applied at 5%, neither the correlations of percent alcohol choice with age nor RFDQ cued craving survived this correction (Benjamini and Hochberg 1995).

	1	2	3	4	5	6	7	8	Mean	SD	Range
1. Percent alcohol choice									42.19	21.61	0-81.25
2. Age	**-.35**								39.05	14.69	19-61
3. Gender	.14	-.20							61.4%		
4. AUDIT total	-.09	-.13	-.09						15.14	6.70	5-30
5. BDI	.004	.09	-.19	.24					11.48	8.49	2-33
6. RFDQ negative affect	.02	-.06	-.05	**.48**	**.60**				3.16	2.24	0-7.86
7. RFDQ social pressure	.23	**-.55**	**.34**	.07	-.14	.12			5.11	2.44	0-9.33
8. RFDQ cued craving	**.31**	**-.50**	.13	**.34**	.17	**.45**	**.53**		3.32	1.80	0-7
9. DTS	-.14	.04	.11	.15	**.44**	**.44**	.08	.11	41.52	11.74	20-64

Table 10.4 – Correlation matrix between baseline percent alcohol versus food picture choice in the task and risk factors measured by questionnaires, with associated means, standard deviations and ranges. For gender, the mean column shows percentage of males. Correlations with gender were rank biserial correlations. P values <.05 are highlighted in bold. AUDIT= Alcohol Use Disorder Identification Test; BDI= Beck Depression Inventory; RFDQ= Reasons for Drinking Questionnaire; DTS= Distress Tolerance Questionnaire.

10.9 Discussion

The aim of Experiment 2 was to address three key limitations in Experiment 1: firstly, to use a block design mood induction rather than an intermixed method, secondly, to supplement our single item measure with a more comprehensive measure of mood across the test phase and, finally, to control the intervention more precisely in a lab procedure to allow clearer conclusions to be drawn from our findings.

The first finding was that the negative mood induction test procedure led to a significant decrease in happiness, and increase in sadness on the two mood Likert

scales. This was the case in both experimental and control groups, with no interaction, providing no evidence that the experimental intervention protected from negative mood induction in terms of resultant negative affect. This is inconsistent with a number of studies which have shown that acute one-off periods of exercise (Bernstein and McNally 2017a; b; Edwards et al. 2017; Mata et al. 2013), bright light exposure (aan het Rot et al. 2008a), and natural surroundings (Gladwell et al. 2012; Jiang et al. 2016; Kahn et al. 2008; Laumann et al. 2003; Parsons et al. 1998; Ulrich et al. 1991) can protect from induced physiological stress and negative mood induction. Both experimental and control groups also showed a significant increase in percent alcohol image choice between baseline and test, with no interaction between this change and group. Ultimately, and contrary to our expectations, the experimental group did not show either reduced emotional reactivity to the mood induction, or protection against enhanced alcohol motivation. This indicates no evidence for the efficacy of our intervention in protecting from negative affect driven alcohol motivation.

The finding that the test phase significantly raised percent alcohol image choice across the sample suggests that a block mood induction design is more appropriate with our population than the intermixed method used in Experiment 1, and as a finding is consistent with a number of studies which have shown that negative affect increases alcohol motivation (Amlung and MacKillop 2014; Field and Quigley 2009; Hardy and Hogarth 2017; Hogarth and Hardy 2018b; Hogarth et al. 2018a; Rousseau et al. 2011; Zack et al. 2006). The disadvantage of the block method is that any increase in alcohol choice is confounded by time. However, no evidence of change in alcohol choice across the two baseline blocks means that it is unlikely that the observed increase in alcohol choice between baseline and test blocks is a linear effect of time raising alcohol motivation.

A secondary finding was that we failed to find a significant correlation between percent choice of alcohol images at baseline and alcohol dependence, as measured by the AUDIT. Prior to correction, baseline percent choice of alcohol images was significantly negatively correlated with age and positively correlated with the RFDQ cued craving subscale. When a control of false discovery rate method (FDR) was applied, neither correlation survived correction, however.

Ultimately, this experiment failed to find a significant effect of a lab-based walking intervention on protection from negative mood induction in terms of either resultant negative affect, or associated alcohol motivation. One possibility is that the artificial nature of our intervention limited its efficacy in protecting from negative affect and associated alcohol choice. However, there is evidence that walking on a treadmill improves mood (Bartholomew et al. 2005; Miller and Krizan 2016), and indoor exercise interventions have been shown to protect against negative mood induction (Bernstein and McNally 2017a; b). Similarly, viewing nature on a screen has been shown to have beneficial effects on mood and stress reactivity (Gladwell et al. 2012; Jiang et al. 2016; Laumann et al. 2003; Ulrich et al. 1991). The artificial nature of our intervention is therefore unlikely to explain the failure to observe any beneficial effect.

Another possibility is that the exercise in our intervention was not intense enough to produce demonstrable effects on alcohol choice. A systematic review found that more intense exercise doses were associated with more protection from stress-induced increases in blood pressure (Hamer et al. 2006), and moderate and intense exercise has been shown to reduce cigarette cravings more effectively than light exercise (Haasova et al. 2014). However, as intensity of exercise increases above a certain threshold so does negative affect, particularly in sedentary individuals (Blanchard et al. 2001; Ekkekakis and Petruzzello 1999; Kilpatrick et al. 2003; Parfitt and Hughes 2009; Treasure and Newbery 1998). This may make it difficult to establish an optimal intensity of exercise.

Finally, if walking relies on a distraction effect to limit negative affect, it may not be as effective as other forms of distraction. A study by Morrow and Nolen-Hoeksema (1990) found that a combined cognitive-motor distraction (walking back and forth to sort cards in an emotion unrelated task) was significantly more effective in neutralising induced negative mood than a purely motor distraction (walking back and forth to complete an emotion-based task). This may be because cognitive distraction limits the generation of mood-related thoughts which promote continued negative affect (Van Dillen and Koole 2007).

Overall, these two studies provide no evidence that a brief nature-based walking intervention can protect from negative affect driven alcohol motivation. In Experiment

1 we failed to find a significant mood induction effect with an intermixed procedure. In Experiment 2, neither negative subjective mood nor negative affect driven alcohol choice was significantly reduced by the intervention. An alternative possible intervention, promotion of emotion acceptance, which may be more appropriate as a short-term intervention is trialled in the following chapter.

Chapter 11. An aversive noise induction procedure shows no evidence of raising alcohol motivation in a treatment-seeking alcohol dependent population, and brief instruction in acceptance-based coping shows no evidence of limiting the annoyance response to this stressor

11.1 Abstract

This study tested whether brief instruction in acceptance-based coping can protect from negative affect driven alcohol motivation in a sample of treatment-seeking drinkers. Forty eight treatment-enrolled drinkers, recruited from the Exeter Drug Project (EDP) Weymouth alcohol service, completed measures of alcohol dependence, depression and coping motives, as well as reporting abstinence status (abstinent, somewhat abstinent, or drinking). Baseline alcohol motivation was measured using a pictorial choice task. Negative mood was induced by means of an aversive noise procedure in both groups. In the intervention phase, the experimental group rehearsed acceptance-based coping statements, while the control group rehearsed neutral statements, with alcohol choice measured concurrently. The noise induction procedure led to a significant increase in annoyance (p<.001, η_p^2=0.18), but not anxiety (p=.533, η_p^2=0.01) across the sample, but there was no significant increase in alcohol choice (p=.497, η_p^2= .01). There were no differences between experimental and control groups in the subjective or alcohol choice responses to stress induction (ps>.234). A secondary finding was that baseline alcohol pictorial choice correlated with a number of markers for dependence. Ultimately, the design reported proved ineffective as a model for assessing the therapeutic effect of acceptance training on negative affect driven alcohol choice.

11.2 Introduction

The previous chapter demonstrated no evidence that a brief nature-based walking intervention protected from negative affect driven alcohol motivation. It is possible that such interventions require long-term implementation in order to be effective, and/or may be initially aversive to lower fitness individuals – reducing both their accessibility and their efficacy as a brief rescue intervention. Maladaptive coping styles, such as a tendency to avoid unpleasant internal states, may be an alternative target, since such coping styles have been associated with problematic alcohol use and sensitivity to negative mood driven relapse (Hasking and Oei 2007; Merrill and Thomas 2013; Moos et al. 1990; Opalach et al. 2016; Tull et al. 2015). While the interventions trialled in Chapter 10 relied on modifying the external environment, interventions to encourage development of internal skills to manage unpleasant affect more adaptively may generalise more effectively across contexts. The aim of the present experiment was to determine to what extent a brief intervention which aims to promote an adaptive coping style, acceptance of emotions, can protect from negative-affect driven alcohol-seeking in treatment-seeking alcohol dependent individuals. This intervention comprises rehearsal of acceptance based standardised statements.

While CBT approaches have traditionally attempted to modify negative emotional states by means of cognitive restructuring, third wave therapies aim instead to cultivate acceptance (Vieten et al. 2010). A general tendency towards acceptance, as opposed to avoidance, of negative emotions has been shown to be beneficial in alcohol treatment: individuals who mindfully accept adverse states, or use adaptive coping strategies when in negative states are less sensitive to stress induced alcohol-seeking behaviour (Merrill and Thomas 2013; Tull et al. 2015), and are more protected from alcohol dependence (Bravo et al. 2016; Fernandez et al. 2010; Murphy and Mackillop 2012; Pearson et al. 2015; Roos et al. 2015). However, no studies have yet examined the effect of a brief acceptance-based intervention on negative affect driven alcohol-seeking within an experimental paradigm, and the aim of the present study is to test this.

Long term interventions have attempted to increase acceptance-based coping in substance dependence. Acceptance Based Coping for Relapse Prevention (ABCRP), for example, targets negative affect driven relapse, and aims to develop non-resistance to,

and capacity to tolerate, unpleasant internal states which drive alcohol use. Preliminary findings indicated improvements in negative affect, emotional reactivity, and perceived stress as a result of this intervention (Vieten et al. 2010). The implication from these findings is that capacity for acceptance-based coping during negative emotions may help protect individuals from maladaptive negative emotionality, and associated relapse to alcohol use, although the latter claim is yet to be demonstrated.

Previous studies have also attempted to manipulate acceptance-based coping experimentally. Instruction in acceptance-based strategies allows more effective toleration of experimentally induced pain in healthy adults (Keogh et al. 2005; McMullen et al. 2008), unpleasant physiological symptoms in individuals with panic disorder (CO_2 challenge - Eifert and Heffner 2003; Levitt et al. 2004), and negative mood induction in remitted depressed adults (Singer and Dobson 2007; 2009) and students (Odou and Brinker 2015). Acceptance has also proved superior to emotion suppression in protecting against increased negative affect in response to anxiety-inducing stimuli (Campbell-Sills et al. 2006). The present study aimed to extend these findings by investigating whether this protection from negative mood induction holds in a sample of alcohol dependent individuals, and whether this effect translates into a reduction in negative affect driven alcohol-seeking. Such findings would indicate that acceptance-based instruction may provide a brief rescue intervention against negative affective triggers in alcohol dependent individuals.

Manipulation of acceptance-based coping in experimental tasks often uses statement rehearsal –participants are presented with a number of written statements instructing in acceptance-based coping to review during the task (e.g. Singer and Dobson 2007; 2009). In the present study, acceptance-based statements were generated from items of the Control of Thoughts and Feelings Questionnaire (Harris, 2008), a measure of the extent to which individuals suppress or accept unpleasant emotions. The nature of this intervention (verbal rehearsal) precluded the use of the standard statement-based Velten mood induction procedure used in our previous experiments. On this basis, the present experiment used a noise induction procedure. Loud noise has been shown to elicit both annoyance and a physiological stress reaction, as well as an overall increase in negative affect (tension, depression, anger, fatigue, and confusion) (Alvarsson et al.

2010; Ising and Kruppa 2004; Lusk et al. 2004; Markus et al. 1998; Peters et al. 1998; Quarto et al. 2014; Willner and Neiva 1986), and to induce an increase in smoking behaviour (Cherek 1985). There is also evidence that anger-related emotions such as irritability and annoyance promote alcohol consumption (Karyadi and King 2011; Rabinovitz 2014). We might therefore expect this method to be equivalent to our Velten mood induction procedure, with the added advantage that it may require lower levels of literacy and engagement in order to manipulate mood.

The aim of the present experiment was therefore, primarily, to determine whether the rehearsal of acceptance-based coping statements such as "I can wait for bad feelings to pass naturally" could protect drinkers engaged in treatment services from negative affect driven alcohol-seeking behaviour. This finding would suggest that rehearsal of acceptance-based coping statements might provide a short-term, easily implemented protective strategy for individuals attempting to maintain abstinence. Participants' motivation to drink was measured at baseline using the concurrent pictorial choice task described previously. In the stress induction phase, negative affect was induced by exposing participants to a 70dB industrial noise through headphones, and alcohol choice measured once more. In the intervention phase of the design, noise stress continued but simultaneously the experimental group read a series of acceptance-based coping statements such as "telling myself it will pass will help calm me down", whereas the control group read neutral statements such as "There are 60 minutes in an hour". The acceptance-based coping group were expected to recover from stress induced alcohol-seeking, i.e. alcohol choice should decrease during rehearsal of the statements, but the neutral control should continue to show elevated alcohol choice as a result of the stressful noise. This experimental finding would suggest that rehearsal of acceptance-based coping statements is a potential brief rescue intervention to prevent negative affect driven relapse. Since baseline and stress induction alcohol choice blocks were identical in procedure across experimental and control groups, an additional aim was to determine whether stress induced alcohol motivation measured across these two blocks was significantly increased in individuals with more depression symptoms, and who drank to cope with negative affect (as in Hogarth and Hardy 2018b; Hogarth et al. 2018a).

11.3 Methods

11.3.1 Participants

Participants were 48 treatment-enrolled drinkers, recruited from the Exeter Drug Project (EDP) Weymouth alcohol service. The majority of participants were, at the time of testing, attending a weekly, CBT-based group intervention to target hazardous drinking and encourage controlled drinking or abstinence. Testing took place on site. Participants were recompensed with £15. This study was granted approval by the University of Exeter Psychology Ethics Committee.

Assuming that the noise mood induction procedure produces a similar effect size to that of our Velten procedure, our sample size is >99% powerful to detect a mood induction effect (η_p^2=0.28-0.32), and >90% powerful to detect a medium effect size (Cohen's *f*=0.25) in a repeated measures, within-between interaction.

11.3.2 Questionnaires

Initial questions recorded age, gender (male = 1, female = 2) and self-reported current drinking status ("Are you currently abstinent from alcohol?" Abstinent = 0, somewhat abstinent = 1, drinking = 2). Questionnaires were as follows: (1) The Alcohol Use Disorders Identification Test (AUDIT) to measure alcohol dependence (Babor et al. 2001). This questionnaire comprises 10 items scored from 0-4, and total sum scores have the following category labels, mild (0-7), hazardous (8-15), harmful (16-19) and possibly alcohol dependent (20+). (2) The Patient Health Questionnaire (PHQ-9: Kroenke and Spitzer 2002; Kroenke et al. 2001), with the suicide item removed, leaving 8 items scored from 0 (not at all) to 3 (nearly every day). Total sum scores have the following category labels, no or minimal depression (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27). (3) The General Anxiety Disorder questionnaire (GAD-7: Spitzer et al. 2006). This questionnaire comprises 7 items scored from 0 (not at all) to 7 (nearly every day). Total sum scores have the following category labels, no or minimal anxiety (0-4), mild (5-9), moderate (10-14), and severe (15+). (4) Drinking to cope with negative affect was measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) measure of coping expectancies adapted for alcohol (Edelen et al. 2014; Shadel et al. 2014). This

questionnaire comprised 12 items scored from 1 (never) to 5 (always). (5) The withdrawal intolerance subscale of the Intolerance for Smoking Abstinence Questionnaire (adapted for drinking – IDQ: Sirota et al. 2010). This scale comprises 12 items scored from 1 (strongly disagree) to 5 (strongly agree). The IDQ was included on the basis that intolerance of withdrawal has been shown previously to predict latency to relapse in smokers (Sirota et al. 2010), and may therefore represent a significant marker of risk in the present sample.

11.3.3 Baseline alcohol choice

On-screen instructions stated: 'In this task you can choose to view images of alcohol and food using the left and right arrow keys. Press the space bar to begin'. An alcohol pictorial choice task, identical to that used in Hardy and Hogarth (2017), was used to measure alcohol motivation. A block of 24 choice trials established participants' baseline preference for alcohol images.

11.3.4 Stress induction

Participants were instructed: 'You will now hear some noise. Please do not take the headphones off. Continue to choose between pictures'. An industrial noise (a sandblaster) was played to participants at 70dB through headphones. Participants completed 12 alcohol choice trials, identical to the baseline phase, to quantify any stress-induced increase in alcohol-seeking.

11.3.5 Statement intervention phase

The industrial noise ceased and participants were instructed: 'Your task now is to read some statements to yourself'. Four statements were presented on the screen for 5 seconds each: "I should read these statements to myself" and "I should think about these statements as I read them" in order, repeated twice.

The industrial noise resumed and participants completed 48 alcohol choice trials, identical to baseline except that a statement was presented for 5 seconds prior to each choice. The experimental and control groups read the acceptance-based coping and neutral control statements respectively (see Table 11.1), with each statement randomly sampled from a set of 16. It was expected that the acceptance based coping group

might show recovery from any stress induced increase in alcohol-seeking, compared to the neutral control group. At the end of this phase, the industrial noise ceased.

11.3.6 Mood repair procedure

All participants completed a positive mood repair procedure. Positive music was played (Mozart's Eine Kleine Nachtmusik allegro) and participants were presented with 8 randomly selected positive self-statements (see Table 9.1) presented for 5 seconds each, prior to an ITI of 1-2 seconds.

11.3.7 Subjective mood measures

Subjective mood was measured by two onscreen questions in the format 'How [anxious/annoyed] do you currently feel?' with a scale from 1 (not at all) to 5 (very). The two questions were presented sequentially and randomly selected from 'anxious' and 'annoyed'. This measure was obtained after baseline, stress induction, and intervention phases.

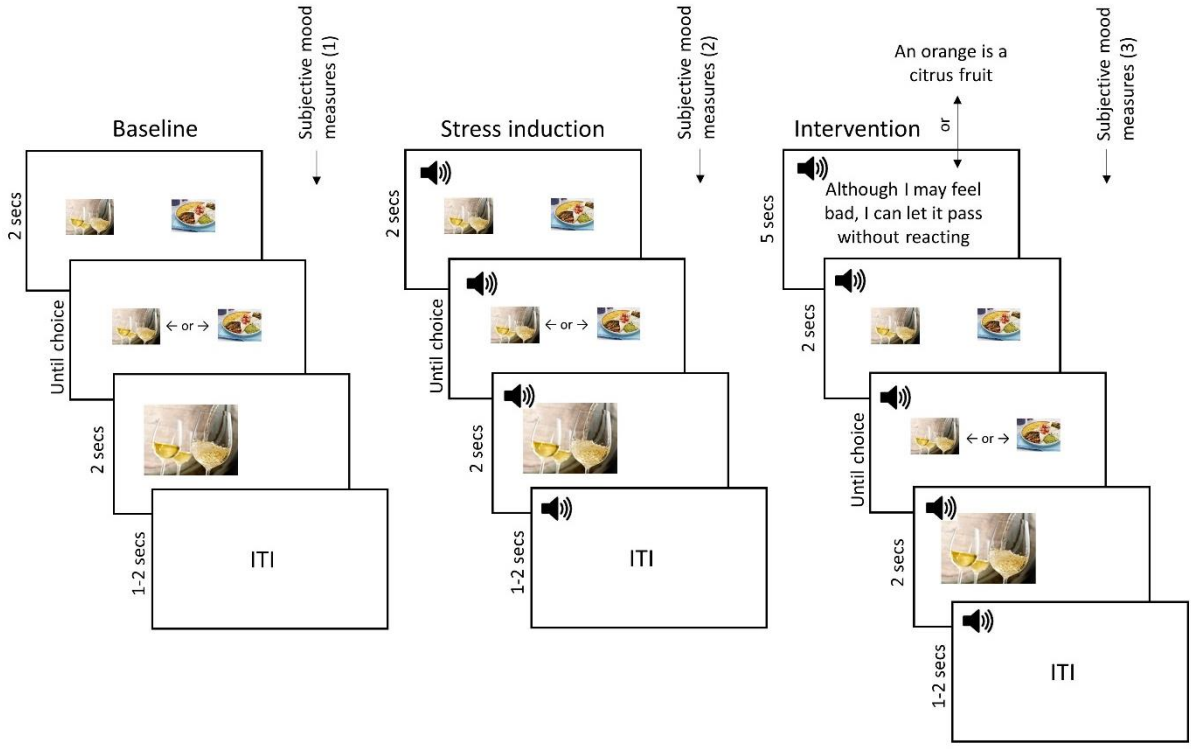

Figure 11.1 - Procedure used to test the impact of an aversive noise induction procedure on alcohol image choice, and to what extent this effect can be mitigated by acceptance-based statement rehearsal. At baseline, alcohol choice was measured by preference to select for enlargement alcohol versus food thumbnail images in two-alternative forced choice trials. In the stress induction phase, alcohol choice was measured during an industrial noise stressor. In the intervention phase, the experimental group received acceptance-based coping statements, while the control group received neutral statements, prior to each alcohol choice trial. The mood repair phase is not shown. Subjective mood (anxiety and annoyance) was reported on a five point scale with 1=not at all, and 5=very. The key question was whether the stress induction would increase percent alcohol choice relative to baseline, and whether this could be mitigated by rehearsal of acceptance-based coping statements. This would provide evidence for the efficacy of this strategy as a brief rescue intervention in high-risk individuals.

Practice statements	
I should read these statements to myself	I should think about these statements as I read them
Acceptance coping statements	**Control statements**
Telling myself it will pass will help me to calm down	There are 60 minutes in one hour
I can accept that bad feelings are a normal part of life	Manchester is in the United Kingdom
I am healthier when I allow negative feelings to come and go	Strawberries are picked in the summer
I can wait for bad feelings to pass naturally	It sometimes snows in winter
I know that this distress will not be significant in the future	Basket weaving was invented before pottery making
It is natural to experience negative feelings sometimes	Perennials bloom every year
Although I may feel bad, I can let it pass without reacting	You have to take the ferry to get to the island
It's OK if I feel uncomfortable emotions	London is the capital of England
I'm not afraid of my feelings	Elephants carried the supplies
I can accept my bad feelings	The Pacific Ocean has fish
I can improve my life by accepting my emotions	Most secondary schools have a choir
My emotions are nothing to feel guilty about	The rug was made according to an old Indian pattern
I can react calmly to bad feelings	Most oil paintings are done on canvas
It is normal to experience ups and downs	An orange is a citrus fruit
I can let bad feelings pass through my mind without reacting	Some say that ladybirds are good for the garden
I can accept my feelings as they are	Diamonds really can cut glass

Table 11.1 – Statements used in the intervention phase

11.4 Results

11.4.1 Participants

Participant characteristics, divided by group, are shown in Table 11.2. There was no significant difference between groups in any of the baseline measures taken. The proportion of participants in the four AUDIT categories were: mild (0%), hazardous (2.1%), harmful (2.1%) and possible dependence (95.8%). The proportion of participants in the PHQ-9 categories were: no or minimal depression (8.3%), mild (18.8%), moderate (22.9%), moderately severe (18.8%), and severe (31.3%). The proportion of participants in the GAD-7 categories were: no or minimal anxiety (14.6%), mild (14.6%), moderate (20.8%), and severe (50%).

	Group		
	1 (experimental) M (*SD*, range)	**2 (control) M (*SD*, range)**	***p***
Age	42.75 (15.08, 19-68)	45.75 (13.10, 20-69)	.446
AUDIT	35.63 (6.48, 19-45)	34.04 (7.61, 14-46)	.442
PHQ-9	22.83 (6.59, 11-32)	22.29 (6.79, 12-32)	.780
GAD-7	21.29 (6.29, 7-28)	18.71 (7.14, 7-28)	.190
IDQ	39.00 (12.02, 16-60)	39.96 (12.11, 15-54)	.784
PROMIS	45.46 (13.80, 21-60)	42.50 (15.73, 12-60)	.492
Percent choice baseline	48.26 (20.88, 4.17-100)	40.10 (23.69, 0-87.50)	.212
Abstinence status	24; 10; 67	17; 38; 46	.093

Table 11.2 – Key demographic variables and questionnaire measures divided by group, and associated p values for between-subjects ANOVAs comparing groups. For abstinence status, numbers for each group represent the percentage of individuals who were abstinent, somewhat abstinent, or drinking, respectively. Abstinence status was compared across groups using a chi square. AUDIT= Alcohol Use Disorders Identification Test; PHQ-9= Patient Health Questionnaire – depression symptoms; GAD-7= General Anxiety Disorder Questionnaire; IDQ= Intolerance for Smoking Abstinence Questionnaire, withdrawal intolerance subscale (adapted for alcohol); PROMIS= Patient-Reported Outcomes Measurement Information System, alcohol expectancies subscale.

11.4.2 Correlations between baseline alcohol choice and key questionnaire variables

These findings are addressed in Chapter 5.

11.4.3 Change in percent alcohol choice between baseline and stress induction phases

Table 11.3 shows the correlation matrix between change in percent choice of alcohol between baseline and stress induction phases and questionnaire variables. Change in percent choice of alcohol was significantly negatively correlated with age, and positively correlated with gender (male=1, female=2), alcohol dependence (AUDIT), anxiety (GAD-7), withdrawal intolerance (IDQ), and drinking to cope with negative affect (PROMIS).

	1	2	3	4	5	6	7	8	9	Mean	SD	Range
1.Percent choice										44.18	22.48	0-100
2.Age	-.16									44.25	14.06	19-69
3.Gender	.14	-.06								70.8%		
4.AUDIT	**.59**	-.27	.06							34.83	7.04	14-46
5.PHQ-9	**.39**	-.16	.03	**.50**						14.56	6.62	3-24
6.GAD-7	**.57**	-.28	.09	**.67**	**.79**					13.00	6.79	0-21
7.IDQ	**.63**	-.10	.03	**.51**	**.40**	**.52**				3.29	1.00	1.25-5
8.Drinking to cope with negative affect (PROMIS)	**.49**	-.22	.19	**.73**	**.58**	**.70**	**.58**			3.66	1.23	1-5
9.Abstinence status	**.48**	.17	-.18	.08	.06	.23	**.30**	.03		20%; 24.4%; 55.6%		
10. Change in percent choice at stress induction	**.52**	**-.30**	**.30**	**.46**	.21	**.35**	**.32**	**.36**	.02	1.65	16.64	-29.17-37.50

Table 11.3 – Correlation matrix between change in percent choice of alcohol between baseline and stress induction phases and risk factors measured by questionnaires, with associated means, standard deviations and ranges. For categorical/ordinal variables (gender and abstinence status), the mean column shows percentage of males, and individuals who were abstinent, somewhat abstinent, and drinking, respectively. Correlations incorporating gender were rank biserial correlations. P values <.05 are highlighted in bold. AUDIT= Alcohol Use Disorders Identification Test; PHQ-9= Patient Health Questionnaire – depression symptoms; GAD-7= General Anxiety Disorder Questionnaire; IDQ= Intolerance for Smoking Abstinence Questionnaire, withdrawal intolerance subscale (adapted for alcohol use); PROMIS= Patient-Reported Outcomes Measurement Information System, coping expectancies subscale. Change in percent choice at stress induction is the change in percent alcohol choice between baseline and stress induction phases.

11.4.4 Annoyance subjective mood scores

A mixed measures ANOVA with the annoyance subjective mood scores shown in Figure 11.2A found a significant effect of time point on annoyance rating ($F(2,92) = 10.39$, $p<.001$, $\eta_p^2=0.18$). There was no significant interaction between annoyance rating time point and group (experiment/control) ($F(2,92) = .80$, $p=.447$, $\eta_p^2=.02$), or main effect of group ($F(1,46)= 0.85$, $p=.361$, $\eta_p^2=0.02$). Pairwise comparisons indicated a significant increase in annoyance between baseline and induction measures ($F(1,47)=14.86$, $p<.001$, $\eta_p^2=.24$), and between baseline and intervention measures ($F(1,47)=14.03$, $p<.001$, $\eta_p^2=.23$), but there was no significant difference between induction and intervention measures ($F(1,47)= 0.86$, $p=.359$, $\eta_p^2=.02$).

Additional pairwise comparisons indicated a significant increase in annoyance between baseline and induction measures for the experimental ($F(1,23)=13.33$, $p=.001$, $\eta_p^2=.37$) but not control groups ($F(1,23)=3.29$, $p=.083$, $\eta_p^2=.13$), a significant increase in

annoyance between baseline and intervention measures for both experimental ($F(1,23)=10.19$, $p=.004$, $\eta_p^2=.31$) and control groups ($F(1,23)=4.78$, $p=.039$, $\eta_p^2=.17$), and no significant change in annoyance between induction and intervention measures for either experimental ($F(1,23)<0.01$, $p>.99$, $\eta_p^2<.01$) or control groups ($F(1,23)=1.43$, $p=.245$, $\eta_p^2=.06$).

11.4.5 Anxiety subjective mood scores

A mixed measures ANOVA with the anxiety subjective mood scores shown in Figure 11.2B found no significant effect of time point on anxiety rating ($F(2,92) = 0.63$, $p=.533$, $\eta_p^2=.01$). There was also no significant interaction between anxiety rating time point and group ($F(2,92) = 1.48$, $p=.234$, $\eta_p^2=.03$), or main effect of group ($F(1,46)= 0.11$, $p=.740$, $\eta_p^2=.002$). There was therefore no evidence for the efficacy of the mood induction procedure in altering anxiety.

11.4.6 Alcohol choice

A mixed measures ANOVA with the alcohol choice scores shown in Figure 11.2C showed no significant main effect of block (baseline, stress induction, and intervention) ($F(2,92) = 0.47$, $p=.497$, $\eta_p^2= .01$) or group ($F(1,46)= 1.30$, $p=.261$, $\eta_p^2=.03$) There was also no significant interaction between block and group (experimental vs. control) ($F(2,92) = 0.06$, $p=.940$, $\eta_p^2=.001$), indicating no significant difference between groups in percent alcohol choice across the three blocks.

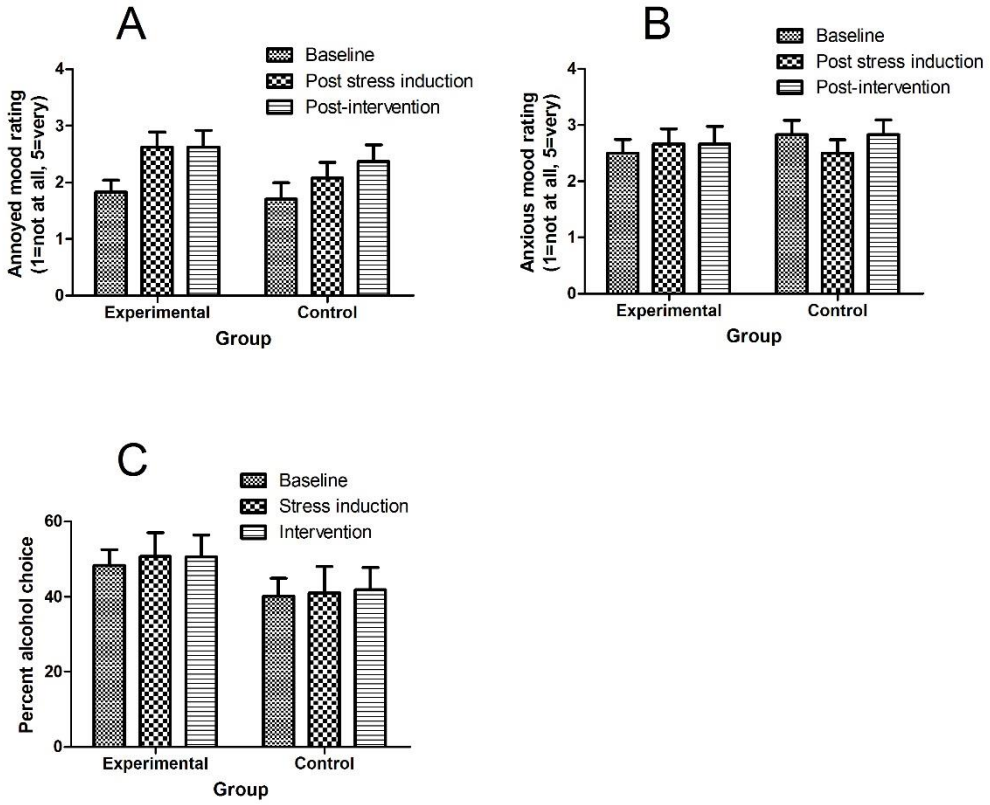

Figure 11.2 - *A: Annoyance mood rating at baseline, post stress induction and post-intervention, divided by group. B: Anxiety mood rating at baseline, post stress induction and post-intervention, divided by group. C: Percent alcohol choice during baseline, stress induction, and intervention phases, divided by group.*

11.5 Discussion

The purpose of the present study was to determine to what extent rehearsal of emotional acceptance based standardised statements in treatment-seeking alcohol-dependent individuals could protect against negative-affect driven alcohol-seeking. The first finding was that change in percent alcohol choice between baseline and stress induction phases was significantly correlated with alcohol dependence (AUDIT), anxiety (GAD-7), withdrawal intolerance (IDQ), and drinking to cope with negative affect (PROMIS), but not with depression (PHQ-9). The relationship between drinking to cope and sensitivity to negative affect driven alcohol motivation is consistent with findings from Hogarth and Hardy (2018b); Hogarth et al. (2018a), although these studies also found an effect of depression. The correlations observed indicate an overlap between factors that confer sensitivity to negative affect driven alcohol choice and those that confer risk for development and maintenance of dependence more

generally. A secondary finding of this study was that preferential choice of alcohol images over alternative images at baseline was significantly correlated with alcohol dependence (as measured by the AUDIT), and a number of risk factors which have been demonstrated previously to be prospective markers for dependence formation and relapse. These findings are discussed in Chapter 5.

The second finding was that the noise mood induction procedure led to a significant increase in annoyance, but not anxiety, across the sample between baseline, post stress induction, and post-intervention measures. This is consistent with studies which have shown that loud, uncontrollable noise promotes negative affect, annoyance, and a physiological stress response (Ising and Kruppa 2004; Lusk et al. 2004; Quarto et al. 2014). There was no interaction between this effect and group, providing no evidence that our acceptance-based intervention limited annoyance in response to the noise stressor. This is inconsistent with studies which have shown that brief instruction in emotion acceptance limits induced negative affect in response to both negative mood induction and anxiety-inducing stimuli (Campbell-Sills et al. 2006; Singer and Dobson 2007; 2009).

It is unclear why our intervention failed to significantly reduce annoyance. One possibility is that acceptance-based coping is more effective in promoting recovery from negative emotions following termination of an unpleasant stimulus, rather than protecting against emotions during stimulus exposure. In the present experiment, the unpleasant noise was present from the stress induction phase onwards, with no recovery period. In line with this explanation, a study by Campbell-Sills et al. (2006) found that individuals instructed in acceptance as opposed to suppression showed equal levels of distress during an anxiety-provoking film, but that groups diverged during the post-film recovery period with the acceptance group showing more rapid recovery. However, other studies have shown that instruction in acceptance can improve pain tolerance concurrently with exposure to negative stimuli (e.g. in cold pressor tasks, Keogh et al. 2005 and self-administered electric shock tasks, McMullen et al. 2008). Acceptance can therefore appear to have restorative effects during stimulus exposure, at least in the case of physical discomfort.

Despite the observed increase in annoyance, we failed to find a significant increase in percent alcohol choice between baseline and stress induction blocks, or between baseline and intervention blocks, across the two groups. This means that we are unable to address the key question of our study: whether acceptance-based statement rehearsal can limit negative affect-driven alcohol choice. One possibility is that the induction procedure was ineffective in raising alcohol motivation - only one other study has, to our knowledge, shown a motivational effect of a noise stressor on drug-seeking (in smokers - Cherek 1985). This study was conducted in a sample of healthy smokers, who likely differed from our sample on a number of key metrics. In particular, our participants were actively engaged in CBT for alcohol reduction. While we would have ideally used the standard Velten mood induction procedure of our previous experiments, the statement-based nature of our intervention precluded this.

A second possibility is that our measure of mood did not accurately reflect negative affect across the stress induction/intervention phases. Retrospective evaluations of emotional events are particularly subject to biases, including a tendency to disproportionately weight the most extreme (peak) and final (end) moments (Baumgartner et al. 1997; Olsson et al. 2017; Sayette et al. 2000; Schreiber and Kahneman 2000; Wilson and Dunn 2004). If our retrospective mood measure provided an overinflated estimation of annoyance caused by the procedure, this might explain why we failed to observe a significant effect of the procedure on alcohol motivation. Future studies might instead use momentary assessment of mood.

An alternative interpretation of findings is that the task of reading and thinking about statements during the intervention phase was distracting for both control and experimental groups, and this distraction was responsible for our failure to find an induction effect on alcohol motivation. Van Dillen and Koole (2007), for example, found in a series of experiments that higher demand on working memory was associated with reduced negative mood in response to negatively-affecting stimuli. This included tasks in which participants read externally-oriented statements (e.g. 'Canada's biggest industry is lumber'), identical to our control procedure. Task-related statements in our experiment (either acceptance based or neutral) may have replaced stress-induced ruminations in working memory (Morrow and Nolen-Hoeksema 1990;

Van Dillen and Koole 2007), limiting their effect on alcohol motivation. If this was the case, distraction-based interventions may hold promise for limiting negative affect driven alcohol choice, although these distraction effects may not always occur reliably (Josephson 1996; Wegner et al. 1993).

Overall, the findings of this study suggest that the alcohol pictorial concurrent choice task provides an effective metric for alcohol dependence and associated risk factors in a treatment-seeking alcohol dependent group. We also found that a noise stress induced increase in alcohol motivation was associated with negative coping motives, alcohol dependence, anxiety, and withdrawal intolerance. However, although we found a significant effect of the stress induction procedure on annoyance, we found no increase in percent alcohol choice between baseline and stress induction blocks, or between baseline and intervention blocks. This meant that we were unable to test our key prediction – that rehearsal of acceptance based coping statements limits negative affect driven alcohol choice. While the findings presented here are not conclusive, our failure to validate a mood induction procedure which can be used concurrently with statement rehearsal within our established paradigm means that further investigation of this intervention (which by definition requires statement rehearsal) is not within the scope of this project. Our finding that rehearsal of acceptance-based statements failed to show any evidence of reducing annoyance in the experimental group can increase our confidence in this decision.

Chapter 12. Engagement with pleasant environmental images significantly reduces negative affect driven alcohol choice in individuals who wish to visit the locations shown (high liking), compared to low liking individuals and controls

12.1 Abstract

This study tested whether engagement with pleasant environmental images (as a proxy for environmental enrichment) can protect from negative affect driven alcohol motivation in a sample of student drinkers. Eighty students who reported drinking at least occasionally completed measures of alcohol dependence, depression and coping motives. Baseline alcohol motivation was measured using a pictorial choice task. Negative mood was then induced by means of self-referential negative affective statements and sad music. In the test phase, the experimental group rated how much they would like to visit the pleasant location shown in the image, while the control group rated how interesting they found neutral images, with alcohol choice measured concurrently. Alcohol choice significantly increased across the sample in the test phase compared to baseline (p=.002, η_p^2=.12), but no interaction was found between this effect and group (p=.159, η_p^2=.03). However, post hoc analysis using self-reported desire to visit locations in environmental images ('liking') indicated that the effect of negative mood on alcohol motivation was abolished in a high liking group, compared to low liking and the control group (interaction: p=.005, η_p^2=.14). These findings provide preliminary evidence for the efficacy of pleasant environmental images in limiting alcohol choice under conditions of negative mood. Secondary analyses indicated that baseline alcohol choice correlated with alcohol dependence severity (r=.42, p<.001), loss of control over alcohol use (r=.38, p=.001), and drinking to cope with depression (r=.43, p<.001), and anxiety (r=.38, p=.001), and to be social (r=.36, p=.002), and conform (r=.23, p=.048).

12.2 Introduction

Thus far, all of our interventions have been chosen on the basis of prior evidence that the manipulation in question limits negative affect in response to negative mood induction. This may be a problem since it is unclear to what extent reduced emotional reactivity translates into reduced alcohol motivation. The intervention trialled in this chapter, environmental enrichment, is unusual in having prior evidence of protecting against negative affect driven alcohol choice specifically. If the manipulation trialled proves effective, a low-cost, accessible intervention could then be developed which incorporates the principles of environmental enrichment.

The aim of the present study was to determine whether engagement with positively-reinforcing environmental images (as a proxy for environmental enrichment) can protect against negative-affect driven alcohol-seeking in an experimental paradigm. Environmental enrichment is defined as the provision of an environment which is more complex and novel than standard environments, providing a greater degree of natural reward (Kühn et al. 2017). Rats given environmentally enriched, as compared to standard, housing show decreased psychostimulant self-administration and drug-seeking (Green et al. 2002; Puhl et al. 2012), and greater resilience to stress (Lehmann and Herkenham 2011). Critically, evidence also indicates that environmental enrichment can reduce stress-driven increases in alcohol- (Marianno et al. 2017) and cocaine-seeking (Chauvet et al. 2009). The implication is that interventions of this type may protect against negative affect induced relapse in humans. The study by Marianno et al. (2017), to our knowledge, provides the only evidence for an acute intervention to protect against negative mood driven alcohol motivation.

In humans, behavioural economic theory suggests that the prevalence of substance using behaviours is determined by the availability of alternative reinforcing behaviours (Magidson et al. 2011). In line with this, substance use is associated with deprived environments (Correia and Carey 1999; Correia et al. 2002; Correia et al. 2003; Higgins et al. 2004; Lee et al. 2018; Magidson et al. 2011; Van Etten et al. 1998). For example, active cocaine users were found to engage in significantly fewer pleasant activities than non-users, and density of pleasant activities correlated negatively with severity of dependence (Van Etten et al. 1998). While studies of this type do not establish cause

and effect (it may be that more dependent individuals become increasingly focused on the drug, to the exclusion of other behaviours), they do suggest that one way to reduce maladaptive substance use may be to provide dependent individuals with an environment with numerous pleasant, non-drug related activities.

Interventions in humans for substance dependence have aimed to improve wellbeing by increasing the availability of alternative pleasant activities. The Life Enhancement Treatment for Substance Use (LETS ACT), for example, is based on principles of behavioural activation and aims to identify substance-unrelated sources of positive reinforcement in depressed substance users. This intervention has been shown to increase environmental reward, reduce rates of depression, and increase retention in substance abuse treatment (Daughters et al. 2008; Magidson et al. 2011), as well as improve abstinence rates at 3, 6 and 12 months post-treatment (Daughters et al. 2018). Ultimately, these findings suggest that engagement with alternative, non-substance related forms of positive reinforcement may improve outcomes in treatment of substance dependence.

While long term behavioural activation interventions have demonstrated initial efficacy in the treatment of substance use, the extent to which environmental enrichment of this type can reduce negative affect driven drinking acutely remains unclear. The aim of the present experiment, therefore, was to determine whether engagement with positively-reinforcing environmental images (as a lab-based proxy for environmental enrichment) protects from negative affect driven alcohol choice in an experimental procedure. We might predict that the presence of alternative reinforcement, in the form of the pleasant images, will lower alcohol's augmented value under conditions of negative mood, as proposed in Marianno et al. (2017). This would be consistent with behavioural economic theory. However, the presence of natural features in the images might also, as we predicted in Chapter 10, reduce rumination and sympathetic activation, limiting negative affect (Bratman et al. 2015; Li et al. 2011). Alternatively, engagement with the images may introduce a distraction effect, protecting against negative affect (Van Dillen and Koole 2007). In any case, a positive effect of our intervention would provide preliminary evidence that exposure to alternative, pleasant forms of reinforcement may represent a useful protective

strategy for individuals who drink in response to negative affect. Such a result would also provide a translation from animal models, where there are preliminary findings that environmental enrichment can protect against stress induced alcohol-seeking.

Participants were 80 university students who reported drinking at least occasionally. The present sample was chosen to allow rapid recruitment, and since initial proof of concept in a non-clinical population would be useful prior to application of this experimental procedure to a clinical population with additional needs. Participants' motivation to drink was measured at baseline using our standard pictorial choice task (alcohol vs. food images). All participants then experienced a standard Velten negative mood induction procedure with sad music and statements, which continued throughout the test phase. During this phase, participants continued to make concurrent choices between alcohol and food. In the experimental (environmental enrichment) group, choice trials were interspersed with pleasant environmental images, and participants were asked how much they would like to visit the place shown. Images were chosen on the basis of their complexity, novelty, and potential for engagement. They also incorporated natural space where possible, since this has been identified as a feature of enriched environments for humans (Kühn et al. 2017). In the control group, choice trials were interspersed with neutral images, low in complexity, novelty, and potential for engagement, and participants were asked how interesting they found each image. We expected a significant negative affect induced increase in alcohol choice in the control group, but for this effect to be abolished in the experimental group. This would indicate a protective effect of engagement with alternative, pleasant reinforcement on negative affect driven alcohol-seeking. A secondary aim of this experiment is to test the sensitivity of our alcohol pictorial choice task to alcohol dependence and risk factors for dependence, as in previous experiments.

12.3 Methods

Participants were 80 students from the University of Exeter (64 female) who were not teetotal and reported drinking at least occasionally. Participants were recompensed with £5. Ethical approval was obtained from the University of Exeter Psychology

Ethics Committee. This sample size is >99% powerful to detect a mood induction effect (η_p^2=0.28-0.32), and 99% powerful to detect a medium effect size (Cohen's *f* =0.25) in a repeated measures, within-between interaction.

12.3.1 Procedure

12.3.1.1 Baseline measures

Questionnaires were as follows: 1) the Alcohol Use Disorders Inventory Test (AUDIT: Babor et al. 2001) to index alcohol use and associated problems. 2) the Drinking Motives Questionnaire Revised (DMQR: Grant et al. 2007b) to measure coping motives. 3) the Patient Health Questionnaire (PHQ-9 with the suicide item removed: Kroenke and Spitzer 2002; Kroenke et al. 2001) to measure depression. 4) the Generalised Anxiety Disorder assessment (GAD-7: Spitzer et al. 2006) to measure anxiety. 5) the Patient-Reported Outcomes Measurement Information System (PROMIS) measure of loss of control over drinking (Pilkonis et al. 2016).

12.3.1.2 Baseline alcohol choice

Participants completed 24 trials of the concurrent choice task, identical to Hardy and Hogarth (2017), to establish baseline preference for alcohol images.

12.3.1.3 Mood induction

Participants were instructed: 'You will now hear some music and be shown a series of statements that represent a particular type of mood. Please read each emotion statement to yourself and try to imagine yourself moving into that state'. Participants were played sad music (Barber's Adagio for Strings) and presented with 6 negative mood statements, randomly selected from a pool of 16, each for 10 seconds prior to an ITI of 1-2 secs (see Table 9.1). This mood induction procedure has been shown to be effective in raising alcohol motivation in hazardous drinkers (Hardy and Hogarth 2017).

12.3.1.4 Test phase

Participants were randomly assigned to either the experimental or control group. During the test phase, sad music continued to play, and a negative statement was selected from the set of 16 and presented for 4 seconds prior to a choice between

alcohol and food images (identical to baseline). Prior to each trial in this phase, the experimental group was presented with a full screen pleasant landscape image (randomly selected from a set of 32) for two seconds and asked 'How much would you like to visit this place?', answering on a scale from 1 (not at all) to 5 (a lot) (see Figure 12.1). The image remained on the screen until a response was made. In contrast, the control group was presented with a neutral image from the International Affective Picture Set (IAPS) (Lang and Bradley 1997) for two seconds, before being asked 'How interesting do you find this image?', again answering on a scale from 1 (not at all) to 5 (a lot) (see Figure 12.1). Participants experienced 32 trials of this type.

12.3.1.5 Mood repair

Participants then experienced a mood repair procedure – they were played happy music (Mozart's Eine Kleine Nachtmusik) and presented with 8 positive mood statements (e.g. 'I feel cheerful and lively'), each for four seconds.

12.3.1.6 Subjective mood measures

Subjective mood was measured by two onscreen questions in the form 'How [happy/sad] do you feel?' with a scale from 1 (not at all) to 5 (very). The two questions were presented sequentially and randomly selected from 'happy' and 'sad'. This measure was obtained after baseline and test alcohol choice blocks (as shown in Figure 12.2).

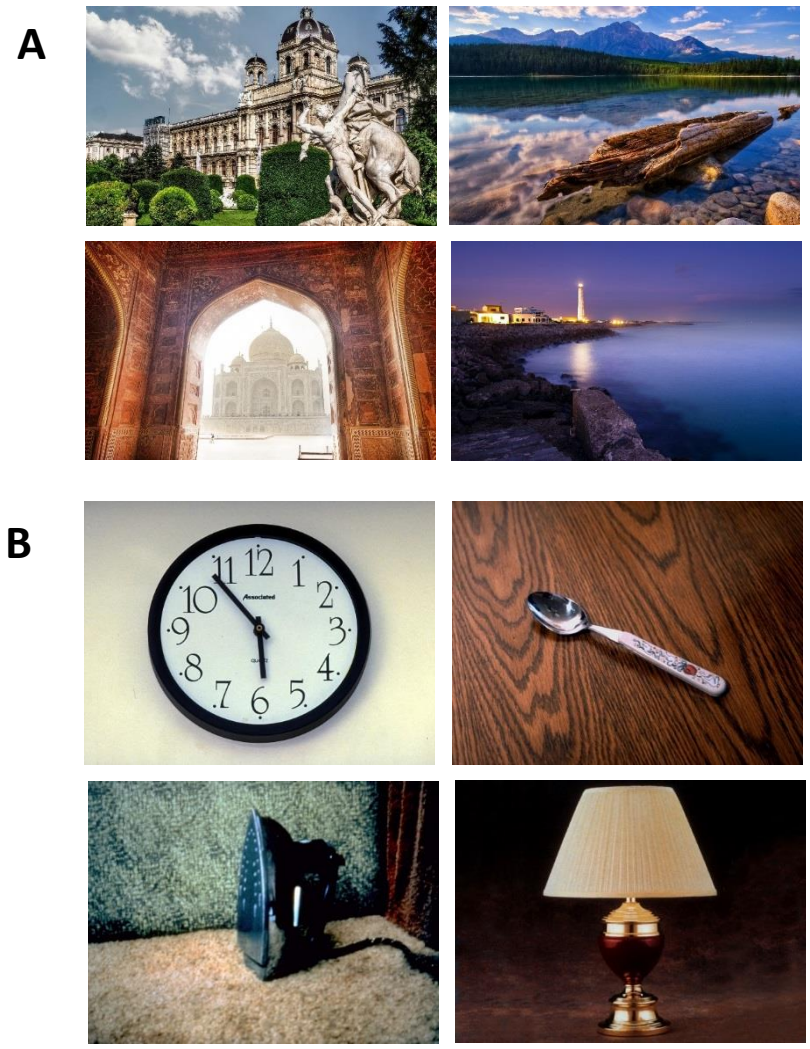

Figure 12.1 – Example stimuli used in the test phase of the task. A: environmental enrichment images, B: neutral control images.

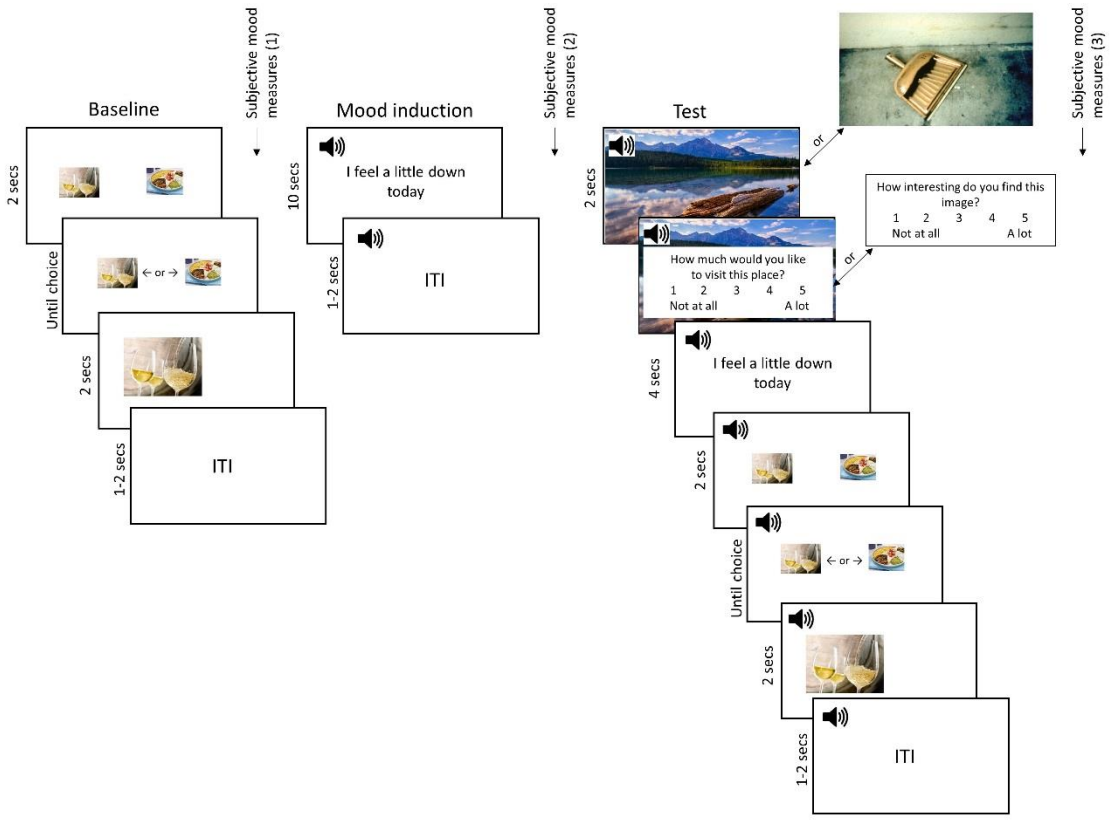

Figure 12.2 - Procedure used to test the impact of a negative mood induction procedure on alcohol image choice, and any mitigation of this effect by engagement with pleasant environmental images. At baseline, alcohol choice was measured by preference to select for enlargement alcohol versus food thumbnail images in two-alternative forced choice trials. In the mood induction phase, participants were exposed to negative Velten mood statements and sad music. In the test phase, the experimental group were shown a pleasant landscape image, while the control group were shown a neutral image, prior to each alcohol choice trial. Subjective mood (happiness and sadness) was reported on a five point scale with 1=not at all, and 5=very. The key question was whether the negative mood induction would increase percent alcohol choice relative to baseline, and whether this would be mitigated by exposure to pleasant environmental images. This would provide evidence for the efficacy of environmental enrichment in protecting against negative affect driven alcohol motivation.

12.4 Results

Participant characteristics, divided by group, are shown in Table 12.1. Four participants (two in each group) were excluded on the basis of being outliers in change in percent alcohol choice between baseline and test (1.5 x the interquartile range) (Ghasemi and Zahediasl 2012).

There was no significant difference between groups in any of the baseline measures taken. The proportion of participants in the four AUDIT categories were: mild (46%), hazardous (50%), harmful (3%) and possible dependence (1%). The proportion of participants in the PHQ-9 categories were: no or minimal depression (42%), mild

(32%), moderate (20%), and severe (7%). The proportion of participants in the GAD-7 categories were: no or minimal anxiety (30%), mild (49%), moderate (14%), and severe (7%).

	Group		
	1 (experimental) **M (SD, range)**	**2 (control)** **M (SD, range)**	***p***
Age	22.49 (6.18, 18-54)	23.50 (6.57, 18-49)	.494
AUDIT	7.71 (4.71, 1-26)	8.84 (4.78, 1-18)	.351
PHQ-9	6.45 (4.00, 0-20)	6.66 (4.84, 0-16)	.787
GAD-7	6.92 (3.82, 1-17)	7.16 (4.48, 1-18)	.585
DMQR depression	2.29 (2.45, 0-7.78)	1.95 (1.80, 0-7.11)	.520
DMQR anxiety	4.22 (2.19, 0-8.25)	4.13 (2.19, 0-8)	.848
DMQR social pressure	6.34 (1.44, 3.60-9.00)	6.86 (1.72, 2.80-10.00)	.156
DMQR enhancement	4.57 (1.98, 0.80-9.00)	5.49 (2.50, 0-9.60)	.079
DMQR conformity	2.21 (2.15, 0-7.20)	2.03 (2.06, 0-7.40)	.704
PROMIS (loss of control)	1.92 (0.66, 1-3.86)	2.10 (0.62, 1-3.14)	.256
Baseline percent alcohol choice	33.55 (21.53, 0-83.33)	36.40 (20.50, 0-91.67)	.655

Table 12.1 – Key demographic variables and questionnaire measures divided by group, and associated p values for between-subjects ANOVAs comparing groups.

12.4.1 Happiness subjective mood measure – baseline to post-test

A mixed measures ANOVA with the happiness subjective mood scores shown in Figure 12.3A found a significant main effect of block (baseline to post-test) on the happiness subjective mood measure ($F(1,74)=62.42$, $p<.001$, $\eta_p^2=.46$): happiness decreased significantly baseline to post-test. There was no significant interaction between change in this measure and group ($F(1,74) = 0.02$, $p=.886$, $\eta_p^2<.001$) or main effect of group ($F(1,74)= 0.01$, $p=.940$, $\eta_p^2<.001$). Pairwise comparisons indicated a significant reduction in happiness in both experimental ($F(1,37)= 23.81$, $p<.001$, $\eta_p^2=.39$) and control groups ($F(1,37)= 43.95$, $p<.001$, $\eta_p^2=.54$).

12.4.2 Sadness subjective mood measure – baseline to post-test

An identical ANOVA with the sadness subjective mood scores shown in Figure 12.3B found a significant main effect of block (baseline to post-test) on the sadness subjective mood measure ($F(1,74)=54.56$, $p<.001$, $\eta_p^2=.42$): sadness increased significantly baseline to post-test. There was no significant interaction between this measure and group ($F(1,74) = 0.01$, $p=.910$, $\eta_p^2<.001$) or main effect of group ($F(1,74)= 1.23$, $p=.271$, $\eta_p^2=.02$). Pairwise comparisons indicated a significant increase in sadness in both the experimental ($F(1,37)= 28.44$, $p<.001$, $\eta_p^2=.44$) and control groups ($F(1,37)= 26.28$, $p<.001$, $\eta_p^2=.42$).

12.4.3 Alcohol choice

A mixed measures ANOVA with the alcohol choice scores shown in Figure 12.3C showed a significant main effect of block (baseline versus test) on alcohol choice ($F(1,74)= 10.46$, $p=.002$, $\eta_p^2=.12$). The test block was associated with a significant increase in alcohol choice compared to baseline. There was, however, no significant interaction between block and group ($F(1,74)=2.02$, $p=.159$, $\eta_p^2=.03$), providing no evidence of a differential change in alcohol choice between groups, or main effect of group ($F(1,74)= 1.04$, $p=.311$, $\eta_p^2=.01$). Pairwise comparisons indicated no significant increase in alcohol choice between baseline and test in the experimental group ($F(1,37)= 1.76$, $p=.193$, $\eta_p^2=.05$) but a significant increase in the control group ($F(1,37)= 10.18$, $p=.003$, $\eta_p^2=.22$) suggesting the null interaction may have been due to insufficient power. The test phase significantly increased alcohol choice in the control group, but not the experimental group.

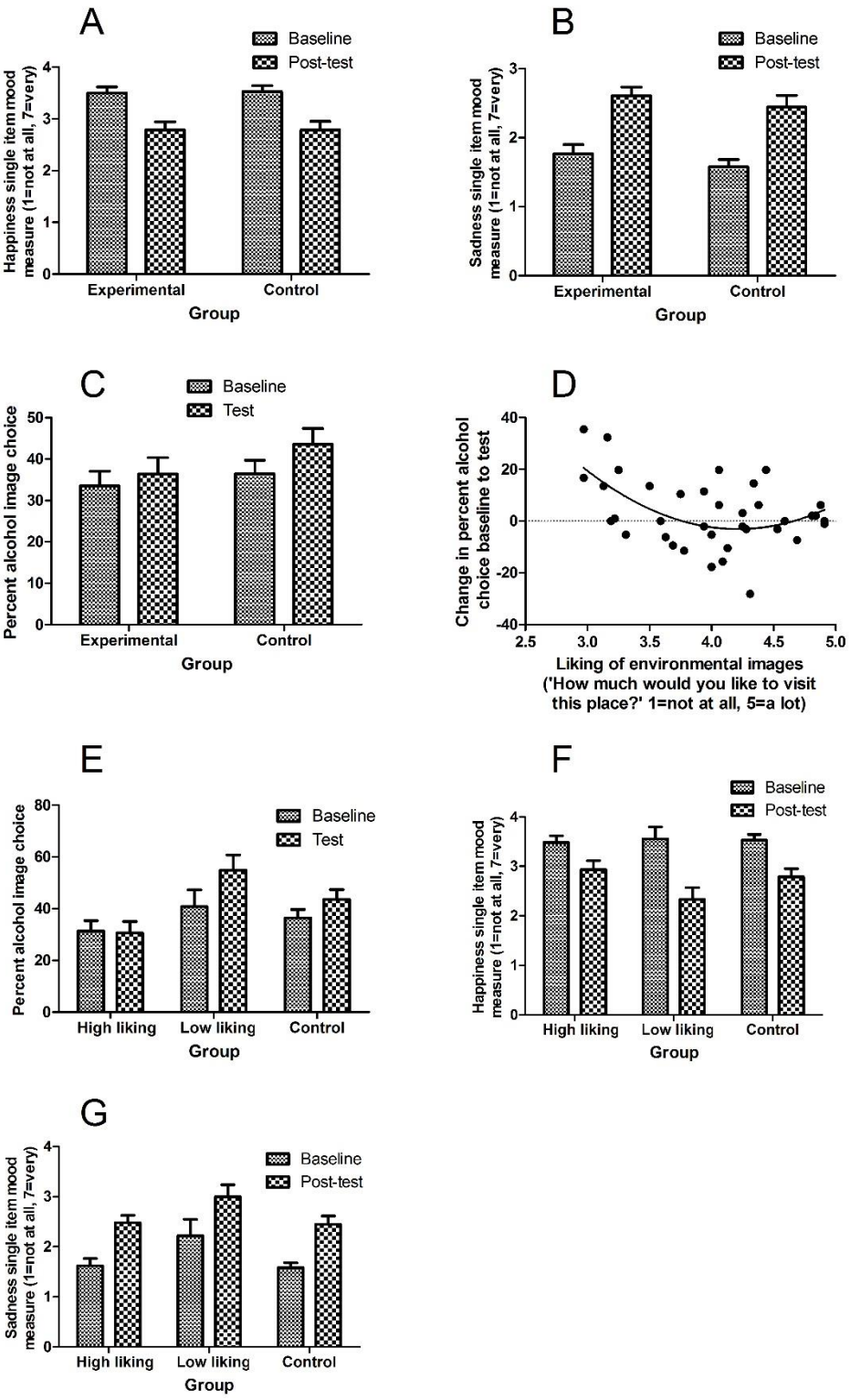

Figure 12.3 A-C: Planned analyses. A: Happiness subjective mood rating at baseline and post-test, divided by group. B: Sadness subjective mood rating at baseline and post-test, divided by group. C: Percent alcohol choice during baseline and test phases, divided by group. Figures D-G: Post hoc analyses using desire to visit locations in environmental images ('liking'). D: Scatterplot showing the relationship between liking of environmental images and change in alcohol choice baseline to test. E: Percent alcohol choice during baseline and test phases, divided by liking group (high liking, low liking, control). F: Happiness subjective mood rating at baseline and post-test, divided by liking group. G: Sadness subjective mood rating at baseline and post-test, divided by liking group.

12.4.4 Secondary analysis - correlation between baseline alcohol choice and key questionnaire variables

Spearman's rank order correlations were used to test the relationship between baseline percent choice of alcohol versus food images and risk factors assessed by questionnaires. Table 12.2 shows the correlation matrix. Percent choice of alcohol images at baseline was significantly correlated with alcohol dependence (AUDIT), loss of control over drinking (PROMIS), drinking to cope with depression (DMQR depression), anxiety (DMQR anxiety), drinking in response to social pressure (DMQR social pressure), and to conform (DMQR conformity). No significant correlations were found between percent choice and depression (PHQ-9) or anxiety (GAD-7). When a control of false discovery rate method (FDR) was applied at 5%, all significant correlations with baseline percent alcohol choice remained significant apart from DMQR conformity (Benjamini and Hochberg 1995) (see Figure 12.4).

	1	2	3	4	5	6	7	8	9	10	11	Mean	SD	Range
1.Percent choice baseline												34.98	20.93	0-91.67
2.Age	-.14											23.00	6.36	18-54
3.Gender	-.22	.18										21.1		
4.AUDIT	**.42**	**-.31**	-.15									8.28	4.75	1-26
5.PHQ-9	.16	-.11	-.03	.17								6.55	4.41	1-18
6.GAD-7	.07	-.07	-.14	.14	**.65**							7.04	4.14	1-18
7. DMQR depression	**.43**	-.14	**-.34**	**.28**	**.32**	**.38**						2.12	2.14	0-7.78
8. DMQR anxiety	**.38**	.03	**-.23**	**.23**	.22	.20	**.74**					4.17	2.18	0-8.25
9. DMQR social pressure	**.36**	-.17	**-.32**	**.45**	**.27**	.21	**.49**	**.50**				6.60	1.59	2.80-10
10. DMQR enhancement	**.45**	-.07	**-.39**	**.49**	.12	**.24**	**.60**	**.65**	**.59**			5.03	2.29	0-9.60
11. DMQR conformity	**.23**	-.19	**-.24**	.15	**.40**	**.32**	**.52**	**.41**	**.55**	**.24**		2.12	2.09	0-7.40
12.Loss of control (PROMIS)	**.38**	-.21	**-.26**	**.64**	.19	.17	**.60**	**.53**	**.57**	**.62**	**.36**	2.01	0.64	1-3.86

Table 12.2– Correlation matrix between percent alcohol versus non-alcohol picture choice at baseline and risk factors measured by questionnaires, with associated means, standard deviations and ranges. For the categorical variable gender, the mean column shows percentage of males. Correlations incorporating gender were rank biserial correlations. P values <.05 are highlighted in bold. AUDIT= Alcohol Use Disorders Identification Test; PHQ-9= Patient Health Questionnaire – depression symptoms; GAD-7= General Anxiety Disorder Questionnaire; DMQR= Drinking Motives Questionnaire Revised; PROMIS= Patient-Reported Outcomes Measurement Information System, loss of control subscale.

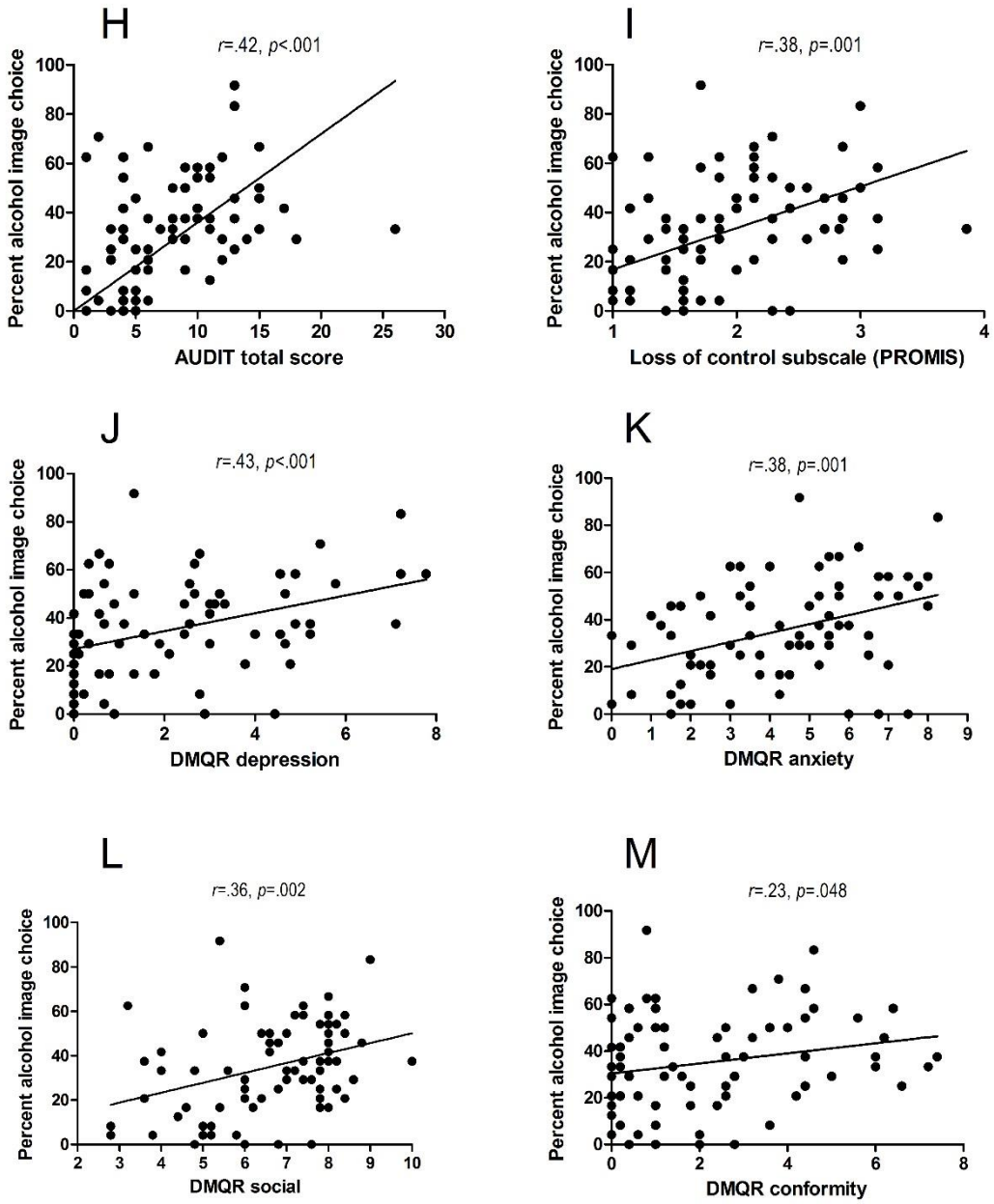

Figure 12.4 – Figures 1H to 1M – Spearman's rank correlations between percent choice of alcohol versus food pictures at baseline and key questionnaire variables. Associated test statistics are shown above each graph. AUDIT = Alcohol Use Disorders Identification Test; PROMIS = Patient-Reported Outcomes Measurement Information System; DMQR = Drinking Motives Questionnaire Revised. When a control of false discovery rate method (FDR) was applied at 5%, all significant correlations with baseline percent alcohol choice remained significant apart from DMQR conformity.

12.5 Post hoc analysis

12.5.1 Experience of environmental images

A curve estimation procedure indicated that a quadratic function between self-reported desire to visit locations in environmental images ('How much would you like to visit this place?' – 'liking') and change in alcohol choice between baseline and test captured significantly greater variance in this relationship ($F(2,35)= 6.61$, $p=.004$, $R^2=.27$) than a linear model ($F(1,36)= 5.09$, $p=.030$, $R^2=.12$) (see Figure 12.3D).

On the basis of this quadratic function, participants in the experimental group were divided into two subgroups based on their liking of environmental images across the test phase (high liking: mean response >3.5, low liking: mean response ≤3.5). Analyses were re-run with this new three group structure (high liking, low liking, and control). Table 12.3 shows key participant characteristics in the experimental group, divided by liking (high and low liking). There was a significant difference between groups in depression (PHQ-9), anxiety (GAD-7), and drinking to cope with depression (DMQR depression), with the low liking group scoring significantly higher than the high liking group on these measures.

12.5.2 Happiness subjective mood measure – baseline to post-test

Analyses on subjective mood scores were repeated to identify any significant differences between control, high and low liking groups. There was a significant main effect of block (baseline to post-test) on the happiness subjective mood measure ($F(1,73)=60.71$, $p<.001$, $\eta_p^2=.45$): happiness decreased significantly baseline to post-test (see Figure 12.3F). There was no significant interaction between change in this measure and group ($F(2,73) = 2.57$, $p=.084$, $\eta_p^2=.07$) or main effect of group ($F(2,73)= 0.41$, $p=.666$, $\eta_p^2=.01$). Pairwise comparisons indicated a significant reduction in happiness in the control group ($F(1,37)= 43.95$, $p<.001$, $\eta_p^2=.54$), in the low liking group ($F(1,8)= 19.36$, $p=.002$, $\eta_p^2=.71$), and in the high liking group ($F(1,28)= 11.67$, $p=.002$, $\eta_p^2=.29$).

12.5.3 Sadness subjective mood measure – baseline to post-test

There was a significant main effect of block (baseline to post-test) on the sadness subjective mood measure ($F(1,73)=35.46$, $p<.001$, $\eta_p^2=.33$): sadness increased

significantly baseline to post-test (see Figure 12.3G). There was no significant interaction between this measure and group ($F(2,73) = 0.03$, $p=.970$, $\eta_p^2=.001$), but an unexpected significant main effect of group ($F(2,73)= 3.15$, $p=.049$, $\eta_p^2=.08$), with greater subjective sadness scores in the low liking group. Pairwise comparisons indicated a significant increase in sadness in the control group ($F(1,37) = 26.28$, $p<.001$, $\eta_p^2=.42$), in the low liking group ($F(1,8)= 5.77$, $p=.043$, $\eta_p^2=.42$), and in the high liking group ($F(1,28)= 21.99$, $p<.001$, $\eta_p^2=.44$).

12.5.4 Alcohol choice

Percent alcohol choice was entered into a mixed measures ANOVA with the within-subjects variable block (two levels: baseline and test) and the between-subjects variable group (three levels: high liking, low liking, and control) (see Figure 12.3E). There was a significant main effect of block (baseline versus test) on alcohol choice ($F(1,73)= 15.15$, $p<.001$, $\eta_p^2=.14$) and interaction between block and group (high liking, low liking, and control) ($F(2,73)= 5.77$, $p=.005$, $\eta_p^2=.14$), but no significant main effect of group ($F(2,73)= 2.74$, $p=.071$, $\eta_p^2=.07$). Pairwise comparisons indicated a significant increase in alcohol choice between baseline and test in the control group ($F(1,37)= 10.18$, $p=.003$, $\eta_p^2=.22$), and in the low liking group ($F(1,8)= 9.16$, $p=.016$, $\eta_p^2=.53$), but no such effect in the high liking group ($F(1,28)= 0.13$, $p=.719$, $\eta_p^2=.01$).

When variables which significantly differed between high and low liking groups (depression (PHQ-9), anxiety (GAD-7), and drinking to address depression (DMQR-depression)) were included as covariates, the interaction between block (baseline vs. test) and group (high liking, low liking, and control) remained significant ($F(2,70)= 4.99$, $p=.009$, $\eta_p^2= .13$).

	Group		
	1 (High liking) M (SD, range)	2 (low liking) M (SD, range)	*p*
Age	23.04 (6.90, 18-54)	20.78 (2.59, 18-27)	.348
AUDIT	7.41 (3.76, 1-15)	8.67 (7.19, 2-26)	.493
PHQ-9	5.55 (3.25, 0-12)	9.33 (5.00, 2-20)	.011
GAD-7	6.10 (3.34, 1-17)	9.56 (4.25, 3-17)	.016
DMQR depression	1.14 (1.65, 0-5)	1.88 (1.36, 0-4)	.044
DMQR anxiety	1.14 (1.65, 0-5)	1.63 (1.41, 0-3)	.523
DMQR social pressure	6.30 (1.37, 3.80-9.00)	6.49 (1.72, 3.60-8.40)	.731
DMQR enhancement	4.41 (1.78, 1.40-7.80)	5.09 (2.57, 0.80-9.00)	.378
DMQR conformity	2.21 (2.17, 0-7.20)	2.22 (2.21, 0.20-6.40)	.985
PROMIS (loss of control)	1.82 (0.55, 1-3.14)	2.24 (0.91, 1.14-3.86)	.101
Percent choice baseline	31.32 (21.90, 0-83.33)	40.74 (19.74, 8.33-70.83)	.257

Table 12.3 - Table of demographics for high and low liking subgroups within the experimental group, and p statistics from between subjects ANOVAs.

12.6 Discussion

The purpose of the present study was to determine to what extent engagement with positively-reinforcing environmental images can protect against negative-affect driven alcohol-seeking in an experimental paradigm. The first finding was that the negative mood induction test procedure led to a significant decrease in happiness, and a significant increase in sadness across the sample. This was the case in both experimental and control groups, with no interaction, providing no evidence that the experimental intervention protected from negative mood induction in terms of resultant negative affect. There was also a significant increase in percent alcohol choice between baseline and test phases across the sample as a whole, but when experimental and control groups were considered separately, this effect was present only in the control group. There was, however, no significant interaction between the change in alcohol choice between baseline and test and group. This failure to find a significant interaction limits our confidence in the efficacy of our intervention in protecting from negative affect driven alcohol motivation. This finding is inconsistent with animal models which found that environmental enrichment protected from stress driven increases in alcohol (Marianno et al. 2017) and cocaine (Chauvet et al. 2009) motivation.

Post hoc analysis focused on experimental participants' experience of the environmental images as places they would like to visit (liking), since behavioural economic theories would predict that experience of the images as positively reinforcing would determine their efficacy as a protective agent. When the experimental group were divided into high and low liking groups, and compared with the control group, both the control and low liking groups showed a significant increase in alcohol choice baseline to test, with no such effect in the high liking group. There was a significant interaction between group (high liking, low liking, and control) and alcohol choice baseline to test. This suggests that the intervention was protective against negative affect driven alcohol choice specifically in individuals who liked the images, compared to those who did not like them, or those who experienced neutral control images.

We might conclude that the high liking group found the environmental images positively reinforcing, and the presence of this alternative form of reinforcement limited the value of alcohol under conditions of negative mood. This finding provides a direct translation from Marianno et al. (2017)'s finding in rats that an enriched environment limits stress-driven alcohol-seeking behaviour. It is also consistent with previous evidence that substance dependence is related to a lack of alternative reinforcing activities (Correia et al. 2003; Higgins et al. 2004; Magidson et al. 2011; Van Etten et al. 1998), and that interventions which increase exposure to substance-unrelated activities improve abstinence rates (Daughters et al. 2018). However, it may also be that individuals who liked the images more engaged with the activity to a greater extent (i.e. a distraction effect). A study by Erber and Tesser (1992) found that negative mood was neutralised more effectively in individuals who invested high effort in a distracting task than in those who invested low effort. High liking individuals may have invested more effort in the intervention task (rating their liking of the images), limiting the effect of the negative mood induction on alcohol choice.

In addition, it is important to note that the high and low liking groups differed in depression (PHQ-9), anxiety (GAD-7), and drinking to cope with depression (DMQR depression), with the low liking group showing significantly higher scores on these measures. We know that individuals with depression and who drink to cope are particularly sensitive to the motivational effect of negative mood on alcohol motivation

(Hardy and Hogarth 2017; Hogarth and Hardy 2018b; Hogarth et al. 2018a), and so any difference between high and low liking groups may have been a function of this difference, rather than an intervention effect. Alternatively, the low liking group may have experienced the images as less reinforcing as a function of elevated depression (Huys et al. 2013), limiting their efficacy in protecting against negative mood driven alcohol choice. However, when depression, anxiety, and drinking to address depression were controlled as covariates, the interaction between negative affect driven alcohol choice and group (high and low liking and control) remained significant. This suggests that the effect observed is more likely to be a function of liking and/or engagement with the images, than of individual differences between the groups.

One inconsistency in our findings is that we failed to find any evidence that the environmental enrichment procedure limited induced negative affect in the high liking group. This is explicable given that we did not necessarily expect the intervention to prevent an increase in alcohol choice by limiting the negative affect experienced during the mood induction. However, our retrospective measurement of mood has the same limitations as those described in Chapter 11, and so should be treated with caution.

A secondary finding was that preferential choice of alcohol images was significantly correlated with alcohol dependence (as measured by the AUDIT), and a number of associated variables, including loss of control over drinking, drinking to cope with depression, anxiety, drinking for social pressure, and to conform. All of these correlations apart from DMQR conformity remained significant when controlling for multiple comparisons using the false discovery rate method. This finding is consistent with Hardy and Hogarth (2017) and Hardy et al. (2018a), and further validates our pictorial choice measure.

Overall, this study initially found no evidence that engagement with pleasant environmental images (as a form of environmental enrichment) protected from negative mood induced alcohol choice in an experimental compared to a control group. However, post hoc analysis using liking of the images indicated that the effect of negative mood on alcohol motivation was abolished in a high liking group, compared to low liking and the control group. While these findings must be treated

with caution, they provide preliminary evidence for the efficacy of pleasant environmental images in limiting alcohol choice under negative mood. The mechanism by which this occurs remains unclear and requires further investigation.

Chapter 13. General Discussion

The purpose of the present thesis was to investigate mechanisms of substance dependence and develop novel interventions to limit acute drug motivation. A review of the literature indicated that supernormal valuation of the drug, as conceptualised in behavioural economic models, correlates reliably with dependence severity, and therefore might represent a primary underpinning mechanism of dependence. However, this mechanism may be insufficient to account for a subgroup of treatment-seeking, dependent individuals for whom the course of dependence is chronic and relapsing, and who persist in drug use despite negative consequences and intentions to quit. This thesis investigated three candidate secondary mechanisms. Processes of cue reactivity and insensitivity to costs were not significantly associated with dependence, and were therefore eliminated as candidate mechanisms. However, elevated choice of the drug over alternative reinforcement was reliably associated with dependence, consistent with behavioural economic theory. We found that a pictorial measure of drug choice, suitable for use with clinically-dependent populations, provided a reliable behavioural assay of drug value, and could therefore be used to test manipulations to increase or decrease drug motivation. Our final candidate mechanism was sensitivity to negative affective triggers. This thesis found that experimental induction of negative affect significantly increased drug motivation, as measured using our pictorial choice task, and sensitivity to this effect correlated with a number of risk factors for dependence. Finally, this thesis trialled a number of novel, brief rescue interventions to limit or abolish negative affect driven drug motivation. Engagement with pleasant environmental images (as a proxy for environmental enrichment) proved most successful. In this discussion, each finding is considered in more detail, with limitations and directions for future research.

13.1 Cue reactivity and insensitivity to costs in dependence

This thesis firstly investigated the relationship between dependence severity and two candidate mechanisms: cue reactivity and insensitivity to costs. In Chapter 3, a biconditional task demonstrated that alcohol cues can promote alcohol-seeking by means of hierarchical (S:R-O), rather than binary (S-O-R), associative mechanisms. However, there was no evidence that the magnitude of the motivational effect of

alcohol cues varied based on severity of dependence. In Chapter 4, severity of dependence was not significantly associated with greater discounting of either opportunity or delay costs imposed on an alcohol reward in a concurrent choice task. These findings undermine cue reactivity and cost insensitivity accounts of dependence. However, further substantive evidence would be required to discount these theories entirely. Future research might aim to replicate findings in Chapters 3 and 4 in clinically-dependent, as opposed to student, samples, and with designs which more accurately model the drug-associated costs and cues encountered in naturalistic settings.

Both of these studies did, however, find that greater dependence severity was associated with greater preferential choice of the alcohol reward (in the form of points) over alternative reinforcement. This provides support for a key tenet of behavioural economic theory: that dependence is underpinned by the ascription of greater relative value to the drug reward. Since points-based measures of drug value in which participants expect to receive the reward are ethically-problematic in treatment-seeking populations, we developed a novel pictorial choice task based on Moeller et al. (2013) and Moeller et al. (2009).

13.2 Concurrent pictorial choice as a behavioural assay of drug value

The second aim of this thesis was to test whether a novel pictorial concurrent choice procedure could provide a reliable behavioural assay of drug value, sensitive to variation in this value as a function of dependence severity. Across the thesis, percent choice of drug images at baseline in our pictorial choice task significantly correlated with severity of dependence in six experiments after adjustment for multiple comparisons, with two null findings, (the two experiments in Chapter 10: henceforth referred to as 10a and 10b). Significant correlation coefficients ranged from r=.24 to r=.59, i.e. moderate to large effect sizes. These data indicate that our pictorial choice task provides a robust marker of dependence severity. Choice of drug images also correlated with a range of risk factors which predict dependence formation and propensity to relapse, including symptoms of depression and anxiety, negative coping motives (drug use to cope with negative affect), craving, and current abstinence status. Significant correlations are indicated for each experiment in Table 13.1. Considered

together, these findings indicate that drug image choice in our task likely measures a latent variable common to these risk factors - the relative value ascribed to the drug – and is sensitive to variation in this value as a function of dependence severity.

This task has proved a valid methodological option for measurement of relative drug value across a range of subclinical and clinical populations, and in both smoking (one experiment) and alcohol (five experiments). This task is ethically appropriate to use with dependent populations, is simple to administer, and requires minimal participant literacy. In terms of application, the task might be used to identify manipulations to acutely raise drug value, modelling processes such as relapse, and interventions to limit these effects.

The null findings in two experiments in Chapter 10 provide some cause for concern. In these experiments, percent drug image choice did not significantly correlate with dependence or associated risk factors. This is surprising since these samples were of similar dependence severity to that in Chapter 6, which found significant correlations in an identical task with dependence, depression, and negative coping motives. Future research might investigate the conditions under which the pictorial choice task fails to adequately represent drug value and/or modifications to enhance its efficacy. However, the weight of evidence presented in this thesis generally supports the efficacy of this task.

Chapter	Drug	Population	Dependence	Depression	Anxiety	Negative coping motives	Craving	Abstinence status	Withdrawal intolerance
6	Alcohol	Hazardous drinkers	✓	✓	-	✓	-	-	-
7	Alcohol	Student drinkers	✓	n.s.	-	✓	-	-	-
8	Alcohol	Student drinkers	✓	✓	-	✓	-	-	-
9	Tobacco	Recently-hospitalised smokers	✓	✓	-	✓	✓	✓	-
10a	Alcohol	Hazardous drinkers	n.s.	n.s.	-	n.s.	-	-	-
10b	Alcohol	Hazardous drinkers	n.s.	n.s.	-	n.s.	-	-	-
11	Alcohol	Dependent drinkers	✓	✓	✓	✓	-	✓	✓
12	Alcohol	Student drinkers	✓	n.s.	n.s.	✓	-	-	-

Table 13.1 – Table showing significant correlations between percent choice of drug images at baseline and key variables, across studies. Columns show the chapter number, drug investigated, and population sampled. A tick indicates a significant correlation between the labelled variable and percent choice of drug images at baseline, following correction for multiple comparisons. n.s. indicates a non-significant correlation following correction. A dash indicates that this relationship was not tested.

13.3 The motivational effect of negative affect on drug choice

The third candidate mechanism investigated in this thesis was sensitivity to negative affective triggers. Negative reinforcement theories propose that negative affect should acutely raise drug motivation to mitigate this aversive state, and that drug-seeking behaviour may become increasingly controlled by this mechanism in the transition from recreational drug use to dependence (Baker et al. 2004; Heilig et al. 2010; Koob et al. 1997). The exact means by which negative affect promotes drug motivation is unclear, with negative reinforcement accounts based on both automatic (typically S-R) and intentional learning mechanisms (in which an augmented expected value of the drug promotes use). The third aim of this thesis was to verify the motivational effect of negative mood on drug motivation within our pictorial choice paradigm. A secondary aim was to distinguish between automatic and intentional accounts of this effect, since this could inform potential interventions.

A variety of methods were used to model negative affect driven drug motivation in this thesis. A block mood induction procedure with Velten negative affective statements (sometimes in conjunction with sad music) proved most reliable, significantly augmenting drug motivation in Chapters 6, 7, 10b, and 12. An intermixed procedure, in which both positive and negative affective statements were presented in randomly intermixed order, and drug choice measured following each statement, proved less reliable. Negative affective statements produced a significant increase in alcohol motivation amongst student drinkers with high negative coping motives (Chapter 8), but did not significantly augment drug choice in Chapters 9 or 10a with recently-hospitalised smokers and hazardous community drinkers, respectively. The intermixed procedure addresses a common criticism of block designs by controlling for time and/or fatigue effects, but may require a larger sample size owing to its smaller effect size. Finally, an aversive noise induction procedure significantly increased self-reported annoyance in an alcohol dependent sample, but did not significantly increase alcohol motivation (Chapter 11). This procedure was chosen in order to trial rehearsal of acceptance-based coping statements: an intervention practically incompatible with a statement-based mood induction procedure. This noise stress induction method did not prove effective in promoting alcohol choice.

In order to distinguish between automatic and intentional accounts of negative affect driven drug motivation, Chapter 8 used an outcome-revaluation procedure in which student drinkers chose concurrently between alcohol and chocolate points. Negative affective statements promoted a novel alcohol-seeking response in extinction, precluding control by S-R mechanisms. This finding indicates that negative affect driven alcohol seeking can be controlled by goal-directed, as opposed to automatic mechanisms, and that interventions which modify expected drug value within an intentional decision-making model may prove more effective than those which aim to modify implicit learning mechanisms.

If our intentional account is correct, an increase in drug choice under conditions of negative affect in our task should co-occur with a self-reported worsening of subjective mood, since we presume that this is the primary motivator of enhanced drug choice. Correspondence between subjective mood and drug choice was found in Chapters 6, 7,

10b, and 12. There were two findings of an incongruent relationship between mood and drug choice: in Chapter 11 a worsening of subjective mood (increased annoyance) was not associated with an increase in alcohol choice, and in Chapter 12 reduced alcohol choice in the high liking environmental enrichment intervention group was not associated with reduced negative affect. The finding in Chapter 12 is explicable given that the environmental enrichment intervention may have reduced alcohol's relative value by providing a source of alternative reinforcement, rather than by limiting negative affect. However, findings from Chapter 11 raise concerns about how accurately retrospective evaluation of mood represented participants' average emotional experience during the test phase. Future studies might instead use momentary assessment of mood.

Overall, a significant effect of experimentally-induced negative mood on drug motivation was found in five studies, indicating that our pictorial choice paradigm can reliably model negative affect driven drug motivation. This accords with a substantial body of evidence indicating a motivational effect of negative mood on both drug choice and other metrics of motivation including craving, demand, and actual consumption (Birch et al. 2004; Cooney et al. 1997; Cyders et al. 2016; Kelly et al. 2011; Rousseau et al. 2011; Rubonis et al. 1994; Willner and Neiva 1986). These findings also support negative reinforcement conceptions of dependence (Ahmed and Koob 2005), and extend knowledge by demonstrating that negative affect driven drug motivation can be controlled by intentional, as opposed to S-R, mechanisms. Finally, this method has practical advantages in providing a behavioural, as opposed to subjective, assay of drug motivation under conditions of negative affect, whilst avoiding the technical or ethical burden of actual consumption measures.

13.4 Individual differences in negative affect driven drug choice

If negative reinforcement theory is correct, dependence severity (and risk factors for dependence formation and maintenance) should be associated with increased sensitivity to negative affective triggers for drug-seeking. A secondary aim of this thesis was therefore to determine individual differences which predict sensitivity to negative affective triggers. Chapters 7, 8, and 11 found a significant correlation between negative affect driven alcohol-seeking and drinking to cope with negative

affect, Chapters 7 and 11 a significant correlation with symptoms of depression, and Chapter 11 a significant correlation with anxiety and withdrawal intolerance. These findings demonstrate that sensitivity to negative affect driven drug choice is associated with other risk factors for dependence. This is consistent with strong prior evidence that negative coping motives (i.e. a tendency to use the drug to cope with negative affect) are associated with enhanced sensitivity to negative affective triggers (e.g. Austin and Smith 2008; Rousseau et al. 2011), and provides supportive evidence for more mixed findings regarding the relationship between sensitivity to negative affective triggers and depression (Fucito and Juliano 2009; Hogarth et al. 2017). In Chapters 6 and 9, we failed to find a significant correlation between negative affect driven drug choice and depression or coping motives in a sample of hazardous drinkers and recently-hospitalised smokers, respectively. These findings may be explained by a lack of power and, in Chapter 9 specifically, our use of an intermixed mood induction procedure unsuitable for the population. Overall, then, our findings support a core prediction of negative reinforcement theory: that individuals who are vulnerable to dependence should also be more sensitive to negative affective triggers for drug use. It also delineates a high-risk group of individuals (with depression and/or who drink to cope) for whom negative affect may represent a substantial trigger to continued drug use.

Chapter	Drug	Population	Dependence	Depression	Anxiety	Negative coping motives	Abstinence status	Withdrawal intolerance
6	Alcohol	Hazardous drinkers	n.s.	n.s.	-	n.s.	-	-
7	Alcohol	Student drinkers	n.s.	✓	-	✓	-	-
8	Alcohol	Student drinkers	n.s.	n.s.	-	✓	-	-
9	Tobacco	Recently-hospitalised smokers	n.s.	n.s.	-	n.s.	n.s.	-
11	Alcohol	Dependent drinkers	✓	✓	✓	✓	n.s.	✓

Table 13.2 – Table showing significant correlations between negative affect driven drug motivation (change in percent drug choice between baseline and negative mood induction phases) and key variables, across studies. Columns show the chapter, drug investigated, and population sampled. A tick indicates a significant correlation between the labelled variable and negative affect driven drug motivation. n.s. indicates a non-significant relationship. A dash indicates that this relationship was not tested.

A concerning finding was that greater severity of dependence was associated with greater sensitivity to negative affect driven drug motivation in only one experiment in this thesis (dependent drinkers - Chapter 11). We might conclude on this basis that sensitivity to negative affective triggers is not as central a component to dependence formation and maintenance as supernormal drug valuation, which has been found to reliably correlate with dependence severity. There are a number of alternative interpretations, however. Firstly, measures of dependence used in this thesis (the Alcohol Use Disorders Identification Test in alcohol; the Nicotine Tolerance Questionnaire in smoking) are primarily measures of drug use frequency, and therefore may track enhanced drug value as a component of dependence more effectively than loss of control over drug use in response to negative triggers (Cooper 1994). Loss of control over drug use might be better captured with measures of negative coping motives, which we found did reliably correlate with negative mood induced drug-seeking. Secondly, the fact that negative affect driven drug motivation reliably correlates with depression and drinking to cope is itself suggestive of its contribution to dependence, since both of these traits predict dependence formation and relapse risk (Boschloo et al. 2013; Holahan et al. 2001). Finally, while our findings suggest that supernormal drug valuation may be the central mechanism by which drug use is maintained in dependence, negative affect driven drug motivation may contribute additional risk as a secondary process, particularly in high risk populations

with comorbid depression and who drink to address negative affect. In other words, while baseline supernormal drug valuation may represent the principal motivator of drug use, experience of negative affect may drive additional, acute spikes in motivation in sensitive individuals. In this way, negative affect driven drug choice may confer additional risk of relapse in depressed individuals and those with coping motives: there is indirect evidence that sensitivity to negative affective triggers predicts relapse in dependent drinkers (Brady et al. 2006; Cooney et al. 1997; Sinha et al. 2011). Sensitivity to negative affect driven drug motivation also correlates with abstinence-induced drug-seeking (Hogarth et al. 2017), which itself predicts relapse (Aguirre et al. 2015). Thus sensitivity to mood induced drug-seeking may represent a marker for sensitivity to abstinence induced drug-seeking, which is arguably a powerful driver of relapse. In any case, substantial evidence that negative affect frequently precedes relapse to drug use, and that experimentally-induced negative affect acutely raises drug motivation, provides sufficient incentive to develop brief rescue interventions to limit this effect.

13.5 Brief interventions to limit negative affect driven drug choice

The final aim of this thesis was to trial brief interventions to abolish or limit negative affect driven drug motivation. All interventions trialled were designed to be brief, cost-effective, and have prior evidence of efficacy. Indication of a therapeutic effect in these preliminary trials would justify further development and testing.

The first two interventions trialled (a natural walk intervention: two experiments in Chapter 10, and instruction in acceptance-based coping: Chapter 11) were chosen based on prior evidence of efficacy in limiting induced negative affect, with the expectation that this might translate into reduced alcohol motivation. In Chapter 10, neither indoor nor outdoor walk interventions in hazardous drinkers showed evidence of limiting negative affect driven alcohol motivation. In Chapter 11, we failed to find a significant effect of an aversive noise induction procedure on alcohol motivation in an alcohol-dependent population. However, brief instruction in acceptance-based coping showed no evidence of limiting negative affect in response to this stressor. These findings are inconsistent with previous evidence that acute exercise (Bernstein and McNally 2017a; b) and instruction in acceptance-based coping (Singer and Dobson

2007; 2009) can limit experimentally-induced negative affect. These findings accord more generally, however, with questions regarding the efficacy of substance dependence interventions which aim to limit negative affect. In particular, there is little evidence that antidepressant treatments are effective in improving abstinence in dependent individuals with comorbid depression (Kranzler et al. 2006; Pettinati et al. 2001).

The final intervention (environmental enrichment: Chapter 12) was chosen based on prior evidence of efficacy in limiting stress-induced alcohol seeking in rats (Marianno et al. 2017). Planned analyses indicated no significant difference in negative affect driven alcohol motivation between intervention and control groups. Post hoc analyses indicated, however, that engagement with pleasant images in the experimental group abolished negative affect driven alcohol choice in individuals who reported a desire to visit the locations shown (high liking), compared to low liking individuals and control participants. We might conclude that interventions which provide alternative sources of non-drug reinforcement, and thereby limit relative drug value, hold greatest promise in protecting against acute negative affect driven alcohol choice. This directly translates from findings in animal models of dependence (Chauvet et al. 2009; Marianno et al. 2017), and accords with evidence in humans that interventions which promote engagement with substance-unrelated sources of positive reinforcement improve abstinence rates (Daughters et al. 2018). However, there are a number of caveats. Firstly, the therapeutic effect of environmental enrichment only emerged in post-hoc analysis. Secondly, the sample was students, and the subgroup who showed a therapeutic effect had significantly lower scores on depression and drinking to cope with negative affect than those who showed no therapeutic effect, casting doubt on the applicability of this intervention to higher-risk populations with comorbidities. Individuals with lower depression and drinking to cope scores also typically show smaller induction effects than those with higher scores, which might explain the findings observed, although this explanation was ultimately excluded based on covariate analysis. Finally, there are a number of explanations for the therapeutic effect observed, including a distraction effect wherein attention to pleasant images displaced the negative affective stimuli in working memory. Future research should, firstly, trial

this procedure in a population with greater alcohol dependence severity and, if effective, conduct studies to elucidate the underlying mechanism of action.

An additional strand of research might aim to develop interventions to modify negative coping motives, since these beliefs are reliably related to dependence (Holahan et al. 2001; Kassel et al. 2000) and sensitivity to negative affect driven alcohol motivation (Austin and Smith 2008; Birch et al. 2004; Field and Quigley 2009; Hogarth and Hardy 2018; Hogarth et al. 2018). The majority of interventions which aim to manipulate coping motives do so in the context of long-term, individualised CBT programmes (e.g. Kushner et al. 2013; Litt et al. 2003), making them difficult to test in short experimental studies such as those in this thesis. However, Blevins and Stephens (2016) found that a brief intervention in which students received feedback on their endorsement of coping motives, as well as education in alternative coping strategies, significantly reduced alcohol consumption. Such an intervention could be trialled in its ability to reduce negative affect driven alcohol motivation using our pictorial choice model.

13.6 Concluding remarks

Overall, this thesis fulfilled its aims to various extents: first, in assessing the contribution of cue reactivity, cost discounting, and sensitivity to negative affect to dependence. While cue reactivity and cost discounting both acutely motivate drug-seeking, supernormal drug value was found to be more reliably associated with dependence severity. This is consistent with behavioural economic conceptions of dependence. Negative affect acutely raised drug motivation, and individuals who were depressed and used the drug to cope were particularly vulnerable to this effect, consistent with negative reinforcement theory. Since negative affect driven drug motivation did not consistently correlate with dependence, we might consider sensitivity to negative affect to confer additional risk to dependence and relapse alongside supernormal drug valuation.

Secondly, this thesis fulfilled its aim of developing a novel pictorial choice measure of drug value, suitable for use with clinically-dependent populations. Percent choice of drug images over alternative reinforcement was reliably associated with severity of dependence, and associated risk factors, across a range of clinical and sub-clinical

populations. This task might be used to investigate manipulations to acutely raise drug value, modelling processes such as relapse, and also interventions to limit these effects.

Finally, this thesis aimed to assess the efficacy of brief novel interventions to limit or abolish negative affect driven drug motivation. While none of the interventions trialled proved definitively effective, this nevertheless provides useful information regarding the optimal combination of induction methods and treatment protocol. An environmental enrichment intervention proved most promising. We might predict, overall, that interventions which raise the value of competing alternatives to drugs may prove most effective in protecting against negative affect driven drug-seeking. In treatment of dependence more generally, we might predict a shift in emphasis towards broader, societal-level interventions to improve quality of life and access to sources of positive reinforcement.

Appendix A. Evaluation of the Peninsula Alcohol and Violence Programme (PAVP) with violent offenders

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Abstract

There is clear experimental evidence for a causal link between alcohol misuse and violent behaviour. Treatments for alcohol misuse with offenders are therefore justified on the grounds that they may reduce violent behaviour and thus re-offending. The current paper tested whether a 10-session CBT intervention with offenders still in prison would produce improvements across three time points (pre, post and follow up) in self-reported alcohol expectancies, aggressiveness, impulsivity, and self-efficacy in managing alcohol use and violent behaviour. The programme focused on educating participants on the relationship between alcohol use and violence, modifying unhelpful cognitions, and providing skills based training to manage potential triggers. Data from 49 offenders in prison were collected pre-intervention, post-intervention, and at three month follow up. Long term improvements (from pre- to post-intervention and follow up) were observed with respect to alcohol expectancies (in terms of sociability and liquid courage), impulsive responding to negative affect triggers, trait anger, and confidence in managing alcohol use and offending behaviour. These findings provide preliminary evidence for the efficacy of the CBT programme in reducing harmful alcohol use and associated violence. Limitations and recommendations for future evaluation of the intervention are discussed.

Introduction

There is clear evidence for a link between alcohol misuse and violent behaviour. The Office of National Statistics (2015) reports that 53% of violent incidents between adults involve alcohol, and increasing alcohol abuse is associated with significantly greater rates of violent offending behaviour (Schuckit and Russell 1984; Fergusson and Horwood 2000). A number of experimental studies have also demonstrated that alcohol administration promotes violent behaviour (Bushman and Cooper 1990; Martin 2001; Boden et al. 2013). This evidence suggests that treatments for alcohol misuse with offenders, a population with elevated rates of alcohol dependence (Fazel et al. 2006), may be justified on the grounds that they will reduce violent behaviour and subsequent reoffending.

Interventions with offenders have largely used a cognitive behavioural therapy (CBT) approach, focusing on either alcohol use or anger management in isolation (Henwood et al. 2015; Needham et al. 2015). Anger management programmes aim to reduce anger and associated arousal on the basis that these states often precipitate violent behaviour (Gilbert and Daffern 2010; Novaco 2011). CBT interventions of this type aim to assist clients in identifying dysfunctional cognitions and behaviours related to aggression and replacing them with adaptive alternatives (Deffenbacher 2011), in identifying high-risk situations (relapse prevention - Prisgrove 1991) and in developing coping skills to minimise arousal in such high-risk situations, including breathing techniques (Deffenbacher 2011; Novaco 2011). This approach appears to be effective in reducing violent recidivism. Specifically, a meta-analysis and systematic review by Henwood et al. (2015) found that exposure to CBT based anger management in adult male offenders reduced risk of violent recidivism by 28%, while full completion of treatment reduced risk by 56% (but see Watt and Howells (1999) for a null finding). In general, interventions of longer duration have been found to be more effective in reducing violent offending, as have those that targeted cognitive skills, anger control, relapse prevention, and incorporated homework for offenders (Jollliffe and Farrington 2007).

Programmes targeting alcohol use with offenders are more varied, and incorporate brief interventions to minimise hazardous or harmful drinking (Newbury-Birch et al. 2014), as well as more intensive CBT based group interventions (Needham

et al. 2015). Three key interventions are the Low Intensity Alcohol Program (LIAP); the Alcohol Specified Activity Requirement (ASAR); and the Addressing Substance-Related Offending Program (ASRO). The ASRO has four key components: increasing motivation to change, developing self-control, relapse prevention, and encouraging lifestyle change (Palmer et al. 2011). A review by Needham et al. (2015) of these three cognitive behavioural alcohol treatment programmes found that offenders who completed a programme were 2.5 times less likely to re-offend than those who did not participate, and these programmes were effective for both violent (crimes against persons) and non-violent offenders. In addition, the Prison Addressing Substance-Related Offending (P-ASRO) – an adaption of the ASRO in prisons – showed improvements from pre- to post-intervention in offender locus of control, impulsiveness, problem solving and motivation to change drug use behaviour (Crane and Blud 2012).

The foregoing evidence suggests that separate CBT programmes for alcohol and violence produce improvements in a range of subjective and behavioural outcome measures. Given the causal link between alcohol and violence, it is possible that a combined CBT programme that targets both problems simultaneously might be a cost-effective approach for delivering treatment to offenders in prison. Consistent with this view, at least one study has provided preliminary evidence that combined treatment addressing both substance abuse relapse prevention and violence is more effective in reducing recidivism than relapse prevention alone (Marquis et al. 1996). One other programme, the Control of Violence for Angry Impulsive Drinkers (COVAID) programme, has sought to address alcohol and violence simultaneously. COVAID is a group-based CBT implemented with repeat offenders currently in the community, which instructs in a range of topics including anger self-monitoring, stress management, problem solving, expectations of alcohol in relation to violent behaviour, relapse prevention, and crime reduction. Pilot data has shown that the COVAID programme has a positive impact on alcohol self-efficacy (i.e. greater confidence in reducing consumption), beliefs about controlling alcohol-related aggression, confidence in social problem solving, anger control and actual re-offending rates (McMurran and Cusens 2003; McCulloch and McMurran 2008). In addition, an RCT of COVAID found that, 17 months post release, 13% fewer participants in the COVAID

programme were reconvicted for a violent offence compared to controls (Bowes et al. 2014). Intermediate outcomes of this trial also indicated significant improvements in alcohol-related aggression beliefs and alcohol self-efficacy, but not state or trait anger (Bowes et al. 2012).

The current study provides an evaluation of the Peninsula Alcohol and Violence Programme (PAVP) – a programme similar to COVAID in that it aims to target violence alongside alcohol use. Specifically, the PAVP aims to use components of CBT to teach offenders skills to identify and modify unhelpful cognitions relating to violence, to monitor and appropriately respond to anger, to identify maladaptive aggressive and drinking behaviour and increase motivation to change, and to provide alternative strategies to respond to high risk situations for violence. This programme was run with offenders in prison who at pre, post and follow up time points completed a set of questionnaires assessing alcohol expectancies, alcohol-related aggression, self-efficacy in control of alcohol use, depression and anxiety, impulsivity, anger, and control over drug use, alcohol use, and offending behaviour. We anticipate improvements on these measures given that other similar CBTs have reported improvements in self-reported alcohol expectancies, alcohol-related aggression, self-efficacy, control of anger, and impulsivity (Deffenbacher et al. 1996; McMurran and Cusens 2003; McCulloch and McMurran 2008; Young et al. 2011). Measures of depression and anxiety were also taken pre-intervention, post-intervention, and at follow up to establish any transfer of skills from the PAVP, and because these traits are elevated in offender samples (Deffenbacher et al. 1996; Bland et al. 1998). Demonstration of an improvement following this intervention, from pre to post and follow up time points, would provide preliminary support for the efficacy of the PAVP programme, and would justify further research to test whether the intervention is superior to a control procedure on more direct outcome measures such as post-release alcohol use, violence, and re-offending, within a randomised controlled trial.

PAV Programme

The PAVP incorporates ten structured group-work sessions ideally run over a month, each lasting roughly 2.5 hours. The programme focused on five key elements listed below (the specific topics covered in each of the 10 sessions are described in full in supplementary materials): (1) Alcohol psychoeducation. This element of the

programme focused on educating participants on safe levels of drinking, strategies for achieving controlled drinking or abstinence, and the relationship between alcohol and violent behaviour. Alcohol psychoeducation interventions in learning disabled offenders have driven increases in motivation to change drinking behaviour, knowledge, and self-efficacy (Burns et al. 2011). (2) Relapse prevention, adapted for prevention of violent behaviour. Clients were taught a number of cognitive skills, including identification of the sequence of behaviours which typically precede aggression or violence, recognition of high-risk situations, and development of adaptive responses to prevent aggressive behaviour (Marlatt and Gordon 1985; Prisgrove 1991). The focus was on understanding alcohol use as a precipitant of violence, and developing behaviours to avoid or respond adaptively to alcohol-related high-risk situations. Relapse prevention has shown efficacy both in treatment of problematic alcohol use (Irvin et al. 1999), and in reducing recidivism (Dowden et al. 2003) and anger in offenders (Dowden and Andrews 2000). (3) Cognitive restructuring. PAVP aimed to teach participants to recognise and modify unhelpful thought patterns common in high-anger individuals, which may contribute to violence in high-risk, alcohol-related situations (Dodge et al. 1990; Ford 1991; Epps and Kendall 1995; Stuckless et al. 1995). Cognitive restructuring of this type has been shown to be effective in reducing anger and aggressive and impulsive behaviours, and improve social problem solving (Guerra and Slaby 1990; Hudley and Graham 1993). (4) Assertiveness training. This aims to provide clients with appropriate, non-aggressive ways in which to express negative emotion (Rahaim et al. 1980). Social skills training of this type has shown significant positive effects on trait and expression of anger, and anger-related physiological arousal in student samples (Deffenbacher et al. 1994; Deffenbacher et al. 1995). (5) Self-monitoring and management of arousal. Participants were given skills based training to self-monitor and manage arousal, including relaxation training (Hazaleus and Deffenbacher 1986). Relaxation training is predicated on evidence that association of relaxation with arousing stimuli should reduce subsequent anger (Bowman Edmondson and Cohen Conger 1996). Anger control training has shown positive effects on recidivism (Lipsey et al. 2007), and relaxation training specifically has shown efficacy in reducing self-reported and physiological anger (Bowman Edmondson and Cohen Conger 1996).

In addition to the ten core therapeutic sessions, there were three one-to-one keyworker sessions: one prior to and two during the therapeutic programme. In-cell work after each session was required to prepare for the subsequent session. Pre-intervention questionnaire data was collected in a single group session a week prior to commencement of the programme. Post-programme questionnaire data was collected in a single group session on the afternoon of the final therapeutic session, while follow up questionnaire data was recorded in a single group session three months later.

Materials and Method

Ethics Statement

All participants provided informed consent prior to participation in the programme. The study was approved by the HMPPS National Research Committee (NRC) and the National Health Service Research Ethics Committee.

Participants and handling of missing data

Participants were prisoners attending the Peninsula Alcohol and Violence Programme. All questionnaire data were collected in prison. Analysis was performed on 49 participants who participated in the PAV programme. The proportion of participants completing questionnaire data at one, two, and all three time points was 100%, 82% and 57%, respectively. The proportion of participants who contributed pre-intervention, post-intervention, and follow up questionnaire data was 96%, 82% and 61% respectively. Missing data were replaced by the median of the aggregate questionnaire subscales calculated from data available at each time point. The high frequency of missing data at follow up limits confidence in the findings from this time point (combined with the confounding effects of time). Consequently, the pre and post time points are the primary focus for evaluating the potential impact of the programme.

It is important to test whether participants with missing data were systematically different from those who completed all three time points. A difference in pre-intervention between these groups would suggest that the estimated treatment effects of the programme could be biased (overestimated) by the selective attrition of participants whose data is replaced by the median of those remaining. By contrast, equivalence between these groups at pre-intervention would suggest that selective

attrition and missing value replacement did not bias the estimated treatment effects. To this end, we contrasted the pre-intervention questionnaire data (including adjudications) of participants who completed questionnaires at all three time points versus participants who missed either post or follow up measures. There was no significant difference at pre-intervention between these groups when contrasts were corrected using the Bonferroni-Holm method (the contrast of the Alcohol Self-Efficacy social subscale was significant uncorrected, $F(1,45)=4.69$, $p=.036$, and all other measures were non-significant uncorrected $Fs \leq 2.97$, $ps \geq .092$). This analysis suggests that the estimated treatment effects were not biased by selective attrition of participants. Various factors were responsible for non-completion of questionnaires, including transfer mid-programme to a different prison, release, poor health and self-removal. The data included in this study are from four programmes in a single prison.

Recruitment for the PAVP was focused on individuals who were classified as at medium or greater risk of reoffending, and who had a history of alcohol-related violence. Risk of reoffending was determined using the Offender Group Reconviction Scale (OGRS3) (Howard et al. 2009) which predicts risk of reoffending within 2 years of discharge from custody using age, gender, and criminal history. Criterion for a history of alcohol-related violence was at least two instances of alcohol-related violence which were not sexual or domestic in nature. Offenders were nominated for inclusion by their substance misuse recovery worker or by offender supervisors. Priority was given to those who were closer to being released, and each programme was a closed group with capacity for 12 offenders.

Demographic measures

Participants completed a self-report measure of historical head injury. In this, participants indicated whether they had experienced a head injury which caused them to be knocked out, dazed or confused; how many head injuries of this type they had experienced; severity of head injury; the last occasion of head injury; and severity of post-injury symptoms. Data from participants regarding their age, ethnicity, adjudications during prison, substance use, mental health conditions, and medication used in treatment of alcohol dependence (disulfiram or naltrexone) were extracted from the Prison National Offender Management Information System (P-NOMIS).

Questionnaire measures

All measures were administered prior to the programme's commencement, immediately following the programme's completion, and three months post completion, to provide an indication of whether change was maintained over time. Measures obtained at these three time points were the Alcohol Expectancy Questionnaire (AEQ - Brown et al. 1987); the Alcohol Related Aggression Questionnaire (ARA - McMurran et al. 2009); the Alcohol Abstinence Self-Efficacy Scale (AASE - DiClemente et al. 1994); the Mood and Anxiety Symptom Questionnaire (MASQ - Watson et al. 1995); the UPPS Impulsive Behaviour Scale (UPPS - Whiteside and Lynam 2001); the State Trait Anger Expression Inventory – 2 (STAXI-2 - Spielberger 2010), and the Drug and Alcohol Outcome Star (DAOS - Burns and MacKeith 2012). Questionnaires and individual subscales are described in greater detail in supplementary materials.

Analytical plan

A repeated measures ANOVA was conducted on each individual questionnaire subscale to test for any change across the three time points (pre, post, and follow up). ANOVAs were corrected for type 1 errors due to multiple comparison using the Bonferroni-Holm method (Holm 1979). The p value and effect size (partial eta squared) of ANOVAs is reported above the corresponding bars in Figure 1A. A significant main effect of time in each of these ANOVAs (above the Bonferroni-Holm corrected threshold) was followed by three repeated-measures t-tests comparing each time point against one another. Significant differences between time points are indicated in the graphs with asterisks. The results are described in four groups based on the interpretation they offer. 1. A possible sustained therapeutic effect was proposed where a questionnaire scale showed an improvement at both the post-intervention and three month follow up time points compared to pre-intervention (i.e. a short term improvement that was sustained). 2. A possible short term therapeutic effect was proposed where a questionnaire scale showed an improvement at the post-intervention time point compared to pre-intervention, but not at the three month follow up time point (i.e. a short term improvement that was not sustained). 3. A change due to time related factors was assumed to have occurred when questionnaire scales showed no difference between the pre-intervention and post-intervention time points, but follow

up differed from either the pre- or post-intervention time point. In this case, the change at follow up is assumed to have been driven by time related factors, rather than a delayed therapeutic effect. 4. No evidence of a change was concluded where there was no difference between any of the three time points. We were primarily interested in the possible sustained therapeutic effects as preliminary evidence of the intervention's efficacy. As noted above, missing values were replaced with the sample median for each questionnaire subscale, and as such the degrees of freedom for all ANOVAs were (2, 96), and (48) for the t-tests. Figures show mean scores on each subscale represented as a proportion of the total possible score to facilitate comparison of the numerical magnitude of changes.

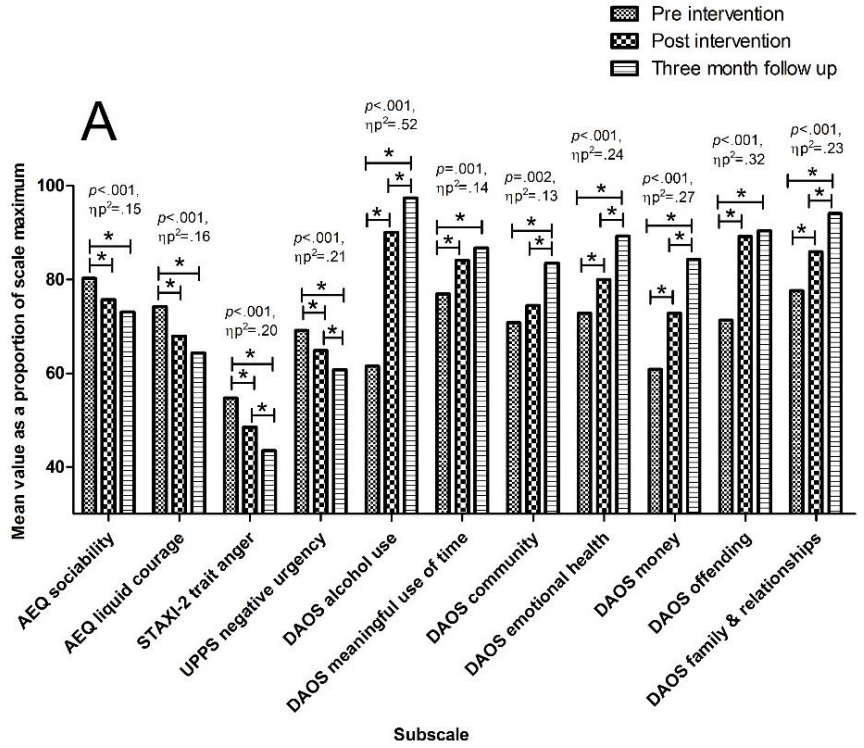
Results

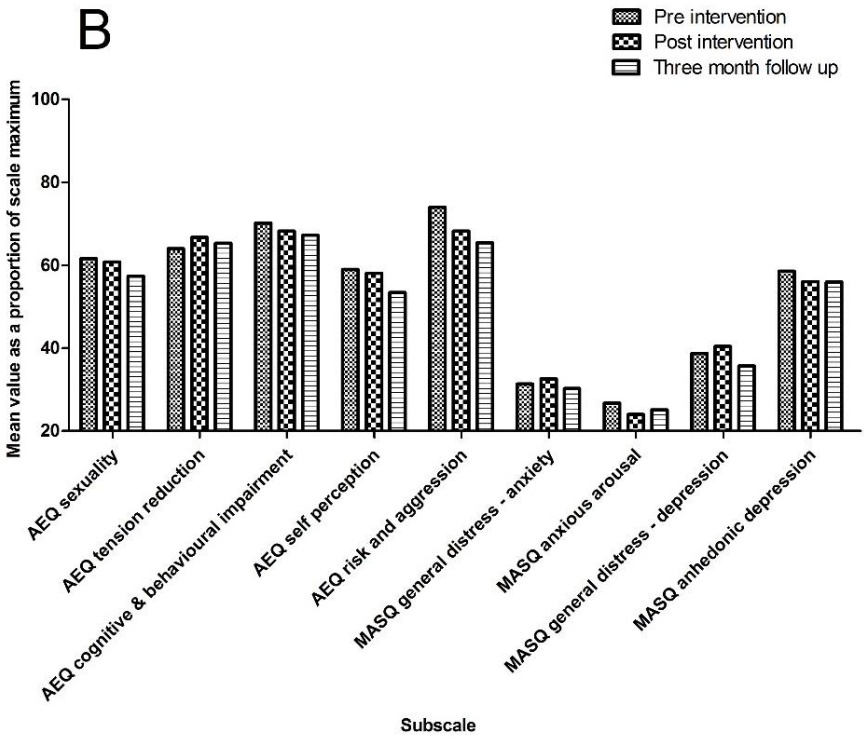
Sample demographics

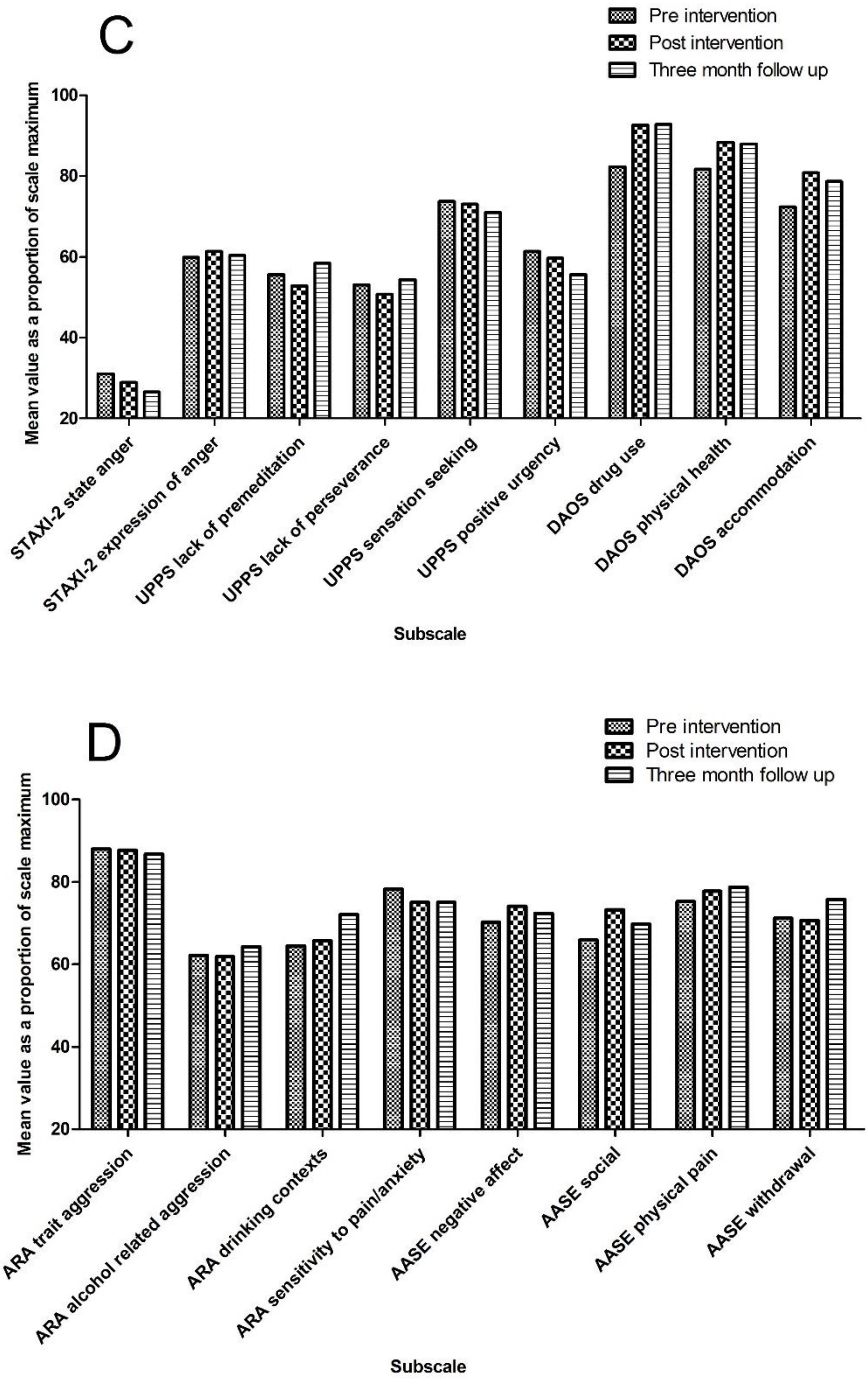
Key characteristics of the sample relating to age, ethnicity, head injury, adjudications, and mental health are shown in Table 1.

Age & Ethnicity	
Age of sample, *M* (*SD*, range)	34.81 (12.97, 22-71)
Proportion of sample who identified as White British, %	98
Prevalence of head injury	
Ever had head injury in which you were knocked out and/or dazed and confused, %	70
Number of head injuries amongst those who answered yes, *M* (*SD*)	4.39 (4.57)
Severity of head injury	
Lost consciousness during worst injury, %	71
Symptoms experienced after worst injury, % none, mild, moderate, severe	38, 13, 38, 13
Time since last injury in months, *M* (*SD*)	75.07 (83.10)
Adjudications	
At least one reported adjudication prior to programme commencement, %	57
Number of adjudications, *M* (*SD*)	5.32 (9.88)
Mental health	
Number of participants with recorded substance use (including tobacco but not alcohol), %	85
Number of participants with a recorded mental health issue, %	57
Number of participants using either disulfiram or naltrexone for alcohol dependence, %	9

Table 1. Characteristics of the sample


A
Pre intervention
Post intervention
Three month follow up
Mean value as a proportion of scale maximum
100
80
60
40
p<.001, ηp²=.15
p<.001, ηp²=.16
p<.001, ηp²=.20
p<.001, ηp²=.21
p<.001, ηp²=.52
p=.001, ηp²=.14
p=.002, ηp²=.13
p<.001, ηp²=.24
p<.001, ηp²=.27
p<.001, ηp²=.32
p<.001, ηp²=.23
AEQ sociability
AEQ liquid courage
STAXI-2 trait anger
UPPS negative urgency
DAOS alcohol use
DAOS meaningful use of time
DAOS community
DAOS emotional health
DAOS money
DAOS offending
DAOS family & relationships
Subscale


B
Pre intervention
Post intervention
Three month follow up
Mean value as a proportion of scale maximum
100
80
60
40
20
AEQ sexuality
AEQ tension reduction
AEQ cognitive & behavioural impairment
AEQ self perception
AEQ risk and aggression
MASQ general distress - anxiety
MASQ anxious arousal
MASQ general distress - depression
MASQ anhedonic depression
Subscale



Figures 1A to D. Mean scores for each subscale pre-intervention, post-intervention, and at three month follow up. All scores are represented as a proportion of the total possible mean score to facilitate comparison across different questionnaire measures. Figure 1A shows subscales that showed a significant change across the three time points. In all questionnaires apart from the DAOS and AASE, a reduction in number represents an improvement in that construct. Note that all effects are potential sustained therapeutic effects of the intervention (improvement from pre to post and follow up) apart from DAOS community, which is a potential time-based effect (change at follow up, but not from pre to post). Asterisks indicate significant t-test results. P values and partial eta squared values are shown for significant ANOVAs which survived a Bonferroni Holm correction. Non-significant ANOVAs following correction for multiple comparisons: Fs≤ 6.31, ps≥.004. AEQ = Alcohol Expectancy Questionnaire; DAOS = Drug and Alcohol Outcome Star; MASQ = Mood and Anxiety Symptom Questionnaire; STAXI-2 = State Trait Anger Expression Inventory – 2; UPPS = UPPS Impulsive Behaviour Scale; ARA = Alcohol Related Aggression Questionnaire; AASE = Alcohol Abstinence Self-Efficacy Scale.

Possible sustained therapeutic effects

As shown in Figure 1A, there were possible sustained therapeutic effects (improvement from pre to post and follow up) with respect to the sociability and liquid courage subscales of the Alcohol Expectancy Questionnaire (AEQ), the trait anger subscale of the State Trait Anger Expression Inventory - 2 (STAXI-2), and the negative urgency subscale of the UPPS Impulsive Behaviour Scale. In the Drug and Alcohol Outcome Star (DAOS), there was a possible sustained therapeutic effect of the intervention on self-reliance with respect to alcohol use, meaningful use of time, emotional health, money, offending, and family and relationships. Two other aspects of the DAOS (drug use and physical health) initially showed significant improvement, but did not survive adjustment for multiple comparisons.

Possible short term therapeutic effects

No measures showed a significant initial improvement pre- to post-intervention which was not sustained at three month follow up.

Possible changes due to time

Measures which showed no evidence of improvement from pre- to post-intervention, but a significant change at follow up relative to either of the first two time points, were interpreted as driven by time rather than the intervention. The community measure of the DAOS showed a significant improvement pre-intervention to follow up and post-intervention to follow up, but not pre- to post-intervention (Figure 1A). Measures which initially showed this effect, but did not survive adjustment for multiple comparisons were: AEQ risk and aggression (Figure 1B), STAXI-2 state anger, UPPS lack of premeditation, and UPPS positive urgency (Figure 1C), and ARA drinking contexts (Figure 1D). Given that these measures did not change immediately following treatment, any improvements observed are unlikely to have been driven by the programme.

No evidence of therapeutic improvement

There were no significant changes across the three time points in the remaining subscales represented in Figures 1B to 1D. This was either due to insensitivity of the questionnaire, or lack of therapeutic effect on the dimension measured by the questionnaire.

Discussion

The PAVP was developed as a cognitive behavioural intervention to reduce recidivism in offenders with a history of alcohol-related violence. This programme aims to educate on the relationship between alcohol and violence, to modify maladaptive cognitions and behaviours related to alcohol and aggression, and to motivate change, with the ultimate aim of reducing future reoffending. Questionnaire data was collected in one prison to establish whether the programme led to an improvement in various related aspects of offender attitudes and behaviour. Participation in the PAVP programme was found to be associated with significant improvements on a number of questionnaire measures across the three time points at which measures were taken.

Ten possible sustained therapeutic effects of the programme (from pre to post and follow up time points) were observed after correction for multiple contrasts. These were a reduction in the expectation that alcohol would improve sociability and courage in the Alcohol Expectancy Questionnaire; a reduction in trait anger in the State Trait Anger Expression Inventory – 2; and a reduction in the belief that negative emotions would trigger impulsive behaviours (for example, 'In the heat of an argument, I will often say things that I later regret') in the UPPS Impulsive Behaviour Scale. These improvements appeared immediately post-intervention and were sustained at three month follow up. These improvements are promising given the stated aim of the PAVP to reduce maladaptive alcohol use and violent behaviour. These improvements also corroborate related CBT evaluation studies which have found improvements in beliefs about controlling alcohol-related aggression, confidence in social problem solving, and re-offending rates (McMurran and Cusens 2003; McCulloch and McMurran 2008; Bowes et al. 2014), and locus of control, impulsiveness, problem solving and motivation to change drug use behaviour (Crane and Blud 2012), and expression of anger (Trimble et al. 2015).

Sustained improvements were observed on the Drug and Alcohol Outcome Star (DAOS) in six areas: self-reliance in managing alcohol use, meaningful use of time, emotional health, money, offending, and family and relationships. Of the ten areas assessed, the alcohol use and offending axes are two of the key target areas of the PAVP. We can therefore conclude that the PAVP improved the dimensions it hoped to improve, but also had a wider impact on self-reliance amongst participants. In other

words, improvements in other aspects of the DAOS not directly targeted by PAVP may represent an additional benefit of this programme, although this cannot be concluded definitively in the absence of a control group.

It is important to note that a number of subscales did not show any significant changes pre- to post-intervention, where they might have been expected. In particular, participants did not show any significant improvements on any of the four Alcohol Abstinence Self Efficacy subscales (ability to control drinking during social occasions, during negative affect, when experiencing physical pain, and when experiencing withdrawal). This is counter to what might be expected given that the PAVP aims to increase confidence in abstinence. In contrast to this finding, evaluations of COVAID by McCulloch and McMurran (2008) and Bowes et al. (2012) found significant improvements in self-efficacy, indicating that the PAVP may not currently be targeting this construct effectively. While the PAVP currently focuses to a large extent on reducing triggers to violence when drunk, it may also do well to introduce skills based training to reduce initial drinking behaviour under negative (e.g. when sad, experiencing pain or unpleasant symptoms of withdrawal) or positive (e.g. during social occasions) conditions. There is good evidence that negative states in particular have a significant impact on motivation to drink (e.g. Hardy and Hogarth 2017; Hogarth and Hardy 2018; Hogarth et al. 2018), and therefore this is a worthwhile target of treatment which the PAVP does not currently appear to address.

We also failed to observe significant changes pre- to post-intervention in a number of other questionnaire measures, including all subscales of the Alcohol Related Aggression Questionnaire (ARA), and two subscales of the State Trait Anger Expression Inventory – 2 (STAXI-2). These findings suggest that the PAVP did not have the anticipated effect on these aspects of aggression. The failure to observe a change in state anger on the STAXI-2 might be reasonably attributed to a floor effect, given the positively skewed distribution of scores pre-intervention. The null findings for the ARA, however, represent a failure to replicate McCulloch and McMurran (2008)'s findings in COVAID. It may be the case that measuring such changes in aggression would be more appropriately done following release - as was the case in the COVAID study - when prisoners have had the opportunity to implement the coping skills taught in PAVP. Alternatively, PAVP may benefit from providing greater

opportunity for offenders to practice or role play anger management skills learnt in-session (as in Anger Control Training, for example - Sukhodolsky et al. 2009).

In evaluating the mental health benefits of PAVP, it is noteworthy that we found non-significant improvements in the Mood and Anxiety Symptom Questionnaire, which contains four subscales assessing anxiety and depression. The implication is that PAVP did not have a benefit on these aspects of mental health, and so might be developed to include a brief intervention for anxiety and depression. No therapeutic effect was also observed for four subscales within the UPPS Impulsive Behaviour Scale (lack of perseverance, lack of premeditation, sensation seeking, and positive urgency). These findings are consistent with Aboulafia-Brakha et al. (2013), who observed no change in the UPPS measure following a cognitive behavioural intervention for anger in those with traumatic brain injury (TBI). Given the inflated rates of TBI in our sample, impulsivity may represent a more enduring trait, less amenable to change by this intervention. We did, however, observe a significant improvement in one aspect of impulsivity on the UPPS – negative urgency.

The key limitation of this study was the lack of a control group. This was due to the unethical nature of recruiting offenders for an intervention which has no known therapeutic effect (the control group), when resources and access to treatment are limited in this population. As a consequence, however, we cannot conclude that the improvements over time points were driven by the PAVP programme, as opposed to other factors such as the passage of time, incarceration etc. The fact that a consistent pattern of improvements has been observed across participants in a number of programme-relevant areas can increase our confidence that these changes are driven by the programme rather than alternative confounding variables. It is important to note that all follow up data were collected while participants were still in prison, and therefore any effects observed in follow up are not confounded by release.

A second limitation concerns missing data. The transient nature of a prison population and measurement at three independent time points increases the likelihood of missing data when conducting this type of study. In order to retain power and therefore allow a clearer understanding of trends in questionnaire measures over time, missing data on aggregate questionnaire subscales was replaced by a median score from data available at each time point. By replacing missing values we can statistically

compare time points without omitting clients, thus improving the accuracy of the estimate of changes across time. However, it is important to note that missing data was particularly concentrated around the follow up time point, and therefore improvements observed here must be treated with caution, especially given the confounding effect of time and lack of a control group. In short, we may have less confidence in the sustained nature of the proposed therapeutic effects due to the high rates of missing values at follow up.

A final limitation concerns the possibility of social desirability bias. Offenders may be motivated to present themselves positively post-intervention, particularly if they believe that the outcome of the intervention will affect their legal status (Andrews and Meyer 2003; McEwan et al. 2009; Fernandez et al. 2017). The fact that we observed improvements in a small number of subscales relevant to the PAVP, while other measures where positive self-presentation might have been expected (for example, expression of anger) showed no such change, reduces the likelihood that these changes were driven by a generalised social desirability effect.

In conclusion, the PAVP was developed to target a gap in current prison services to support offenders with a history of alcohol-related violent offending. The programme specifically addressed triggers and coping mechanisms for these behaviours in the hope of reducing re-offending rates after release from prison. We found improvements in expectations of alcohol (in terms of sociability and liquid courage), impulsivity (in terms of negative urgency), and trait aggression, as well as increased self-reliance in management of alcohol and offending. While these improvements cannot be attributed definitively to participation in the programme, these findings provide preliminary evidence for PAVP's efficacy and justify a future randomised controlled trial to fully evaluate its effectiveness.

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