UNIVERSITY OF SOUTHAMPTON

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Psychology

An Investigation of Learning Mechanisms in the Alcohol Cue-Exposure Therapy Paradox

by

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ABSTRACT

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Cue exposure therapy as a treatment programme for alcohol addiction has not been shown to have to same level of success as it has for treating other behavioural disorders. This discrepancy is referred to in this thesis as the *Alcohol Cue Exposure Therapy Paradox* (ACETP). This thesis explored several candidate explanations for the ACETP. Chapters 3 and 4 examined individual differences in acquisition, extinction, and recovery of Pavlovian conditioned responses in light, heavy, and dependent drinkers. Light and heavy drinkers did not differ but dependent drinkers showed slower extinction than light drinkers. Chapter 5 examined the effect of reinforcer type, food versus alcohol, on the acquisition, extinction, and recovery of Pavlovian conditioned responses in light and heavy drinkers. There was no evidence of differences between light and heavy drinkers with respect to conditioning with different reinforcer types and there was no difference in conditioning with the different reinforcer types. Chapter 6 looked at Pavlovian instrumental transfer (PIT) using different reinforcer types, food and alcohol, and compared light and heavy drinkers. In the Pavlovian phase of the Chapter 6 PIT study there was no evidence of differences between light and heavy drinkers with respect to conditioning the different reinforcer types, replicating the results from previous chapters. There was also no evidence of differences between light and heavy drinkers on PIT. However, conclusions about individual differences and effects of reinforcer type on devaluation were not possible due to a failure

to obtain a devaluation effect. In summary these studies suggest that the ACETP cannot be understood to be due to a peculiarity of alcohol as a reinforcer nor can it be understood in terms of individual differences in PIT. Nevertheless, individual differences in Pavlovian extinction do suggest a route for further enquiry. Dependent drinkers are slower to extinguish Pavlovian conditioned responses. The implication is that cue-exposure treatments for alcohol dependence may need extending in order to achieve adequate extinction of conditioned responses to alcohol cues.

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Research Thesis: Declaration of Authorship

Print name:	Carl Buckfield

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I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
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6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. None of this work has been published before submission

Signature:		Date:	20/06/2019

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Carl Buckfield

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An Investigation of Learning Mechanisms in the Alcohol Cue-Exposure Therapy Paradox

Chapter 1

Introduction and Theoretical Background
The Alcohol Cue-Exposure Therapy Paradox: A Review of the Current Research and Theory

1.1 Introduction

1.1.1 Associative learning

Associative learning is the process of acquiring knowledge of the predictive or causal link between two events. Contemporary theories state there are two types of associative learning: Pavlovian (or classical) conditioning and instrumental (or operant) conditioning (Rescorla & Soloman, 1967). Pavlovian conditioning is the formation of links between mental representations of environmental stimuli and another stimulus, the occurrence of which is contingent on the presence of the environmental stimuli; this is often referred to as stimulus-outcome pairing. For these associations to develop a conditioned stimulus (CS) must be contingently presented with an unconditioned stimulus (US). An US is a biologically relevant stimulus that produces an involuntary unconditioned response (UR). A CS can potentially be any stimulus in the environment that, prior to conditioning, produces responses unrelated to the UR processes. When the CS-US are reliably presented together, the CS develops the capacity to produce a conditioned response (CR) similar to that of the UR, but in the absence of the US. Demonstrated in a concrete example with Pavlov's (1927) seminal experiments: Food (US) produces salivation (UR). An auditory stimulus e.g. tone of a tuning fork (CS) prior to learning produces nothing, but an investigatory reflex. However, after repeated reliable pairings of tone and food (CS-US), the tone elicits salivation in the absence of food (CR). A schematic of Pavlovian conditioning is represented in Figure 1.1.

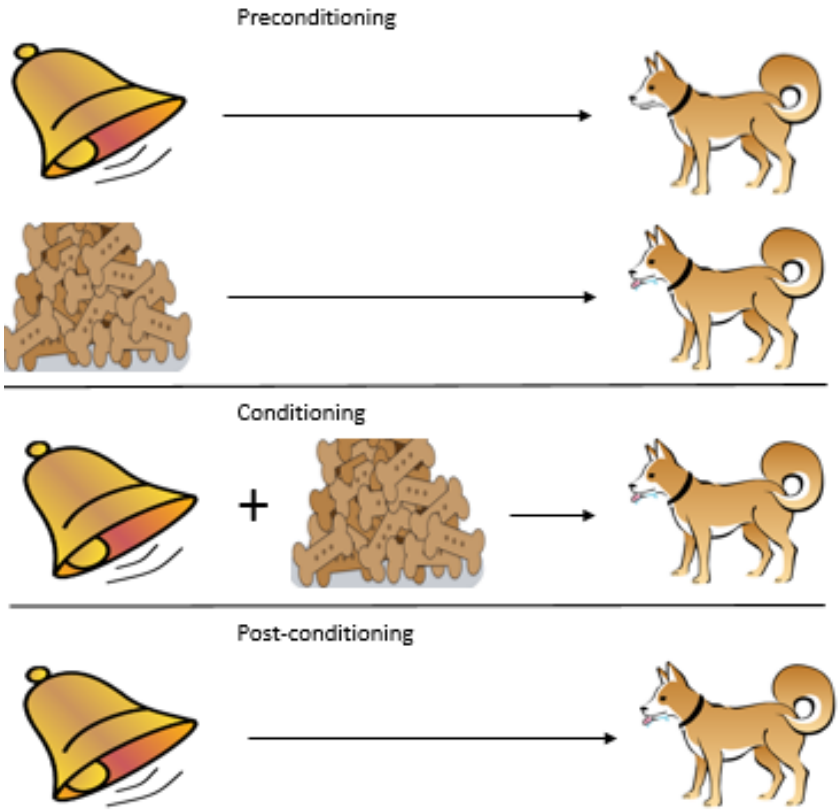


Figure 1.1. A schematic depicting Pavlovian conditioning. In the preconditioning panel the sound of a tone is neutral and elicits no response, however food, being a US, produces salivation. In the conditioning panel the tone and food are presented together resulting in an association between the two. In the post-conditioning panel, hearing the tone alone elicits a memory of food which induces salivation. (All images were taken from webstockreview.net)

Extinction is a phenomenon in Pavlovian conditioning in which a CS's capacity to produce a CR is weakened. To achieve extinction a CS must be repeatedly non-reinforced with an US. Continuing the example from Figure 1.1, after the post-conditioning test, if the tone was to be presented to dogs repeatedly in the absence of food, then it would lose its ability to produce salivation.

There are many theories of how Pavlovian associations form, but the most influential is the Rescorla-Wagner model (1972; [R-W]). The R-W gives formal specification how the associative strength of the CS changes with every CS-US trial. The model assumes that an US can only support a finite amount of conditioning. The model holds that learning will occur when there is a discrepancy between the outcome predicted on the basis of the CS and what actually happens. In other words, the more expected the US is following the CS, the less learning will occur. The model is outlined in the equation below:

$$\Delta V_A = \alpha_A \beta (\lambda - V)$$

Where V is associative strength between the mental representation of the CS and the representation of the US. ΔV_A is the change in associative strength for CS that occurs in a single learning trial. λ represents the occurrence of the US. In this equation λ is set to 1 when the US occurs and 0 when it does not. α and β are learning rate parameters. α_A is the salience of CS and β is the salience of the US. The bigger $\alpha\beta$ the bigger the change in V. The parenthetical term in the equation $[(\lambda - V)]$ is sometimes called the error term. It represents the degree of surprise between the US that is actually present in the trial and expected US predicted by the CS in the trial. When $\lambda - V = 0$ the conditioning strength of a CS can no longer increase because the organism fully anticipates the US follows the CS.

A schematic summary of the R-W being applied to the Pavlov's dog experiments illustrated in Figure 1.1 is depicted in Figure 1.2. In this example $\alpha = .25$ and $\beta = .25$, there for $\alpha\beta = .063$. $\lambda = 1$ as US is present in every trial. Before training the tone has a V of 0. After the first training trial (T1) there is a small increment in associative strength between tone and food indicating a weak association ($CS_{Tone} = .063$). The change in associative strength is .063 due to no prior learning decreasing the error term (.063(1-0)). By the second trial (T2) the associative strength increased ($CS_{Tone} = .122$), but the change in associative strength has decreased ($\Delta V = .059$) due to the previous trial decreasing the error term (.063(1-.063)). By the time the CS has reached asymptote (TX) the associative strength is strong and the ΔV is negligible.

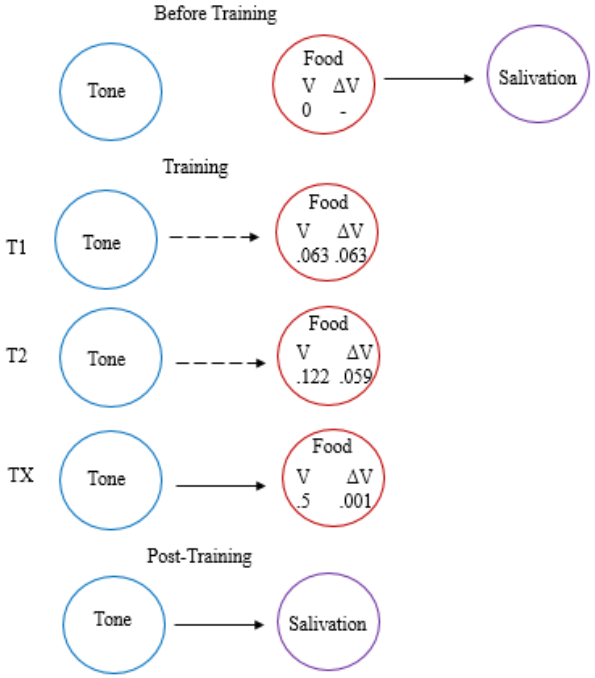


Figure 1.2. A schematic depicting hypothetical associative strength and changes in associative strength of the acquisition of tone-food learning within canines (à la Pavlov, 1927). The circles indicate mental representations of stimuli. Blue represents CS, red = US and purple = UR/CR. Arrows with dashed lines represent the weak excitatory link of associations formed during learning and the arrows with solid lines represents strong associative links. V is associative strength and ΔV is change in strength.

The R-W postulates that extinction is unlearning of a CS-US association. This model states when the US is removed, $\lambda = 0$ so that ΔV is negative and the associative link between CS and US is weakened. After enough non-reinforced extinction trials the CS's associative strength has decreased so much it can no longer produce a CR. Later in this review it will be discussed why this may not be the case and extinction is more likely to be "new learning" within a CS (see section 1.3.3.2 Occasion setting for further details).

Instrumental conditioning is the formation of links between behaviours and outcomes. Outcomes are said to be reinforcers or punishers. Reinforcers increase the probability of behaviours which produce them, punishers reduce the probability of behaviours which produce them. For example a rat is more likely to press a level if it receives something rewarding (e.g. sucrose), this is called positive reinforcement. Moreover, a rat is more likely to jump into an adjacent chamber to avoid an aversive event (e.g. an electric shock), this is called negative reinforcement. In addition to this, positive punishment is the presence of aversive stimuli as a consequence of a response and negative punishment is the removal of a reward as a consequence of a response, both of which with the capacity to make behaviour less likely to be repeated. For example children are less

likely to do something naughty if they get hurt as a result of said behaviour (e.g. falling out a tree) or something rewarding is removed because of said behaviour (e.g. parents taking away favourite toy). Learning plays a part in substance use disorders (SUD) of all drug classes, however this literature review will specifically focus on alcohol (mentioning other drug classes briefly as a comparison), and the emphasis in the first instance will be on Pavlovian conditioning.

1.1.2 The role of learning in the aetiology of alcohol addiction

Over the last seven decades research has shown that associative learning has a central role in the aetiology of SUDs; generating many models in the framework of negative reinforcement, opponent-motivational processes, positive reinforcement, and changes in cognitive control (Everitt & Robbins, 2016). All addiction models have several components in common such as the belief that the onset of drug use is volitional (the majority of which is recreational and positively reinforcing) and through chronic use behaviour transitions into compulsive use despite negative consequences (Wise & Koob, 2014). For the remainder of this thesis focus will be on alcohol dependence (AD) for reasons of simplicity. Alcohol was chosen over other drugs for reasons detailed in section 1.2.2 Meta-analysis overview to do with cue-exposure therapy efficacy. The term drug will only be used when describing the specific models of addiction as they are not drug type specific. Throughout the thesis other specific drugs will only be mentioned briefly for comparison.

In general Pavlovian conditioning model terms: alcohol is the US and the physiological and psychological effects (e.g. tachycardia and euphoria) are the URs. A theoretically infinite number of stimuli can become CSs, but they can be categorised into three broad types. 1) Exteroceptive cues e.g. sight and smell of alcohol/ alcohol brands/ glasses, bottles, and other paraphernalia as well as drinking companions, 2) interoceptive cues e.g. negative affect/ alcohol related imagery/ alcohol intoxication or withdrawal, and

3) contexts e.g. home or public house when the alcoholic beverage is usually consumed. In practice, which CS-US links are created and when during the alcohol consumption episode they occur are quite complicated. Therefore several models have been put forward to explain how Pavlovian conditioning supports addiction.

The earliest Pavlovian accounts for addiction adopted a negative reinforcement approach. Negative reinforcement models hold that a withdrawal state (produced by falling drug levels in the physical dependent drug user) become associated with stimuli present at the time. Said stimuli develop the capacity to elicit conditioned withdrawal state responses to which craving occurs as drug use becomes the desired method to alleviate withdrawal sensations (Wikler, 1973). Alternative, more complex, negative reinforcement models have also been proffered using opponent-process theory.

Opponent-process theory postulates drug administration produces homeostatic disequilibrium in the body. When the drug is used it produces positive hedonic effects. Intrinsic homeostatic mechanisms attempt to counteract the pharmacological imbalance in the body to reduce the hedonic effects and therefore restore homeostasis. Stimuli that are present during drug use signal homeostatic disequilibrium which triggers anticipatory homeostatic mechanisms. The unopposed, drug-opposite homeostatic responses result in aversive withdrawal-like symptoms leading to drug use to alleviate them (Koob, Caine, Parsons, Markou, & Weiss, 1997; Koob & Le Moal, 1997). While withdrawal alleviation may play a role in motivating further drug use in some instances, compelling arguments have been put forward that it is not the most important factor (Robinson & Berridge, 1993). For example, animal and humans self-administer drugs in the absence of withdrawal symptoms and patients in treatment settings do not often display withdrawal symptoms, but instead have strongest urges to use drugs when they are in drug use contexts or even during drug administration.

Others have suggested positive reinforcement models. This approach argues stimuli become associated with positive hedonic effects of drugs. The consequence of this

association is that exposure to the CSs can produce CRs (e.g. a psychological positive motivational state similar to that which occurs after drinking) which whets an individual's appetite and stimulates craving for a source of more potent drug effect (Stewart, de Wit, & Eikelboom, 1984 [see Figure 1.3]). Robinson & Berridge (1993) highlight several arguments against the positive reinforcement model of addiction too. Firstly, nicotine does not produce a euphoric state, but is highly addictive. In addition to this drug intoxication can sometimes be unpleasant, drugs can have competing euphoric and adverse consequences (e.g. hangover/comedown), and in addicts, the aversive consequences of drug use (e.g. loss of job) can outweigh any euphoric feeling. Secondly, reinforced drug self-administration has been demonstrated in detoxified opiate-dependent patients in the absence of subjective pleasure. These patients were split into three groups 1) high dose morphine, 2) low dose morphine and 3) placebo dose. Both the morphine dose groups reliably self-administered, however only the high dose group reported subjective pleasure (Lamb et al., 1991).

These limitations of the positive reinforcement model led to the development of the incentive sensitisation theory (Robinson & Berridge, 1993). This theory states it is not pleasure per se which drives addiction. Instead, individuals start recreational drug use for pleasure seeking motivations. However, chronic drug use leads to long-term adaptations in the brain's reward system in which the reward system becomes hypersensitive to drug CSs. Patients develop a dissociation between wanting and liking, in which the former increases while the latter decreases. As a result of the brain's reward system becoming hypersensitive to drug CSs an individual experiences high levels of wanting or craving the drug when exposed to the CS, a state that persists long after drug use has ceased and long into abstinence.

There is some research which has shown that cravings are not always subjectively experienced before drug use and relapse (Tiffany & Carter, 1998) which led to the development the theory that drug use in the addicted individual is habitual (Tiffany, 1990).

This theory will be discussed in more detail in section 1.3.2 Pavlovian-instrumental transfer so will only be briefly covered here. In summary, this theory states that drug use starts out goal-directed, but during chronic drug use, there is a complex strengthening and interaction between Pavlovian and instrumental conditioning which results in drug CSs acquiring the power to make an addicted individual engage in drug seeking and using behaviour automatically.

Research has shown CRs interact with operant conditioning mechanisms and support drug seeking behaviour (Corbit & Janak, 2007). A common theme within these conditioning models is it suggests drug-related cues may be crucial antecedents which play a role in relapse from abstinence back to a drug using state.

1.1.3 The role of learning in the aetiology of anxiety disorders

The assumption is that the learning mechanisms involved in anxiety disorders (ANX) work on the same general associative learning principles as drug addiction, differing primarily in the stimulus that serves as an US (Barlow, 2002; Mineka & Oehlberg, 2008). Whereas addiction has an appetitive drug US, ANX have an aversive, fear-related US (see Figure 1.3). Using specific phobias as an example, a stimulus that is not feared prior to classical conditioning, develops the ability to elicit fear when paired with an aversive US. The seminal example was demonstrated by Watson & Rayner (1920) in which they instilled murophobia (fear of mice) in a nine month old orphan by repeatedly pairing a rat with a loud bang. Pavlovian conditioning plays a central role in the development of other ANX (Barlow, 2002; Bouton, Mineka, & Barlow, 2001) such as panic disorder, posttraumatic stress disorder, generalised anxiety disorder and obsessive-compulsive disorder (OCD). At the core of all these disorders, an individual has a learned association between an exteroceptive or interoceptive cue and fear from an aversive event. In turn, the individual develops an apprehension that the event could repeat itself and

therefore actively avoids the cues that remind them of the event or in the case of OCD, engages in compulsive behaviour to prevent said event.

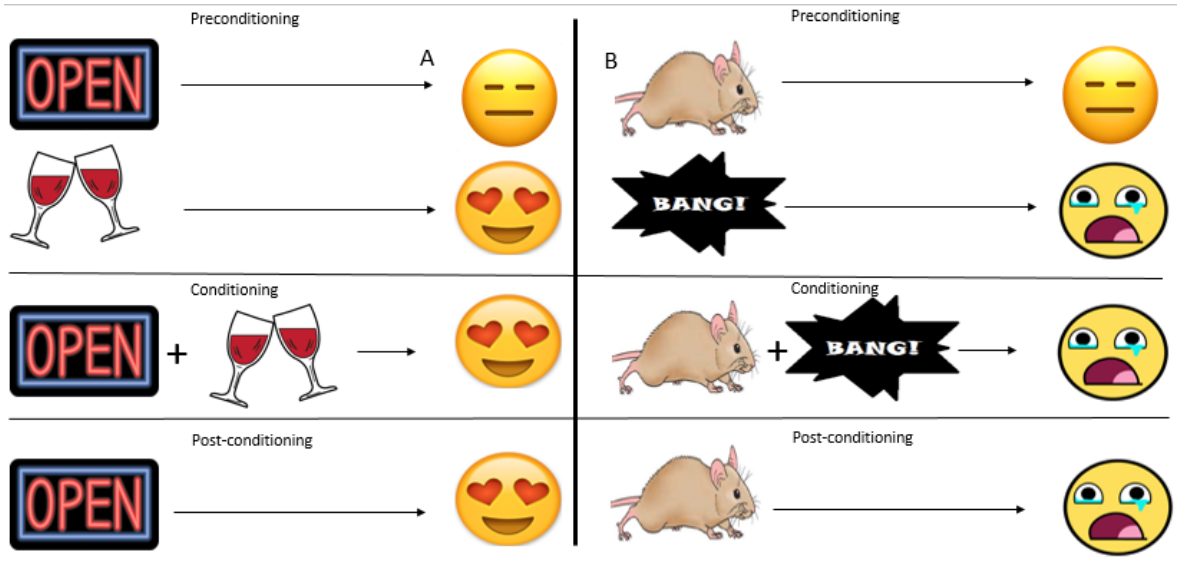


Figure 1.3. A schematic depicting appetitive and aversive classical conditioning. Panel A depicts the conditioning of alcohol-related cues. In the preconditioning box an image open sign is neutral and elicits no response, however alcohol, being a US, produces positive psychological effects. In the conditioning box alcohol and the sign are presented together during alcohol consumption resulting in an association between the two. In the post-conditioning box, sight of the sign alone elicits a memory of the positive psychological effects of alcohol consumption which induces motivational changes such as cravings and increases the propensity of approach behaviour. Panel B depicts fear conditioning. In the preconditioning box an image of a rodent is neutral and elicits no response, however a loud bang, being a US, produces fear. In the conditioning box the loud bang and the rodent are presented together resulting in an association between the two. In the post-conditioning box, sight of the rodent alone elicits a memory of fear which induces motivational changes such as avoidance behaviour. (Images are taken from webstockreview.net, emojipedia.org, or made by author).

1.1.4 The role of learning in the aetiology of binge eating disorder

The DSM-5 (American Psychiatric Association, 2013) characterises binge eating disorder (BE) as a lack of control of eating in a discrete period of time where the quantity of food consumed is much larger than what most people would eat in a similar timeframe. To meet diagnosis criteria, BE episodes are to be associated with three or more of the following: 1) eating more rapidly than normal, 2) eating until feeling uncomfortably full, 3) eating large amount of food when not feeling physically hungry, 4) eating alone due to embarrassment of the quantity consumed, and 5) feeling guilt after eating. In addition to

this BE episodes need to occur on average of once a week for three months. Finally, BE is not associated with compensatory behaviours found in bulimia nervosa e.g. vomiting.

It is also assumed that associative learning mechanisms similar to addiction play a role in the development of BE. The cue overeating model postulates food is an US and exteroceptive cues such as sight and smell of palatable food and time of day and interoceptive cues such as emotions can become CSs that predict excessive food intake (Bouton, 2011; Jansen, 1998; van den Akker, Schyns, & Jansen, 2018). This is supported by research showing food cues reliably elicit cravings in healthy and clinical populations; with cue reactivity being stronger in clinical populations (Sobik, Hutchison, & Craighead, 2005). Successful Pavlovian conditioning has also been demonstrated outside laboratory settings in more ecologically valid field research (van den Akker, Havermans, & Jansen, 2017). In this experiment participants had to complete a questionnaire on a mobile app about food expectancies and food desires at a specific time of day for 15 days. Half the participants were instructed to eat chocolate while completing the questionnaire and the other half were not. The results showed, after five days of conditioning, that the participants who were in the chocolate group had greater expectancy and desire to eat at the time of day they would eat chocolate compared to the no-chocolate group. A recent meta-analysis has revealed that cue exposure and cravings are significant influencers in eating behaviour and weight gain (Boswell & Kober, 2016).

It appears that associative learning mechanisms play a central role in the development of AD, ANX and BE. Therefore, theoretically these disorders should be able to be treated with behavioural treatments that utilise Pavlovian extinction to weaken the CS-US links and inhibit these maladaptive CRs. The next section will discuss the efficacy of such a treatment.

1.2 Cue-exposure therapy efficacy

The previous section described contemporary theories of Pavlovian conditioning models role in the aetiology of AD, ANX and BE. This theoretical grounding has led to the development of a treatment called Cue-Exposure Therapy (CET). CET attempts to weaken the associative CS-US link via extinction. For example in AD, alcohol-related cues are put through extinction training to attempt to weaken the link between the cues and US. Therefore, the CRs (e.g. cravings) attenuate which should, in theory, reduce the chance of relapse. This section will give a brief overview of the CET procedure, a detailed analysis of the efficacy for CET for AD and a brief comparison of CET for ANX and BE.

1.2.1 General CET procedure

For a fully comprehensive review of the CET methodology see Monti and Rohsenow (1999). This section will give a brief description to familiarise the reader. CET takes place in a clinical setting with a therapist present. Typically the patient is presented with the sight and smell of their preferred alcoholic beverage, but withholds from consuming. During this, time measurements such as the patient's physiological reactions and subjective cravings may be made to monitor the effects the cues have on the patients. In addition to this, the patients may sometimes also discuss and practice coping strategies. On occasion, patients may also consume priming doses (usually no more than two glasses of their preferred beverage). Patients may also receive 'homework' where the therapist tasks the patient to high-risk situations to practice alcohol refusal and to monitor and record their cravings and feelings. Very rarely, exposure is not in vivo, but patients imagine themselves in a high risk situation. Exposure sessions may happen as either individual one-to-one sessions between the patient and therapist or as small group sessions. The implications of these variations are discussed below. See Table 1.1 for elements of CET reviewed in the literature below.

1.2.2 Meta-analysis overview

Early case studies of the effectiveness of CET for treating alcohol addiction showed promising results (Blakey & Baker, 1980; Hodgson & Rankin, 1976). Blakey and Baker (1980) observed CET resulted in abstinence in five out of six of their patients in a nine month follow-up. However, overall; meta-analyses of randomised control trials concluded the effectiveness of CET has not yet been reliably or strongly demonstrated. Conklin & Tiffany's 2002 meta-analysis included 18 studies of CET for treating patients with addiction to a variety of drug classes (alcohol, cocaine, nicotine, and opiates). Only four of these studies were for the treatment of AD patients which met DSM-III-R criteria (Rankin, Hodgson, & Stockwell, 1983; Monti et al., 1993; Drummond & Glautier, 1994; Roshenow et al, 2001), and one was to achieve moderation drinking in problematic binge drinkers (Sitharthan, Sitharthan, Hough, & Kavanagh, 1997). Conklin and Tiffany applied meta-analysis techniques to the abstinence and drug-use reduction results to each of the studies. Their results showed that the overall effect size of all studies included in the analysis was weak (d = .0868) meaning that CET had little to no benefits in treatment efficacy over other treatments. However, there was not homogeneity amongst the studies effect sizes and the studies on alcohol use disorder specifically had greater effects sizes that met clinical significance ($d \geq .5$) indicating that CET showed some superiority over other treatments for treating alcohol use disorders and not other SUDs.

In 2010 Martin, Larowe, & Malcolm published a review of all CET studies that were published between 2002-2009. It included 16 studies, eight of which investigated participants undergoing CET with alcohol use disorders. In Martin et al (2010), three out of the eight alcohol studies were randomised control trials; two of which had participants that were AD patients who met DSM-IV criteria (Kavanagh et al., 2006; Loeber, Croissant, Heinz, Mann, & Flor, 2006), and one had participants that were problematic binge drinkers seeking to reduce and control their alcohol consumption (Dawe, Rees, Mattick, Sitharthan, & Heather, 2002). Three of the eight alcohol studies were investigating the theoretical

foundations of CET which can have a significant impact on its effectiveness as a treatment. Specifically, these three studies were manipulating the extinction context. One of these studies had AD participants (Stasiewicz, Brandon and Bradizza, 2007) and two had heavy social drinkers participate (Collins & Brandon, 2002; Mackillop and Lisman, 2008). One of the eight studies was an experiment investigating whether cue exposure using virtual reality with AD patients can reduce subject cravings (Lee, Kwon, Choi, & Yang, 2007). Consistent with Conklin and Tiffany (2002), Martin and colleagues concluded CET did not demonstrate superior efficacy over other treatments. Martin and colleague's review found, in their limited four randomised control trials, that CET was equal to cognitive behavioural therapy (CBT) in treatment efficacy. While the older studies (pre-2002) compared CET to other treatments such as standard treatment (Monti et al., 1993) or relaxation treatment (Drummond & Glautier, 1994; Rohsenow et al., 2001), the more recent studies compared CET to CBT which could have a significant impact on the results (see section 1.2.3 CET efficacy discussion for more details). There was an additional randomised control study that investigated the effectiveness of CET at reducing the physiological and subjective cravings in patients with addiction to a variety of drug classes (Havermans et al., 2007), but the analysis used in this study did not delineate between drug class so this will only be discussed briefly in regards to cravings (see section 1.2.3 CET efficacy discussion).

Finally, Mellentin et al. (2017) conducted a meta-analysis on CET treatment for alcohol use disorders only due to the strong positive effect sizes found in Conklin and Tiffany's results. Six of the studies already listed were included (Dawe et al., 2002; Drummond & Glautier, 1994; Loeber et al., 2006; Monti et al., 1993; Rohsenow et al., 2001; Sitharthan et al., 1997) plus Heather et al. (2000) which was a randomised control study with participants that were problematic drinkers seeking to reduce and moderate their alcohol consumption. Mellentin et al. (2017) applied meta-analysis techniques (if there was sufficient data) on primary outcomes e.g. drinking days and drinks per day and secondary out comes e.g. total drinking score, latency to relapse, and cue elicited subjective cravings.

Mellentin's results showed there was no effect size of the primary outcomes at three months follow-up (d = .07), but a small effect size at six and 12 months follow-up (d = -.2) indicating that after time has passed CET starts to show benefits over other treatments for alcohol use disorder in terms of alcohol consumption frequency and quantity. In addition to this the results showed a more clear benefit for secondary outcomes as there was a small effect size (d = -.2) for total drinking score and a moderate effect size (d = -.68) for latency to relapse. It was also reported that two studies reported no effect of CET on cravings (Monti et al., 1993; Rohsenow et al., 2001), but there was insufficient data to calculate the effect size, therefore CET and cravings will be discussed later (see section 1.2.3 CET efficacy discussion). Therefore, the results of Mellentin's meta-analysis indicate that CET, for alcohol use disorders, appears to be poor at achieving complete abstinence within the treatment population, but does have some small beneficial effects on reducing alcohol consumption and moderate beneficial effects on secondary outcomes.

Mellentin found smaller effect sizes than Conklin and Tiffany. Mellentin's stratification analysis indicated alcohol dependence severity and coping skills strategies adjunct to CET may be a significant variable in influencing the efficacy of CET for alcohol use disorders. These three systematic reviews consistently show the CET research is limited and therefore Mellentin argued other factors such as sample size, sample attrition, cue salience, and comparative control group may also be significant factors that determine the efficacy merits of CET for alcohol use disorder, but more research needs to be conducted to disentangle these. Therefore, the next section of this review discusses the methodologies of the existing CET research for treating alcohol use disorders and the significance these various methodological approaches have in relation to the associative learning literature. The present review used the following search techniques to select studies: 1) studies that were used in the aforementioned systematic reviews, 2) the following key search terms "cue exposure alcohol dependence" and "cue exposure therapy alcohol randomised control trials" were entered into PubMed, PsycINFO, ScienceDirect,

and the University of Southampton's library search engine DelphiS. The following criteria were to select suitable studies: a) cue exposure had to have been one of the experimental treatment methods and a primary focus (e.g. cue reactivity studies with an extinction element or impulsivity studies with an cue exposure element were excluded), b) there needed to be a control comparison group, c) there had to be an alcohol consumption follow-up, d) participants had to be from a clinical or subclinical alcohol use disorder population with no comorbidity with other psychiatric disorders, and e) participants had to be $\geq$ 18 years old. When possible, searches were ordered as "newest" / "most recent" (going back to 1976) and "most relevant". 3) The references lists of the aforementioned systematic reviews and CET studies were scanned with the same criteria as the second study search method. The results yielded no studies of CET without adjunct pharmacological treatment for the treatment of alcohol use disorders beyond the ones already mentioned. See section 1.2.4 Adjunct pharmacological treatment for a separate discussion on CET with adjunct pharmacological treatment.

Therefore, in the last 42 years, there have only been nine randomised control trials investigating the efficacy of CET without adjunct pharmacological treatment, (and three with), for treating alcohol addiction. This is a remarkably limited number of studies considering there are strong theoretical reasoning and moderate empirical evidence suggesting that CET could yield clinical benefits and more research is needed to 1) fully pinpoint the specific benefits CET can give and 2) determine whether a modified CET can augment its current efficacy. At the present, any conclusions drawn should be handled cautiously due to the limited number of research and heterogeneous nature of the existing research. Clearly a lot more research is needed to fully understand CET's full capacity to treat alcohol dependence.

Table 1.1. A summary of all cue-exposure research reviewed in this thesis

	Study	n[a]	I/G[b]	Goal[c]	Mean # of sessions	Mean length of session (Mins)	Adjunct treatment[d]	Control[e]	Cues[f]	Interoceptive[g]	Homework[h]	Follow-up (months)	Outcome
Alcohol													
	Dawe et al (2002)	105 (80)	I	MOCE	8	33-40	N	BSCT	IV	PD	Y	8	Both groups equally decreased number of drinking days and number of drinks consumed on drinking days from pre-treatment to follow-up
	Drummond and Glautier (1994)	35 (32)	I	A	10	40	N	RLX	IV	N	N	1, 3, 6	CET group was better than control in increasing their latency to heavy drinking and decreasing quantity consumed
	Heather et al (2000)	108 (77)	-	MOCE	7	88	-	BSCT	-	-	-	6	Both groups equally reduced quantity consumed and reduced alcohol severity measured by SADQ-C
	Kavanagh et al (2006)	163	I	MOCE	8	75	CBT	CBT	IV	PD, NA	Y	3, 6, 9, 12	All groups equally reduced subjective cravings from first to last treatment sessions. Also all groups equally had reduced alcohol consumption at follow-up
	Kiefer et al (2015)	76 (32)	I	A	8	30-90	DCS	PBO	IV	N	N	3	Both DCS and placebo groups equally reduced subjective cravings and had the same propensity to relapse after CET treatment
	Loeber et al (2006)	63 (60)	G	A	9	90	CS	CBT	IV, I	N	N	3, 6	Both groups were equal in their reduction of subjective cravings, latency to drink and quantity consumed posttreatment
	Monti et al (1993)	40 (34)	I	A	6	55	CS	STD	IV, I	N	N	3, 6	CET compared to standard treatment consumed less alcohol, were more likely to be completely abstinent, and had a higher percentage of abstinent days
	Monti et al (2001)	165 (111)	G	A	5	90	NTX, CS	ED/RLX, PBO	IV, I	N	N	3, 6, 12	CET had fewer heavy drinking days than the control group. NTX group had fewer heavy drinking days and drank less while taking medication, but there was no difference between NTX and placebo when treatment ceased.
	Rankin et al (1983)	10	I	A	6 or 12	45	N	MED	IV, I	PD	N	N	IV CET is more potent than I CET as shown by IV CET having greater reductions in desire to drink and difficulty to resist alcohol
	Rohsenow et al (2001)	100 (84)	I	A	10	50	CS	CST/ED	IV, I	N	N	6, 12	CET had reduced number of drinking days and reduced quantity consumed compared to control
	Sitharthan et al (1997)	52 (42)	G	MOCE	6	90	N	CBT	IV	PD	Y	6	CET was superior over CBT in reducing drinking, reducing addiction severity measured by SADQ-C and increasing self-efficacy
	Watson et al (2011)	16 (14)	I	A	3	60	DCS	PBO	IV, P	N	N	.25	There was a significant reduction in craving, but DCS and placebo groups did not differ
Nicotine													
	Corty and McFall (1984)	39 (30)	I	A	8	-	N	RS	IV, A, I	S	Y	1, 3, 6	The RS group had greater abstinence compared to CET, but this was not statistically significant

	Culbertson et al (2012)	15 (11)	I	A	16	30	CBT	PBO, VR	VR	N	N	N	The CET VR produced significantly more abstinence and reduction in number of cigarettes smoked then placebo VR
	Götestam and Melin (1983)	21	I	A	6	-	N	RLX, WL	I	N	Y	1	All three groups equally reduced smoking by the end of treatment, but increased by follow-up. This is mirrored by cravings.
	Kamboj et al (2012)	32	I	A	2	30	DCS	PBO	I, IV, V	N	N	.5	Cue-exposure reduced subjective and physiological cravings, but there was no difference between DCS and placebo groups
	Lowe et al (1980)	44 (42)	G	A	8	-	N	SC	IV	N	Y	3, 6	There were high levels of abstinence at 3 months equal between groups. All groups equally relapsed by 6 months.
	McLernon et al (2007)	20 (16)	I	A	3	-	RNC	N	P, S	NIC	Y	1	Number of cigarettes smoked per day decreased and 4 participants were abstinent
	Niaura et al (1999)	129 (126)	I	A	5	75-90	CBT, NG	CBT	IV, I, S	NIC	Y	1, 3, 6, 12	Groups equally increased in number of relapsing participants over the follow-ups
	Park et al (2014)	30	I	A	4	25	N	CBT	VR	N	N	3	Number of cigarettes smoked and dependence severity significantly decreased. Cravings decreased but not significantly. There was no difference between groups in these reductions. Likewise, the number of abstinent participants was equal between groups too
	Raw and Russell (1980)	49	G	A	7	45	N	SUP, RS	IV, S	N	Y	3, 6, 12	CET had greatest reduction in cigarettes per day smoked, but this was not statistically different from each group. There was also no difference between groups in number of abstinent
	Santa Ana et al (2009)	25	I	A	2	270	DCS	PBO	IV	N	N	.25, 1	Participants within the DCS group had greater reduction in physiological and subjective cravings, however there was no difference in smoking behaviour at follow-up
	Unrod et al (2014)	143 (76)	I	A	6	75	CS	N	P, IV	N	N	N	Cravings were reduced both within and between exposure sessions
	Yoon et al (2013)	47 (29)	I	A	12	20	DCS, CBT	N	VR	N	N	.25	VR exposure reduced cravings and smoking behaviour, but there was no difference between DCS and placebo groups in these outcomes
Opiates													
	Childress et al (1986)	6	G	A	20	60	N	N	A, V, IV	N	N	N	CET eliminated cravings and withdrawal responses.
	Dawe et al (1993)	69 (43)	I	A	6	41-80	STD	STD	P, V, IV	N	N	1.5, 6	Craving and withdrawal responses decreased equally between CET and STD. Likewise relapse rates were comparable between groups at follow-up
	de Quirós Aragón et al (2005)	24	G	A	12	60-75	STD	STD	V, IV	S	N	6	There were no differences in subjective cravings pre- and post-CET.
	Du et al (2014)	45	G	A	12	60	STD	STD	V	N	N	N	Cravings decreased after CET
	Franken et al (1999)	16	I	A	9	45-50	N	N	P, V, IV	N	N	1.5	There was a reduction in cravings and withdrawal responses after CET

	Kasvikis et al (1991)	19 (13)	I	A	14	45	N	N	P, IV	N	N	1, 3, 6	Not many patients showed cue reactivity, but those who did showed within and between session habituation. The majority of participants relapsed.
	Marissen et al (2007)	127 (114)	I	A	9	60	N	RLX	IV	N	N	3	Both groups equally decreased cravings. The CET group had greater relapse than the control
	McLellan et al (1986)	56 (35)	I	A	35	10-15	CBT	CBT, STD	P, A, V, I, IV	N	N	N	The CET and CBT group were equal and greater than STD in improvement on addiction severity scores.
	Powell et al (1993)	56 (21)	I	A	2	45-50	N	N, CA	P, IV	N	N	N	There was a significant reduction in cravings for CET, but not the no treatment control group.
Cocaine													
	O'brien et al (1990)	30	I	A	15	60	PSY, STD	PSY, STD	A, V, S	N	N	N	Cravings reduced, but were still persistent after 15 sessions
	Price et al (2010)	10	I	A	2	60	DCS	PBO	IV, V	N	N	.25	DCS increased cravings after cue presentation in the first session, but there was no difference between DCS and placebo groups in cravings in the second or follow-up sessions
	Price et al (2013)	32	I	A	3	60	DCS	PBO	I, IV, V	N	N	.25	Cue-exposure reduced cravings in DCS and placebo groups, however, placebo had greater attenuation of cravings than DCS.
	Santa Ana et al (2015)	47 (46)	I	A	3	167	DCS	PBO	IV	N	N	.25	Both DCS and placebo groups reduced cravings equivalently

an: number of participants assessed, parenthesis are number of participants included in the analysis after attrition and exclusion;
btherapy: I = individual sessions; G = group sessions;
cgoal: desired outcome of treatment A = abstinence, MOCE = moderation-oriented cue exposure;
dadjunct treatment: N= none, CBT = cognitive behavioural therapy, CS = coping skills, CBT = cognitive behavioural therapy, PSY = supportive-expressive psychotherapy, STD = standard drug counselling, NTX = naltrexone, DCS = D-cycloserine, RNC = reduced nicotine content, NG = nicotine gum;
econtrol treatment: BSTC= behavioural self-control training, RLX = relaxation, MED = meditation, CST/ED = coping skills training and education, RS = rapid smoking, PBO = placebo, WL = waiting list, SUP = support, SC = self-control training, CA = cognitive aversion, N = none;
fCues used: A = audio; P = photographic; V = video; I = imagery; IV = in vivo; S = sham use, VR = virtual reality;
ginteroceptive cues used: PD = priming dose, NA = negative affect, S = stress, NIC = nicotine patch, N = none;
hhomework of extra-session self-guided exposure: Y = yes, N = no;
- = information not give or clearly specified.

1.2.3 CET efficacy discussion

Several methodological issues have already been identified within the CET literature which could account for the aforementioned systematic reviews conclusions. This section will examine and discuss the CET without adjunct pharmacological treatment literature only. The desired goal of standard CET is complete abstinence. Five out of the nine randomised control trials had a goal of achieving complete abstinence. What is evident from these five studies is that CET is very poor at achieving said goal as only three reported a miniscule amount of participants achieving complete abstinence (Drummond & Glautier, 1994; Monti et al., 1993; Rohsenow et al., 2001). However, these five studies did consistently show the participants in the CET condition increase their delay to relapse, drink less on drinking days and have decreased urges to drink in the short-term. The craving outcome is in contrast to what Mellentin et al (2017) reported. That meta-analysis reported there were only two studies which reported CET had no effect on cue-induced cravings (Monti et al., 1993; Rohsenow et al., 2001). There are other studies supporting Mellentin's claim. Havermans et al. (2007) compared CET to relaxation treatment for drug-dependent patients whose dependence range across all drug classes. There were 70 participants overall, 36 of which were AD. Participants were randomly assigned to six individual sessions of CET or relaxation treatment. CET consisted of in vivo and imaginal exposure. The dependent measures were cue reactivity (various physiological and self-report urge measurements) recorded immediately before and after each session. Of the 70 participants, six dropped out before participation began and 26 participants dropped out before the end of the final session; it is unknown how many of these were AD. Cue reactivity failed to extinguish in the CET condition. This could be due to the influence of other drug classes. Drug class was not controlled for in the analysis and as the authors point out, previous research has shown cocaine physiological cue reactivity were the most persistent responses to cocaine cues which were not fully extinguishing after 15 sessions

(O'Brien, Childress, McLellan, & Ehrman, 1990). Therefore it is unknown what the pattern of behaviour was like for the AD participants specifically.

While Monti et al. (1993) did report CET had no effect on participants daily urges, a more nuanced look at the results showed for cue-specific urges, the participants in the CET condition had greater decreases in cue reactivity urges in the posttreatment measurement compared to pretreatment after controlling for "urge reactors" (i.e. participants who demonstrated cue elicited urges pretreatment). Likewise, Rohsenow et al. (2001) demonstrated both cue reactivity urges and salivation decreased post-CET treatment, but only the salivation reduction was greater in CET compared to the comparison groups. Moreover, Loeber et al. (2006) reported participants cravings decreased post-treatment and Rankin et al. (1983) used speed of alcohol consumption as a proxy measure of cravings, the results show consumption time increased for the CET, but not control group. Likewise, the moderation-oriented cue exposure (MOCE) studies that reported cravings or urges data have shown that CET reduces cravings equivalently to the comparison group (Kavanagh et al., 2006) or CET reduces cravings greater than the comparison group (Sitharthan et al., 1997). In addition to in vivo exposure, CET achieved through virtual reality has also been shown to reduce cravings (Lee et al., 2007).

The research discussed here has shown CET is superior to standardised treatment, relaxation and meditation treatments (Drummond & Glautier, 1994; Monti et al., 1993; Rohsenow et al, 2001). CET appears to be as effective as CBT in reducing cravings and drinks consumed (Dawe et al., 2002; Heather et al., 2000; Kavanagh et al., 2006; Lee et al., 2007; Loeber et al., 2006) and in one case CET was superior to CBT (Sitharthan et al., 1997). One reason why CET is on par with the CBT treatments could be because of overlap between them. CET could increase coping skills and self-efficacy (explicit goals of CBT training) with every successful resistance to drink. In fact, alcohol treatment programmes include an element of naturalistic cue exposure each time the person resists uncontrolled use of alcohol (Kavanagh et al., 2006).

When CET is conducted in a group setting its effectiveness at reducing craving, and consumption has been shown to be inconsistent. Sitharthan et al. (1997) showed CET was only superior to CBT in reducing the number of drinks consumed and severity of alcohol dependence, while Loeber et al. (2006) showed CET was only superior to CBT in self-efficacy; a dependent measure that Sitharthan et al. (1997) found equivalence between them. One reason for this inconsistency could be due to differences in the methodologies of the two studies. Sitharthan et al. (1997) used both priming doses of alcohol and 'homework' whereas Loeber et al. (2006) had neither. This could explain the discrepancy in two ways 1) Sitharthan et al. (1997) participants had both exteroceptive and interoceptive cues (rising BAC from the priming dose) that could have been extinguished. Therefore when the participants of Loeber et al. (2006) lapsed their rising BAC cue reactivity had not been attenuated which facilitated relapse. 2) While both studies had six treatment sessions only Sitharthan et al. (1997) had 'homework' which could have facilitated the treatment sessions and acted like additional sessions, which concordantly with the former explanation would optimise any benefits from the treatment. It seems unlikely that priming doses alone would increase the efficacy of CET as the limited experiments that used priming doses showed CET to be comparable to CBT (Dawe et al., 2002; Kavanagh et al., 2006) and therefore it is unlikely to add anything to the therapeutic gains of CET. Likewise 'homework' alone is unlikely to add any therapeutic gains to CET for the same reason as Kavanagh et al. (2006) showed CET and CBT being equivalent in efficacy. Therefore it is possible the combination of group sessions of CET with a larger array of exteroceptive and interoceptive cues and 'homework' is a better procedure for treating alcohol dependence. This could be due to the potential boost in coping skills patients receive from having peers to experience and discuss with in conjunction with an increased number of sessions where vital CS-US' were extinguished in drug-related contexts specific to the patient (See section 1.3.3.1 Context in cue-exposure extinction for more details on contexts).

To extend in relation to interoceptive cues, there is a severe lack of research that extinguishes interoceptive cues as part of the CET methodology. Four of the nine studies attempted to extinguish both exteroceptive and interoceptive cues (Dawe et al., 2002; Kavanagh et al., 2006; Rankin et al., 1983; Sitharthan et al., 1997). In all these studies interoceptive cues were rising BACs from priming doses; in addition to this Kavanagh et al. (2006) also included negative affect in patients whose alcohol use manifested during periods of dysphoria. As discussed earlier priming doses (at least in isolation from other procedural changes from standard CET) may not benefit CET. With an abstinence goal priming doses are probably counter-productive as consuming alcohol defeats the point of extinction. However, for research with a MOCE goal with non-dependent alcohol users, priming doses may be useful.

Kavanagh et al. (2006) is the only study to use negative affect as in interoceptive cue to be extinguished. In this study there were 163 participants (71 male). Participants were non-dependent alcohol users who only abused alcohol when experiencing dysphoria. Participants were randomly allocated to one of three groups, of which they received eight 75 minutes individual sessions of their respective treatments. The control group was standard CBT. The other groups were 1) CBT + standard CET in which participants received priming doses, in vivo exposure and 'homework' similar to that of Sitharthan et al. (1997) and 2) CBT + ECE which is the same as 1), but negative mood inductions were given before and during the exposure sessions. Participants were followed-up at three, six, nine and twelve months with 50% attrition by twelve months. The main dependent measures was self-reported alcohol consumption. The results show neither form of cue exposure had an additional benefit to CBT alone. All three conditions were equal in number of drinks per week at three, six, nine and twelve month follow-ups.

One reason why Kavanagh et al. (2006) did not show CET to be superior to CBT could be because of the methodological overlap between CET and CBT. As stated earlier CET could increase coping skills and self-efficacy with every successful resistance to

drink. All alcohol treatment programmes includes an element of naturalistic cue exposure each time the person resists uncontrolled use of alcohol. Kavanagh et al. (2006) used CBT in all three conditions leaving the possibility for excessive overlap in the skills and learning acquired in both treatments which could have facilitated each other and negated any differences between conditions. A common limitation of Kavanagh et al. (2006), and others, is the lack of an ineffective control group (i.e. waiting list or relaxation treatment). Instead the control group is either CBT or behavioural self-control training; a variation of CBT (Dawe et al., 2002; N Heather et al., 2000; Kavanagh et al., 2006; Loeber et al., 2006; Sitharthan et al., 1997). This lack of placebo group limits the studies interpretation as it cannot be said for certain that the CET or CBT procedures changed behavioural outcomes differently from natural changes overtime without any intervention.

Another major limitation across all CET studies is the small sample sizes and high attrition rate. The sample sizes range from as low as 10 to 163 that completed full treatment. However, participant attrition was around 20% for most studies by the final follow-up. Rohsenow et al. (N=100) argued his own sample size was too small and a larger difference between condition could have been detected with a larger sample. Adequately powered samples could unmask differences where there were none or change the magnitude of existing differences. Another limitation across all CET research are the cues utilised in extinction. Unfortunately, beyond any researcher's control, it cannot be decided or controlled which cues become associated with alcohol and which are the most salient and triggering of relapse. Researchers try their best to select person-specific cues such as favourite beverage prepared in the way the patient usually drinks (e.g. Champagne in a Champagne glass opposed to a plastic cup). The sight and smell of alcohol are not just the only relevant cues. There is a whole constellation of cues such as drinking companions, mood, time of day, spatial contexts which tend to be ignored in CET research.

In summary, CET has been shown in some research to be effective at reducing cravings and drinking behaviour at least equally to CBT, but meta-analyses concluded

overall, CET is better at treating the secondary outcomes of AD over the primary outcomes. Research could potentially demonstrate an increased effectiveness of CET on primary outcomes of AD if more research is conducted which controls variables such as: the control treatment (i.e. reducing methodological overlap), group or individual sessions, number of sessions/ addition of 'homework', cues being extinguished (i.e. constellation of exteroceptive and interoceptive cues). Concurrently, while controlling these variables there also needs to be an increase in sample size for adequate statistical power. The efficacy of CET for treating addiction to other drug classes and treating ANX and BE will be discussed to determine the legitimacy of the hypothesis that the limitations of the CET AD literature accounts for the conclusions of its efficacy (see sections 1.2.5 The efficacy of CET for other drugs and 1.2.6 The efficacy of CET for other psychiatric disorder).

1.2.4 Adjunct pharmacological treatment

Before the efficacy of CET as a treatment for addiction to other drug classes and other psychiatric disorders are discussed, research that has attempted to enhance CET effectiveness for AD with adjunct pharmacological treatments will be discussed first. Reviewing this first will allow for a comparison when discussing CET in the later sections.

1.2.4.1 Naltrexone hydrochloride

Naltrexone hydrochloride (NTX) is one of the prescribed pharmacological treatments for AD. NTX is an opioid receptor antagonist which has been shown to be successful at reducing lapse and relapse back to heavy drinking (Donoghue et al., 2015). This is believed to be through blocking the release of endogenous opioids, induced by alcohol consumption, which are thought to mediate the positive reinforcing effects of alcohol. As a review of the role of the opioid system for reward is beyond the scope of this thesis it will only be briefly reviewed here. For a comprehensive review see Le Merrer et al. (2009). In summary, the opioid system mediates hedonic evaluation of natural rewards.

μ-opioid receptor (and δ-opioid receptor) agonists have positive reinforcing effects, whereas μ-opioid receptor (and δ-opioid receptor) antagonists block the positive reinforcement of drugs. As NTX is a μ-receptor antagonist it also blocks the reinforcing effects of alcohol as can be shown by research which has demonstrated alcohol and cocaine self-administration have been attenuated with prior injections of NTX (Lê et al., 1999; Ramsey, Gerrits, & Van Ree, 1999). In addition to this, AD patients and social drinkers who consume alcohol after oral administration of NTX reported reduced less "high" and positive effects (Volpicelli et al., 1995; Swift et al. 1994). Finally, NTX has been shown to reduce cravings, number of beverages consumed and increased drink consumption time in AD patients (O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002). Therefore, this all indicates that NTX reduces the chance of lapse by attenuating the euphoric and reinforcing effects of alcohol via blocking endogenous opioid peptides. NTX was thought as a potential mechanism to augment CET efficacy due to the combined ability of NTX and CET to have additive effects at craving reduction in AD.

However, research in both animals and humans have shown NTX is not beneficial for cue-exposure. In Williams & Schimmel's (2008) experiment one, rats were trained to lever press for ethanol reward in the presence of olfactory, visual and auditory cues which underwent extinction. The subjects were injected with NTX prior to each extinction session. In their second experiment a different cohort of rats underwent the same procedure as experiment one except they received no injections during extinction. In the next phase of the experiment rats received injections of NTX during 16 weeks of cue-exposure. The results showed NTX did not enhance extinction or cue-exposure.

There has been one randomised control trial utilising adjunct NTX and CET treatments for AD (Monti et al., 2001). In this experiment, participants were randomly allocated to either the CET/ coping skills training (CST) condition or education/ relaxation control condition (ERC). The CET/CST included 90 minute sessions; 45 minutes of active exposure and 45 minutes of coping skills training with passive exposure. The ERC was the

same as Rohsenow et al. (2001). After behavioural treatment participants were randomly allocated to 12 weeks of NTX or placebo. At the six and 12 month follow up the CET/CST condition had fewer heavy drinking days than control condition. The participants on NTX had fewer heavy drinking days and drank less on drinking days than placebo while taking medication, but this difference disappeared during the subsequent nine months when medication treatment ceased. Pharmacological and behavioural treatments did not interact indicating NTX did not have a positive or negative effect on CET outcome. Taken together with the animal research, NTX does not appear to be a promising benefit to CET.

Similar results have more recently been demonstrated with naloxone (Lieb et al., 2013). Naloxone is a μ-opioid receptor antagonist commonly used as an opiate overdose antidote (Beheshti et al., 2015). NTX and naloxone are similar, but naloxone's effects are experienced quicker and it has a shorter half-life. In Lieb et al. (2013) 20 male AD patients were infused with either naloxone or saline via catheter (in a counterbalanced repeated measures manner) before undergoing imaginal, video and in vivo cue exposure. Participants completed the alcohol craving questionnaire (ACQ) before naloxone infusion, after naloxone infusion and after cue exposure. The results showed that neither naloxone nor saline had an effect on cravings as measured by ACQ. In addition to this neither group had changes in cravings post-exposure.

The reason why NTX does not augment CET is likely because it does not have additive effects. The exposure effect is probably impaired by NTX because the patients are not experiencing strong enough CRs to learn to inhibit.

1.2.4.2 D-cycloserine

More recent pharmacotherapy research has investigated the effects of cognitive enhancers for associative learning. The basolateral amygdala, hippocampus, dorsal and ventral striatum and the medial prefrontal cortex; neural substrates which become damaged or impaired from chronic, heavy alcohol use have all been implemented in mediating

extinction learning (Nic Dhonnchadha & Kantak, 2011). Extinction is a result of long-term potentiation (LTP) induced synaptic plasticity (Herry & Garcia, 2002). There are four targets of the glutamatergic system which enhance extinction learning through facilitating LTP and regulating synaptic plasticity through activation of N-methyl-D-asparate (NMDA) receptors (Nic Dhonnchadha & Kantak, 2011). These are 1) glycine site agonist, 2) glycine transporter inhibition, 3) cysteine-glutamate exchange activation and 4) metabotropic glutamate receptor activation. While all these methods have been shown to impact on extinction learning of drug-related cues (for a review see Nic Dhonnchadha & Kantak, 2011) only the glycine site agonist D-cycloserine (DCS) has been used as an adjunct pharmacotherapy with CET for AD. Therefore for brevity, only DCS will be discussed.

Glycine and glycine-binding site agonists indirectly open calcium ion-channels. This enables excitatory neurotransmission without directly increasing extracellular levels of glutamate which therefore prevents glutamate-induced excitotoxicity. DCS is a partial agonist at the glycine binding site of the NMDA receptor (Hood, Compton and Monahan, 1989). Animal research has shown DCS enhances extinction of ethanol cues (Vengeliene, Kiefer, & Spanagel, 2008). Vengeliene et al. (2008) first trained rats to lever press for ethanol in the presence of an auditory CS. Next, the subjects received injections of DCS (or placebo) 60 minutes prior to extinction sessions. The results showed drinking behaviour in the presence of the CS was reduced for the DCS group. DCS has also been shown to generalise extinction to non-extinguished CSs (Ledgerwood, Richardson, & Cranney, 2005). DCS has also been shown to augment the effectiveness of CET when it is used as an adjunct treatment for social anxiety disorder (Guastella et al., 2008). A recent meta-analysis concluded DCS enhances extinction in rodents and CET in humans with anxiety disorders, but noted the effects of DCS is most potent when administration is limited (Norberg, Krystal, & Tolin, 2008). This suggests DCS is a promising advocate for pharmacological augmentation of CET for AD.

To date there have only been three studies that have investigated the effects of DCS on CET in AD and the results are inconsistent (Kiefer et al., 2015; MacKillop et al., 2015; Watson et al., 2011). In Watson et al (2011) 16 participants who were undergoing CET were randomly assigned to either DCS (250 mg) or placebo medication. Only cravings measured with alcohol use questionnaire (AUQ) was the main dependent measure. The results showed CET decreased alcohol craving, but DCS did not facilitate CET.

These results were inconsistent with subsequent research. For example, MacKillop et al. (2015) administered participants with 50 mg of DCS or placebo one hour before extinction sessions. The results showed alcohol-related cues increased cravings for both groups equivalently in the first exposure session, but cravings decreased over time with the decrease being greater for the DCS groups. The results also showed the DCS group decreased the amount of alcohol consumed while on treatment, but not by the follow-up. Kiefer and colleagues (2015) conducted a similar experiment giving participants 50 mg doses of DCS or placebo and also collecting fMRI data before and after treatment. The study measured subjective cravings on a visual analogue scale. This study found DCS augmented CET in reducing cravings. This was supported by imaging data which shows posttreatment reductions of blood-oxygen-level dependent (BOLD) response in mesolimbic and ventral striatal areas. The imaging data is consistent with previous research (Vollstädt-Klein et al., 2011).

There are too few studies to be able to make any conclusions as of yet. All studies have the limitation of very low sample sizes, therefore further research is needed to fully understand this area including the timing and frequency of DCS administration such that it is sufficiently spaced apart to allow for memory consolidation. Another consideration is the number of exposure sessions in which DCS is administered. Hofmann, Hüweler, MacKillop, & Kantak (2012) administered 50 mg of DCS or placebo to non-treatment seeking problem drinkers 50 minutes before exposure sessions. The results showed cravings were higher following alcohol-related cue exposure for the DCS group in the first

exposure session, but not in the subsequent two sessions. Whereas NTX may impair CET due to attenuating cravings, DCS may enhance CET by augmenting cravings. This has indirect support from (Norberg et al., 2008) which concluded limited DCS administration is the most beneficial for CET effectiveness for anxiety disorders. However, MacKillop et al. (2015) did not report greater craving in the first CET session in the DCS group, therefore more research is needed.

In summary, the current experimental pharmacotherapy agents used to augment CET for AD have not been reliably demonstrated to be successful. The opioid system antagonists appear to be less effective than the glutamatergic system compounds. Further research is needed on both, but DCS at present appears promising.

1.2.5 The efficacy of CET for other drugs

Some traditional theories have viewed addiction as a unified disorder with dependence to the different drugs as variations of a homogenous disorder. However, differences between behavioural and neurobiological responses across a range of drugs suggests, dependence to one drug class is a heterogeneous disorder that shares commonalities with the other drug classes and generalisation of responses from one drug class to another should be exercised with caution (Badiani, Belin, Epstein, Calu, & Shaham, 2011). The efficacy for CET for other drug classes will now briefly be reviewed to determine if the same issues discussed in the alcohol literature are present and relevant in the literature for nicotine, opioids and cocaine. The same literature search methods use for the alcohol literature were applied here except "alcohol" was replaced with either: "Nicotine", "Smoking", "Opiates", "Heroin", or "Cocaine". A summary of the reviewed studies are presented in Table 1.1.

1.2.5.1 Nicotine

Over the last three decades there have only been 14 published papers on CET for nicotine dependence (ND). Eight out of the 14 were randomised controlled clinical trials

that directly compared the long-term efficacy of CET (without adjunct pharmacological treatment) to other treatments (Corty and Mcfall, 1984; Culbertson, Shulenberger, De La Garza, Newton, and Brody, 2012; Götestam and Melin, 1983; Lowe, Green, Kurtz, Ashenberg and Fisher, 1980; McClernon et al., 2007; Niaura et al., 1999; Park et al., 2014; Raw and Russell, 1980). Two of the 14 used VR CET and only measured changes in cravings (Lee et al., 2004; Moon and Lee, 2009) and one used photographic CET (Unrod et al., 2014). The Lee and colleagues studies are flawed with small samples and no control condition. Finally, three out of 14 used DCS to attempt to augment CET effectiveness. One of these three only measured cravings (Kamboj et al., 2012) and two were randomised control trials investigating the effectiveness of CET on behaviour as well as cravings (Santa Ana et al., 2010; Yoon et al., 2013).

Of the eight randomised control trials, the results show a similar pattern to the alcohol CET literature, but to a weaker degree (which is to be expect from Conklin and Tiffany (2002) result). When compared to the comparison group, the CET group resulted in equal reduction of (which did not always reach significant reduction) in number of cigarettes smoked per day and the number of abstinent participants immediately after post-treatment. In addition CET was comparable to the comparison group in the number of relapsers during the follow-ups (Corty & Mcfall, 1984; Götestam and Melin, 1983; Lowe et al., 1980; Niaura et al., 1999; Raw & Russell, 1980). In terms of CET influencing cravings the results are inconsistent; in some cases reducing cravings (Götestam and Melin, 1983; Unrod et al., 2014) and some having no effect or increasing them (Niaura et al., 1999; Park et al., 2014).

The CET nicotine literature shared a lot of limitations as the alcohol literature, but also addressed some of them. All the studies have small sample sizes and therefore may not have adequate sample strength. A couple of studies had adjunct treatment of CBT meaning the procedural overlap may confound interpreting the results (Culbertson et al., 2012; Niaura et al., 1999). Only two studies extinguished interoceptive cues in the form of

blood nicotine levels from intradermal patches and gum (McClernon et al., 2007; Niaura et al., 1999) and stress (Corty & Mcfall, 1984). A lot of the nicotine literature does however, have adequate control groups comparing CET to rapid smoking (Corty & Mcfall, 1984; Raw & Russell, 1980), relaxation and waiting list (Götestam and Melin, 1983), and self control training (Lowe et al., 1980). In addition to this, McClernon et al. (2007) addressed some of the most critical procedural adjustments to CET that could improve the efficacy. This experiment incorporated interoceptive cues, sham smoking and extinction in multiple of the participants personal life contexts. The results showed the number of cigarettes smoked per day decreased and that at the one month follow-up four participants were abstinent. The results of this study are quite supportive for the benefits of a modified CET for treating ND. Sham drug use would extinguish the response-outcome (R-O) alongside the stimulus-outcome (S-O) associations. This has been theorised to be beneficial to CET (Conklin and Tiffany, 2002; Troisi II, (2013), see section 1.3.2 Pavlovian-instrumental transfer for more details). There are several limitations to this study however. The two most important are small sample size and lack of control comparison. The participants of this experiment also wore nicotine patches. The authors argued this is not problematic because they release a steady stream of nicotine and therefore nicotine administration is not contingent on smoking or cues, however it would be interesting to see this study replicated without the patches and a longer follow-up.

The literature on the effectiveness of DCS augmenting CET for ND is inconsistent, but less positive than the alcohol literature. Santa Ana et al. (2010) showed DCS significantly decreased physiological and subjective cravings over placebo, but had no effect on number of cigarettes smoked. A more recent study had participants that achieved 18 hours of abstinence following four weeks of CBT entered into the CET procedure. In this procedure participants received either DCS or placebo 50 minutes before CET sessions. The results showed DCS augmented both reductions in cravings and higher abstinence rates (Otto et al., 2019). A limiation of these studies however, is there were no

control treatment to comapred CET to. Yoon et al. (2013) showed DCS had no effect on cravings or smoking behaviour. Craving and smoking decreased equivalently between CET and CBT groups immediately post-treatment, but did not last long enough at follow-up. A limiation of this study is the lack of ineffective control group. Another limiation is the sample are concurrently cocaine and noctine dependent, seeking smoking cessation. This comorbidity may confound the result. Kamboj et al. (2012) also reported DCS does not enhance CET effectiveness at attenuating cue reactivity. In summary, CET appears to have some weak effect at treating ND, but the existing research still needs to be developed on until any firm conclusions can be made.

1.2.5.2 Opiates

Over the last three decades there have only been 11 published studies on CET for opiate dependence (OD). Five out of the 11 studies were experiments that only recorded physiological and/or subjective measurements of cravings, withdrawal and other characteristics of OD before and after exposure sessions and did not report drug use at a follow-up (Childress, McLellan, & O'Brien, 1986; de Quiros Aragon, Labrador, & de Arce, 2005; Du et al., 2014; Franken, De Haan, Van Der Meer, Haffmans, & Hendriks, 1999; Powell, Gray, & Bradley, 1993). All except, de Quiros Aragon et al. (2005), consistently demonstrated participants would reduce subjective cravings and physiological withdrawal responses after CET treatment. Four out of the 11 were experimental trails that measured the effects of CET treatment programme with OD patients. One of the four compared CET to CBT and standard counselling. It did not measure cue reactivity, but did take measurements on the Addiction Severity Index (ASI) pre- and post-treatment. The results showed CET and CBT were comparable and better than standard counselling at improving ASI score (McLellan, Childress, Ehrman, O'Brien, & Pashko, 1986). Kasvikis, Bradley, Powell, Marks, & Gray (1991) measured cue reactivity and drug use pre- and post-CET treatment with no control condition. The results showed not many participants

demonstrated cue reactivity and amongst those who did, the effect of CET was inconsistent. In addition to this there was a high number of relapsers. The remaining two studies were randomised control trials comparing CET to standard psychotherapy (Dawe et al., 1993; Marissen, Franken, Blanken, Van Den Brink, & Hendriks, 2007). The results of these two studies showed that cravings decreased equivalently between groups. Dawe et al. (1993) showed both groups had equal relapse at follow-up. Marissen et al. (2007) was inconsistent with this showing the CET group had higher rates of relapse.

The CET for OD research has many of the same flaws as the AD and ND literature. For example they have small sample sizes and some of the studies do not have control groups (Childress et al., 1986; Franken et al., 1999; Kasvikis et al., 1991). One strength of the OD literature is a lot of the control groups used are standard psychotherapy treatment that inpatients would receive at the time and only one study was confounded with the CBT overlap (McLellan et al., 1986). A lot of the time, the cues used were standardised audio and photographic/ video images of heroin and people using. Except for one study which used stress as an interoceptive cue (de Quiros Aragon et al., 2005) none of the studies used interoceptive cues. Likewise none of the studies had participants do 'homework'. A noteworthy consideration about CET for OD is that experimental extinction does not easily translate into clinical exposure (McLellan et al., 1986). Early cue exposure research showed the technique to be too aversive and provoking for participants with high rates of drop out and relapse. Therefore, a more suitable version of CET was created which consisted off graded hierarchical exposure with exposure sessions ending with relaxation methods. As a result sham-drug use was excluded from the procedure. More recent research still produced high levels of relapse (greater than the control group) within the CET condition (Marissen et al., 2007). It is possible that CET is not a suitable treatment programme for OD because it is too aversive and risky for that sub-category of addicted population. Earlier it was theorised that adding sham-drug use, interoceptive cues such as priming doses and extinction in acquisition contexts might increase CET efficacy.

However, sham-drug use, priming doses and exposure to drug using and buying contexts might be too aversive and increase the risk to relapse in OD when they may not in patients addicted to other substances (de Quiros Aragon et al., 2005; McLellan et al., 1986).

1.2.5.3 Cocaine

Over the last three decades there have only been five published papers on CET for cocaine dependence (CD). One experiment (Prisciandaro et al., 2013) was excluded from this review because the purpose of the paper was to investigate the effects of DCS on changes in brain activation with no mention of subjective or physiological cravings or drug use. The earliest of the remaining four reported changes in subjective cravings and physiological cue reactivity and drug use after CET sessions (O'Brien et al., 1990). The remaining three investigated whether DCS augmented CET in reducing cravings without reporting drug use (Price et al., 2010, 2013; Santa Ana et al., 2015).

The early research on CET and CD was promising. The research on opiates produced from O'Brien and Childress' research team allowed for a quick refine of the CET procedure for cocaine-dependent patients. Unlike opiates where stimuli could associate with cravings and/or withdrawal, it was realised conditioned craving for cocaine was closely related to episodes of cocaine use (Childress, McLellan, Ehrman, & O'Brien, 1988). O'Brien et al. (1990) assigned 30 CD patients to one of four treatment groups. They were assigned to Supportive-Expressive psychotherapy with exposure sessions (SE-X) or with 'control activities' (SE-C) or standard drug counselling with exposure sessions (DC-X) or with 'control activities' (DC-C). 'Control activities' sessions of self-help which were equal in length and number of exposure sessions. The exposure sessions consisted of 15 1-hour inpatient sessions followed by eight outpatient sessions. Subjective cravings, physiological arousal measured by temperature and Galvanic skin response (GSR) to cues and drug use were the dependent measures. The study only reported analysis of the inpatient sessions. Exposure consisted of audio, video and simulated administration ritual.

The results showed cravings reduced slowly across all 15 sessions. Both temperature and GSR did not fully extinguish over the 15 sessions. The mean time for treatment drop-out for control groups were one to three weeks with enormous attrition. The preliminary data showed the mean time for the CET groups were seven weeks with less attrition than the controls. While no patient achieved complete abstinence, the CET groups have more weeks of less cocaine use than the controls.

The preliminary findings from O'Brien et al. (1990) were encouraging for CET's therapeutic gains for CD. There has been no published research since that has studied the efficacy of CET without adjunct treatment for CD. Recently, there has been attempts to augment the reduction of conditioned craving to cocaine cues with DCS (Price et al., 2010, 2013; Santa Ana et al., 2015). The procedure for these experiments are fairly similar. CD participants are randomly assigned to 50 mg of DCS or placebo and complete two (Price et al., 2010) or three (Price et al., 2013; Santa Ana et al., 2015) CET sessions. The CET sessions consist of in vivo and video exposure. Participants receive their drug administration either two hours (Price et al., 2010), 15 minutes (Price et al., 2013) or 30 minutes (Santa Ana et al., 2015) prior to CET sessions. The results of three experiments do not support the use of DCS to supplement CET. At best DCS had no effect on reductions in cravings gained from CET (Santa Ana et al., 2015) and at worst DCS was associated with increasing conditioned cravings (Price et al., 2010, 2013).

In summary, the CET literature is limited for all drug classes and future research is needed to address the issues of small sample sizes, adequate control groups, types of cues extinguished, and 'homework' to name the most prominent issues. Research using DCS to augment CET needs to include behavioural measures of drug use in a long-term follow-up to see how this relates to subjective cravings. It is also possible that the very nature of CET research might make it an unsuitable treatment programme for OD.

1.2.6 The efficacy of CET for other psychiatric disorder

1.2.6.1 Anxiety disorders

The principles of CET to treat ANX are the same as AD. In ANX, patients are exposed to the fear-related cues in extinction and the CRs are inhibited. The effectiveness of CET treatment of anxiety disorders has been demonstrated convincingly. For specific phobias, CET and VRCET were equivalent and superior over waiting list for treating fear of flying with 93% in the CET and VRCET group having flown by follow-up (Rothbaum, Hodges, Smith, Lee, & Price, 2000). In fact CET has been shown to be so effective for treating specific phobias that a one-off exposure session has been shown to be an effective treatment over waiting list, manual based treatment and CBT with long-term effects remaining at the one year follow-up (Hellström & Öst, 1995; Öst, Alm, Brandberg, & Breitholtz, 2001; Lars Göran Öst, Hellström, & Kåver, 1992). However, CET + relaxation treatment has been shown to be inferior to CBT (Clark et al., 2006).

A similar result is shown for social anxiety disorder (formally called social phobia). Research has shown that CET is better than waiting list at symptom reduction with treatment effects remaining just as strong or increasing by the six month follow-up (Andersson et al., 2006; Butler, Cullington, Munby, Amies, & Gelder, 1984). However, the Butler et al. study showed CET effectiveness was augmented with adjunct anxiety management treatment. Likewise, there is research showing cognitive reconstruction (a core component of CBT) improves CET efficacy (Mattick & Peters, 1988), but a meta-analytic review and subsequent research of VRCET have demonstrated CET and CBT are equivalently effective treatments for social anxiety disorder (Feske & Chambless, 1995; Klinger & Bouchard, 2005). Attempts to augment CET with adjunct pharmacological treatment for social anxiety disorder have been more successful than addiction. While nasal oxytocin administration did not improve CET effectiveness (Guastella, Howard, Dadds, Mitchell, & Carson, 2009), DCS has (Guastella et al., 2008; Hofmann et al., 2006).

Exposure treatment for OCD is usually called exposure-ritual prevention in the literature. For the treatment of OCD, one study compared CET + placebo, CET + clomipramine, clomipramine alone and placebo alone. The results showed CET with and without clomipramine was better than clomipramine alone and placebo (Foa et al., 2005). A limitation of this study was there was no behavioural control group. Some studies comparing CET to CBT have shown CET and CBT to be equivalent in treatment outcomes (Vogel et al., 2004; Whittal, Thordarson, & McLean, 2005). However a more recent study has shown the effectiveness of CET to be superior to CBT in treating OCD (Olatunji et al., 2013). The first study to use adjunct DCS treatment to augment CET did not show added benefits (Storch et al., 2007). However, other research has suggested DCS increases CET effectiveness in the first four treatment sessions, but becomes equivalent with placebo by the tenth (Kushner et al., 2007).

For the treatment of posttraumatic stress disorder (PTSD), CET has been shown to be more effective than stress inoculation training and waiting list for treating PTSD (Foa et al., 1999; Hensel-Dittmann et al., 2011). However, CET has been shown to be comparable to CBT in reducing PTSD symptoms in refugees (Paunovic & Ost, 2001). A large meta-analysis review has demonstrated that CET is superior to waiting list in treating the primary and secondary outcomes of PTSD with 86% of patients in the exposure group having better treatment outcomes over the control group. However when CET was compared to CBT and stress inoculation training it was shown to have equivalently effectiveness in treating PTSD (Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010). Adjunct DCS treatment has been shown to enhance the effect of CET for PTSD (De Kleine, Hendriks, Kusters, Broekman, & Van Minnen, 2012; Difede et al., 2014). However, DCS has also been shown to be inferior than placebo for in its ability to enhance CET effectiveness in measures of primary and secondary outcomes for PTSD in veterans (Litz et al., 2012). One reason for Litz et al's findings however could be due to the fact that the participants in the DCS arm of the randomised control trial had greater scores on the

subjective units of distress scale. Litz argued care needs to be taken to delineate between subgroups of PTSD populations.

For the treatment of panic disorder with agoraphobia (PDA), one study compared exposure to exteroceptive cues only, interoceptive cues only, exteroceptive and interoceptive cue combination and waiting list. The results showed all three exposure groups were equal to each other, but superior to waiting list in the effectiveness of treating PDA in both the short term and one year follow-up (Ito et al., 2001). In addition to this CET has been shown to be a more effective treatment for PDA than relaxation treatment and alprazolam (Marks et al, 1993). However, in a study in which CET was compared to CBT they were equivalent in their effectiveness (Bouchard et al., 1996; Öst, Thulin, & Ramnerö, 2004). However, therapist guided exposure augments standard CBT for treating PDA (Gloster et al., 2011). A Meta-analysis has suggested that CET with CBT is the most effective treatment for PDA (d = .88) when compared to other behavioural and pharmacotherapies (Gould, Ott, & Pollack, 1995). In addition to this other meta-analyses have concluded that in vivo exposure has poor efficacy for the treatment of PDA, but interoceptive exposure is the most effective outcome (van Balkom et al, 1997; Pompoli et al., 2018).

Overall, CET has been shown to be an effective treatment for ANX on both primary and secondary outcomes. This is supported by systematic reviews that analyse CET effectiveness collapsed across anxiety disorder type (Deacon & Abramowitz, 2004; Norton & Price, 2007; Opriş et al., 2012). Norton and Price's meta-analysis concludes that exposure treatment alone has an effect size of d = 1.48 immediately after treatment and d = .2 by follow-up. Likewise CET with CBT has a similar effect size strength in the short term (d = 1.56) and at follow-up (d = .15). This is greatly superior than the effect size of CET collapsed across addiction type that Conklin and Tiffany (2002) generated (d = .08).

1.2.6.2 Binge eating disorder

CET has been used to treat BE with the principle of exposing patients to food-related cues to inhibit the CRs. The earliest research that applied CET to the prevention of binge eating was by Jansen and colleagues. This research showed CET was successful in treating binge eating (Jansen, Van Den Hout, De Loof, Zandbergen, & Griez, 1989; Jansen, Broekmate, & Heymans, 1992). Jansen et al. (1989) reported a case study of a 22 year old female bulimic patient. The patient received 16 1-hour sessions of in vivo exposure at the hospital. She also had to confront binge food without eating it at home. The results showed both cravings and binge eating behaviour decreased. This case study is further supported by Jansen et al. (1992). In this study, patients' comorbid with obesity and bulimia nervosa were randomly allocated to a CET condition or a self-control condition for supressing binge eating behaviour. Results showed 100% of the CET patients had long-lasting binge eating abstinence, while 67% of the self-control condition had relapsed back to binge eating by the follow-up. More recent research has demonstrated that cue exposure in in vivo and virtual reality is also successful in reducing cravings for food and reducing eating in the absence of hunger (Gutiérrez-Maldonado, Pla-Sanjuanelo, & Ferrer-García, 2016; Schyns, Roefs, Smulders, & Jansen, 2018). A recent systematic review also concluded CET is effective at reducing binge eating behaviours (Koskina, Campbell, & Schmidt, 2013).

Finally, it can also be argued that CET is a more effective treatment than CBT for treating bulimia. CBT has been demonstrated as a successful treatment for bulimia and is now the standard treatment (Koskina et al., 2013). Carter & Bulik (1994) argued, from the data available at the time, that it was unclear whether CET enhanced CBT. They argued it could potentially enhance CBT if exposure sessions were adequately long, the sample population was homogenous (e.g. delineating subgroups such as bulimia with and without depression), if there was an adequate comparison group and if there was a clearer distinction and less procedural overlap between CET and CBT. Koskina et al. (2013)

argued the success of CBT in conjuncture with the unclear benefits of CET over CBT has resulted in a dearth of CET research. Recently, research has supported the idea that CET is more effective than CBT at reducing binge eating behaviour. This research has shown that CET completely suppresses binge eating cravings/ behaviour in patients that were previously resistant to CBT treatment (Toro et al., 2003; Martinez-Mallén et al., 2007). It should be noted that the limitations of BE CET literature discussed here are issues such as inadequately powered samples, extinction was limited to only salient exteroceptive cues, and most did not include a control comparison group (Gutiérrez-Maldonado et al., 2016; Martinez-Mallén et al., 2007; Toro et al., 2003). These are the most prominent limitations of the AD and ANX CET literature. Earlier (see section 1.2.3 CET efficacy discussion) it was hypothesised that maybe CET efficacy would increase for AD if these limitations were addressed as more refined and controlled research would generate a clearer picture. However, these limitations are also present in the ANX and BE literature. The ANX and BE literature demonstrate clearly that CET is effective for treating those disorders as shown by the effect size of exposure treatment in ANX compared to AD. There has not been a recent meta-analysis of CET for BE, but a systematic review has argued CET consistently and strongly improves the primary outcomes of BE (Koskina et al., 2013), whereas CET does not for AD (Conklin & Tiffany, 2002; Mellentin et al., 2017). This discrepancy between AD and ANX/BE outcomes will be referred to as the *Alcohol Cue-Exposure Therapy Paradox* (ACETP).

1.2.7 The Alcohol Cue Exposure Therapy Paradox

It should be noted here that the limitations within the CET literature for the treatment of AD are consistently present in the ANX and BE literature. Within the ANX and BE literature there are still a considerable number of studies that compare CET to CBT. In addition to this the range of cues extinguished are limited amongst the small sample sizes. Therefore, this suggests that the discussed limitations within the

methodology in the published CET literature has had little impact on the outcome in regards to the effectiveness difference between AD and ANX.

One reason for the ACETP could be explained by differences in the US valence between AD and ANX. For example, AD has an appetitive US and ANX has an aversive US, however this explanation seems unlikely when it is considered that BE also has an appetitive US. Perhaps the ACETP could be explained by individual differences in learning mechanisms between drug dependent and non-dependent individuals.

While AD and ANX populations have not been tested within a direct comparison, past research suggests AD populations may have different conditioning ability compared to ANX and general populations. For example, it has been shown that individuals within ANX populations have stronger responses to fear-related cues in terms startle and autonomic responses (Mcteague et al., 2009) and exaggerated neural activity that is involved in the processing of fear (Schweckendiek et al., 2011) compared to healthy controls. Likewise, as discussed in more detail in the next section, individuals in an AD population have stronger cue reactivity for alcohol-related cues compared to healthy controls. However, research has shown that clinically anxious children who did respond to CBT treatment had equivalent acquisition and extinction of laboratory induced fear associations to non-clinical children. Both these groups did not acquire greater conditioned negative evaluations of the fear-related CS relative to the neutral CS. Moreover, they successfully extinguished the fear-related CS during extinction training. Whereas, the anxious children who did retained their diagnosis post-treatment had greater conditioned negative evaluation to the fear and neutral CS, compared to controls and never fully extinguished their philological responses to the CSs (Waters & Pine, 2016). This result suggests, excluding a subpopulation of ANX patients, ANX patients are typically similar in general conditioning ability. Meaning that ANX do not develop changes to Pavlovian conditioning as a consequence of their disorder. Therefore, CET may be successful for ANX disorders as their ability to extinguish conditioned responses has not been impaired.

There is however, no research that directly tests the general conditioning ability between AD and control populations in a human sample (this is discussed in greater detail in the next section), but there is reason to believe history of alcohol consumption influences Pavlovian and instrumental abilities. See Chapter 4 for further exploration of this.

Individual differences between AD and non-dependent populations in associative learning may lie within one or more of: 1) learning ability of either CS-US acquisition, extinction, or response recovery (which could further be complicated by the roles of context and occasion setting). 2) The interaction of reinforcer type (e.g. alcohol vs non-drug US) with acquisition, extinction, or response recovery. 3) The interaction between Pavlovian and instrumental learning.

1.3 Individual differences in addiction

The previous section explored the methodological quality of the CET literature and explained how the limitations in the alcohol literature were also present in the anxiety disorder and binge eating literature indicating that these are likely to have had little impact for ACETP. Likewise the difference between the appetitive US of AD and aversive US of ANX is unlikely to account for ACETP as CET is effective for treating BE which has an appetitive US and similar conditioning mechanisms to AD. Therefore, the ACETP may be explained by individual differences between AD and non-dependent populations which can be expressed through 1) reactivity and extinction (i.e. resistance-to-extinction) of CSs which may be mediated by impulsivity, 2) Pavlovian-instrumental transfer and 3) context learning (multiple contexts/occasion setting).

1.3.1 Resistance-to-extinction and impulsivity

As shown from the CET literature in the previous section, alcohol consumption affects an individual's cue reactivity to alcohol-related cues. It has been well documented that AD patients, when exposed to alcohol-related cues, have greater physiological reactivity (e.g. increased heart rate and salivation) and subjective cravings for alcohol

compared to both neutral cues (Carter & Tiffany, 1999; Cooney, Litt, & Morse, 1997; Davidson, Tiffany, Johnston, Flury, & Li, 2003; Fatseas et al., 2015; Gauggel et al., 2010; Kaplan, Meyer, & Virgilio, 1984; Staiger & White, 1991; Witteman et al., 2015) and healthy controls (Lee, Namkoong, Lee, An, & Lee, 2006; Monti et al., 1987; Pomerleau, Fertig, Baker, & Cooney, 1983; Thomas, Drobes, & Deas, 2005). Similar results have been replicated in social drinkers and heavy drinkers (Field & Jones, 2017; Field, Mogg, Zetteler, & Bradley, 2004; Ramirez et al., 2014; Veilleux, Lovett, Skinner, & Ham, 2018). Indeed, Carter & Tiffany (1999) meta-analysis of cue reactivity has shown the overall effect size of subjective cravings are strong when collapsed across all drug classes (d = .92). This study's results also showed that alcohol-related cues elicit weaker cue reactivity than other drugs (opiates, nicotine, and cocaine) but still has a significant moderate effect size (d = .53).

Cue reactivity to alcohol-related cues can be increased by various mediating variables such as negative mood (Cooney et al., 1997), the use of a priming dose (Davidson et al., 2003) and expectations of alcohol availability or knowledge of real alcohol consumption (Davidson et al., 2003; Kaplan et al., 1984). In addition to this, research has also shown reported cravings are stronger when the cues used are idiosyncratic as opposed to general alcohol-related cues (Fatseas et al., 2015; Staiger & White, 1991). Cue reactivity to alcohol-related cues in AD patients has been shown to be a predictor of relapse; research has demonstrated a positive correlation between strength of reactivity and quantity of alcohol consumed during relapse (Fatseas et al., 2015; Rohsenow et al., 1994; Sjoerds et al., 2013). It must be noted however, that cravings do not always predict relapse (Monti & Rohsenow, 1999; Witteman et al., 2015). Research by Papachristou, Nederkoorn, Corstjens, & Jansen (2012) has identified trait impulsivity to be a mediating factor in strength of cue reactivity, but high trait impulsivity has been shown to correlate with a reduced probability of relapse (Papachristou, Nederkoorn, Giesen, & Jansen, 2014). The authors of this study noted that this negative correlation result is

inconsistent with previous research which has shown high trait impulsivity predicts relapse in AD patients (Evren, Durkaya, Evren, Dalbudak, & Cetin, 2012) and argued more research is needed to fully explore this area.

Impulsivity is heavily associated with addiction (Goldstein & Volkow, 2012). It is well documented that heavy social drinkers and alcohol dependent individuals score higher on behavioural tasks and questionnaires that measure impulsiveness (Field, Christiansen, Cole, & Goudie, 2007; Papachristou et al., 2012; Taylor et al., 2016). Response inhibition is fundamental for extinction of Pavlovian CSs. Animals models have shown higher traits of impulsivity are related to resistance-to-extinction ([REX] Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012). REX is the reduced ability to extinguish CS-US pairings where it takes an individual longer to fully inhibit a CR or the CR is never completely supressed. In addition to this, alcohol-related cue exposure has been shown to impair response inhibition (Field & Jones, 2017; Gauggel et al., 2010; Kreusch, Billieux, & Quertemont, 2017).

The results of Papachristou et al. (2012) suggested trait impulsivity and cue availability may have an effect on of cue extinction during CET. For example, highly impulsive AD are aware that during the CET procedure (and during their residence in an inpatients clinic in general) alcohol is unavailable to them. Therefore, the alcohol cue could be less salient during extinction training which according to the R-W model would result in inferior extinction training. When the highly impulsive patient returns to the contexts of their everyday life, there are many signals presented that indicate alcohol is an easily obtainable commodity and therefore alcohol-related cues become highly salient. With the alcohol-cues not fully extinguished and the shift from low-salience to high-salience of the cues and contexts now available, it is theoretically likely that the patient would relapse.

A history of heavy alcohol use has also been associated with REX (Gass et al., 2014). There has been no human research investigating REXs link to alcohol use, however

(Sheynin et al., 2016) has shown male heroin addicts demonstrated REX of avoidance behaviour. In addition to this, Hogarth et al. (2014) indirectly measured REX with nicotine cues. In this experiment Pavlovian cues and behavioural responses (key press) were both trained separately for cigarettes. The Pavlovian CS then underwent extinction training. Participants were then given the chance to make the instrumental response for cigarette while the CS was systematically presented. The results showed that despite the CS undergoing extinction training, participants still increased responding for cigarettes when the CS was present compared to when it was not. Therefore, it is reasonable to assume that heavy alcohol use and impulsivity (or their interaction) in humans is associated with REX of alcohol cues. If this is the case it could explain ACETP.

1.3.2 Pavlovian-instrumental transfer

As mentioned earlier, instrumental conditioning is the second major associative mechanism controlling behaviour. Although the fundamental component of instrumental conditioning is the response-outcome association this associative structure does not exist in isolation. The execution of many responses only produces outcomes under some conditions and the value of the outcome depends on the motivational state of the organism. In fact, discriminative control of instrumental behaviour, whereby instrumental responses occur only in the presence of specific stimuli, requires an interaction between Pavlovian and instrumental processes. Studies of this interaction fall under the heading of Pavlovian-instrumental transfer (PIT). The earliest PIT studies were not referred to with that name, but nevertheless manipulated and measured these variables in animal research (Rescorla & Soloman, 1967). In regards to aversive learning, dogs have been trained to avoid an electric shock by pressing a panel in the sight of a discriminative stimulus (S^D), in this case, when a light would turn off. Next the dogs were paralysed with curare. While under paralysis the dogs were trained to make Pavlovian associations between tones and electric shocks; one tone predicted the onset of an electric shock (CS+) while the other did not

(CS-). Finally, the dogs had to panel press in extinction. The results showed the CS+ had the same magnitude of avoidance responding as the S^D, i.e. panel presses were comparable between when the light turned off with no CS present and when the light stayed on when the CS+ was present. In addition to this the presence of the CS- reduced responding (Solomon & Turner, 1962). In regards to appetitive learning, hungry pigeons were subjected to Pavlovian training to associate a coloured light with a food reward (red and green light colours were counterbalanced as CS+ and CS-). Next they were trained to peck on a variable-interval schedule for food. Finally, they had to peck in extinction while the CS+ and CS- were presented intermittently. The results showed the CS+ and not the CS- increased pecking for food (Morse & Skinner, 1958). Since CSs can influence the expression of instrumental behaviour the PIT effect could potentially explain the ACETP if the PIT effect for alcohol differed from those produced by other types of reinforcer or if individuals with alcohol dependence differed from others in terms of PIT.

Tiffany et al. (1990) put forward a theory that behaviours including drug use can become automatic. This theory holds that drug use is made up of multiple small components of behaviour, for example in regards to alcohol consumption, an individual must locate a source of alcohol (e.g. fridge, off licence, public house), ask for/ reach for the beverage, open beverage with either bottle opener, corkscrew or hands, lift to mouth, pour into mouth, and swallow. Overtime each step becomes practiced and quick and stored as action schemata. If alcohol consumption reliably occurs in the same context or in the presence of the same stimuli they become associated with the actions in the schema. After enough practiced alcohol consumption, the behaviour becomes automatic in the sense that it is performed quickly, efficiently and effortlessly. It is stimulus bound, meaning that activation of the schemata and by extension behaviour is triggered by the alcohol-related contexts/ CSs and the behaviour can be completed without conscious intention or awareness and is hard to impede once started. The theory also postulates that because subjective cravings are not always reported as occurring before a patient relapses, cravings

are not representations of motivation, but are the product of when non-automatic cognitive processes interfere with automatic trigger of schemata.

PIT research has been useful to show how the interaction of Pavlovian and instrumental associative learning leads to habitual behaviours. Contemporary theories hold that instrumental learning is the formation of the association between response and outcome (R-O). It has been shown that R-O associations are bidirectional meaning that the outcome can retrieve knowledge of the appropriate response to achieve said outcome (O-R). De Wit & Dickinson (2009) discussed the role of both R-O and O-R learning in goal directed behaviour. They argued for behaviour to be goal-directed an individual must have both knowledge of the R-O contingency and desire for the outcome. They argued that people do not learn R-O contingencies in isolation, but also learn stimulus-outcome (S-O) associations via Pavlovian conditioning. Therefore, an individual's goal-directed behaviour can be O-R driven; they think of an outcome and complete a response to achieve it. Often CSs can retrieve the memories of outcomes which in turn retrieves a memory of response meaning behaviour can be governed by S-O-R chain. Alternatively an individual's behaviour can be R-O driven; an individual can be presented with two choices 1) go upstairs where the bed is in the bedroom or 2) go down the hall to where the books are in the lounge. Each response retrieves the memory of an outcome to sleep or read and the desired outcome will determine the chosen response. In most situations an individual has multiple responses to choose from and stimuli can help select a response (S: R-O). With every rewarded S-O and R-O, the stimulus and response creates a stronger associative link until the CS can directly retrieve a memory of the response (S-R). When the S-R has been formed behaviour becomes automatic and habitual. This is analogous to Tiffany's (1990) automatization (De Wit & Dickinson, 2009; Hogarth, Balleine, Corbit, & Killcross, 2013) and theorised to be the mechanism of compulsion which contemporary theories posits is the definition of addiction (Everitt & Robbins, 2016; Nick Heather, 2017).

As stated earlier, the PIT paradigm was first used in animal research, but has since been adapted to use with humans. The typical PIT procedure is lengthy and complex as it consists of three stages. 1) Pavlovian conditioning to form S-O associations: in this stage distinct CSs: S_1 and S_2 (i.e. tone and light) are paired with different outcomes, O_1 or O_2 (i.e. alcohol/ ethanol or food). 2) Instrumental conditioning to form R-O associations: in this stage different responses: R_1 and R_2 (i.e. lever-press/chain-pull or button press) are associated with O_1 and O_2 from the first stage. 3) Transfer test: in this stage subjects are allowed to perform R_1 and R_2 in extinction while S_1 and S_2 are intermittently presented. Appetitive PIT experiment results generally show a PIT effect; the CS enhance the response which shares the same reward association as the CS (Allman, DeLeon, Cataldo, Holland, & Johnson, 2010; Cartoni, Puglisi-Allegra, & Baldassarre, 2013; Hogarth & Chase, 2011; Talmi, Seymour, Dayan, & Dolan, 2009). This is referred to as outcome-specific PIT. There is also general PIT where CSs that have been paired with a reward increase general excitatory arousal and increase responses that lead to unrelated awards (Corbit & Balleine, 2005; Corbit, Janak, & Balleine, 2007; Glasner, Overmier, & Balleine, 2005). Therefore, outcome-specific PIT takes into consideration the outcome in the S-O-R chain, because the stimulus elicits a memory of the sensory features and value of the outcome and engages in a behaviour most appropriate to achieve said outcome. Whereas general PIT does not take the outcome into consideration.

As discussed above, habitual behaviours are insensitive to devaluation of the outcome. The development of habit formation has been shown to be influenced by reinforcer type as alcohol-CSs have been shown to increase the propensity for alcohol drinking behaviour after alcohol has been devalued, but food-CSs do not (Corbit et al., 2007; Corbit, Nie, & Janak, 2012; Dickinson, Wood, & Smith, 2002). In devaluation experiments, once successful instrumental training for an outcome has been achieved, devaluation is achieved with either satiety or pairing the outcome with a noxious chemical to induce illness (conditioned taste aversion). Corbit et al. (2012) have demonstrated after

two weeks of training, instrumental self-administration of alcohol is goal-directed, but after eight weeks it transitions to habitual control in their devaluation paradigm. There is evidence to believe that alcohol exposure can also bias an individual towards developing habitual behaviours. Corbit et al. (2012) showed rats that were trained on instrumental response for sucrose and received alcohol pre-exposure were insensitive to devaluation while rats that were also trained in the same R-O association, but did not receive alcohol cue-exposure were sensitive to devaluation. Likewise, Mangieri, Cofresí, & Gonzales (2014) trained one set of rats to lever-press for alcohol and another set of rats to lever-press for sucrose. Next, the instrumental response was put under extinction and the lever-press stopped predicting the reward. Undermining the R-O association is conceptually similar to devaluing the outcome. The alcohol trained rats were insensitive to the degrading of the R-O, but the sucrose trained rats were not. It is not surprising that alcohol CSs produces general PIT and alcohol promotes habitual behaviours because both general PIT and habits do not utilise the outcome properties and value.

Similar insensitivity to devaluation has been shown in AD patients in PIT studies. Sjoerds et al. (2013) found alcohol dependent patients rely on S-R strategies more than healthy controls. In this study participants (AD and controls) had to learn the correct button press for each stimulus to receive the correct outcome. There were three types of R-O associations 1) standard: in which the stimulus and outcome pictures were different, 2) congruent: in which the outcome picture that followed to stimulus picture were identical and 3) incongruent: where the stimulus picture for one trial will be an outcome for another trial and vice versa. Standard and congruent R-O associations can be learned with goal-directed or habit, whereas incongruent is preferential to habit only. Following the discrimination learning phase, some outcomes were devalued and participants had to respond for the still-valued outcomes only. There two main findings were 1) appropriate responding for the incongruent R-O was impaired for both groups indicating participants were still responding for the devalued outcome which was trained with an S-R method. 2)

Regardless of R-O type the AD group had impaired performance compared to the controls indicating they had inferior knowledge of the goal-directed rules.

The transition from goal-directed actions to habitual behaviour could explain why NTX has thus far been unsuccessful in facilitating CET. NTX blocks the rewarding effects of alcohol and is essentially a devaluation technique.

The animal models of addiction has led some to theorise the best treatment for addiction might be a combination of Pavlovian and instrumental learning extinction. Troisi II (2013) argued extinguishing the S-O association alone is insufficient to prevent relapse and both S-O and R-O associations need to be degraded simultaneously. Troisi II (2013) argued alcohol consumption is the terminal of a long operant chain. For example, the "open" sign of the public house can act as a S^D which sets the occasion for alcohol seeking behaviour. This can be exacerbated by interoceptive cues such as an individual being thirsty, angry, sad or celebratory. The individual then responds by walking up to the bar (R_3), receiving a S^D_2 of the bar tender asking what drink the individual wants, followed by responding (R_2) with a drink, followed by an S^D_1 of the sight and smell of alcohol, followed by lifting the glass (R_1) and terminating with consumption and the reinforcement (SR+) from the pharmacological effects of alcohol. Therefore establishing a S^D_3: $R_3 \rightarrow S^D_2$: $R_2 \rightarrow S^D_1$: $R_1 \rightarrow$ SR+ chain, where the S^D acts as both an occasion setter and reinforcer for subsequent operant behaviour. Troisi II (2013) and Conklin & Tiffany (2002) argued the most beneficial addition to CET would be unreinforced alcohol/ drug taking actions e.g. drinking a placebo or mock heroin shoot-up. That would accommodate the extinction of both S-O and R-O contingencies.

While this still needs to be empirically tested directly, there is preliminary support for this (Hogarth et al., 2014; Seabrooke, Le Pelley, Porter, & Mitchell, 2018). Seabrooke demonstrated that the extinction of a Pavlovian CS does not affect the PIT effect (experiment one), but the PIT effect is attenuated when the CS acts like S^D (signals the availability of the reward) and is extinguished via extinction (experiment two and three).

Likewise, Hogarth et al. (2014) demonstrated S^D extinction (experiment two), but not CS extinction (experiment one) attenuates the PIT effect of alcohol seeking behaviour in social drinkers, therefore demonstrating potential of the extinguishing responding from the S^D alcohol seeking behaviour.

While it has been demonstrated that habitual behaviours easily develop in animal models of addiction, the applied human literature is not as supportive of the role of habit in addiction and questions the importance of the role compulsion plays in addiction (or at least for all people with an alcohol use disorder diagnosis). Within all the models of addiction discussed in this thesis, compulsion is the core distinction between addictive and non-addictive behaviour. However, a recent review has summarised and discussed the research that addresses the role of compulsion in addiction and puts together a compelling argument that compulsion does not do a very good job at either explaining or describing addiction and the importance of compulsion is contradicted by a substantial body of evidence that cannot be ignored (Heather, 2017). So while it was demonstrated earlier that habit is the impairment of incentive evaluation, habit may not be all that important for addictive behaviour.

For the sake of brevity only the strongest arguments that doubt compulsion will be summarised here. Firstly, Heather differentiates between strong and weak compulsion. It is argued that strong compulsion arises from aberrant learning (e.g. S-R) and aligns with theories proposed by Everitt & Robbins (2016) and Tiffany (1990).Whereas, weak compulsion comes from motivational states where cravings are the antecedent for addictive behaviour and aligns with positive reinforcement theories (e.g. Robinson & Berridge (1993). These theories would suggest that compulsion arises from Pavlovian learning and stimuli will either trigger drug seeking and use that is automatic or elicit a strong motivational state wherein drug use becomes irresistible.

However, as past research has shown, severe AD patients have chosen monetary rewards over alcohol rewards (even in the presence of partial withdrawal symptoms)

indicating goal-directed action was intact as the non-drug reward had greater incentive at the time of testing (Mello and Mendelson, 1972). In addition to this, research has shown that a priming dose, a delay to reward, and an increase in monetary incentive can influence whether participants remain abstinent. Cohen, Liebson, Louis, & Speers (1971) has shown that when the authors were 'buying' AD abstinence, a priming dose or a delay in receiving reward resulted in a disruption to abstinence, however, this was reversed when the monetary reward was increased.

This goal-directed free-choice between drug or monetary reward is reflected outside the laboratory too. Research has shown that patients who are on contingency management treatment programmes have higher rates of abstinence than other types of treatment (e.g. CET/ CBT). Contingent management treatment is a behavioural treatment that operates on operant learning mechanisms (and therefore ignore Pavlovian learning). Patients in this treatment programme are rewarded for remaining abstinent, usually with a voucher or money. One study showed contingency management resulted in 78% of participants remaining fully abstinent (Dupont & Humphreys, 2011). Meta-analysis reviews have determined contingency management treatment efficacious to achieve abstinence (Benishek, et al. 2015) with one review concluding contingency management was the most efficacious type of intervention for addiction (Dutra et al., 2008).

The second line of research Heather gives is the nature of recovery and relapse. Heather challenges the notion that addiction is long-lasting and chronic by presenting data that shows the majority of patients who recover from addiction have done so without treatment; the majority of these recoveries correlate with improvements in one's life in areas such as marriage and employment. Heather also discusses the case of the Vietnam War veterans. In this case, the service men in Vietnam had access to inexpensive heroin, 20% of which used regularly. Use however dropped off precipitously when they returned home. The main reason the soldiers gave were they considered using heroin sordid, the increase in price, and the fear of arrest. What is interesting was not all soldiers became

abstinent, but some used heroin infrequently and recreationally. Heather also mentions that patients often plan their relapse which directly contradicts the notion that relapse is an involuntary stimulus reaction.

The final line of evidence Heather uses is from rodents. Traditionally, animal research on drug administration has rodents in isolation choosing to administer drugs. However, when rodents are put into enriched cages (e.g. spacious with numerous toys and opportunities for sex), rats mainly chose to drink plain water over morphine-laced water. It could be argued that the second and third line of research can be explained by contextual control of the environment i.e. drug use is to alleviate a negative affect or stressful environment. However, the first line of research about individual choice of incentive cannot be explain by Pavlovian mechanisms. It is beyond the scope of this review to try to resolve the role of compulsion in addiction, but it is important for the reader to be aware of the contradictory research.

In addition to Heather's arguments, PIT studies are useful for gleaming information on how important habit is in a controlled environment. For studies with a human sample, the number of PIT experiments that utilise an alcohol US or have an AD sample is limited so studies with other drugs will be considered here. Some studies do suggest habit is important. For example, it has been shown AD individuals are more susceptible to Pavlovian cues with PIT effects being stronger in an AD population than controls (Garbusow et al., 2014) and the strength of PIT effect predicts risk of relapse (Garbusow et al., 2016). However, as Hogarth et al. (2018) results showed, goal-direct control of behaviour remained intact in treatment-seeking drug user in two different PIT designs.

In summary, Pavlovian CSs can exert influence on behaviours. Usually goal-directed and habitual behaviours interact dynamically for governance of control on behaviour, but exposure to alcohol facilitates habitual control and likely explains the development of strong S-R learning in AD individuals for alcohol seeking behaviour with alcohol consumption in the face of negative consequences and relapse. This has led to the

theory that CET could benefit from S-O and R-O degrading via unreinforced mock drug taking procedures. Caution is needed in moving forward with future research investigating this however, as noted earlier, sham heroin use as a component of the CET procedure may be detrimental for the outcome of OD patients. In addition to this, there are several lines of research that downplay the role of compulsion in addiction, therefore while alcohol and drugs may lead to a SUD patient's reliance on habitual learning, habit may not be fundamental in addictive behaviour. More research is needed to fully determine the role compulsion plays in addiction.

1.3.3 The role of context in extinction learning and occasion setting

1.3.3.1 Context in cue-exposure extinction

Conklin & Tiffany (2002) discussed threats to extinction that could account for CET's inability to achieve abstinence. These threats include 1) spontaneous recovery, which is the return of the extinguished response after a certain time period, 2) renewal, which is the recovery of the extinguished response when an individual is removed from the extinction context and re-entered into the original acquisition context or a novel context, and 3) reinstatement, which is where the extinguished response re-emerges after post-extinction exposure to the US.

As Conklin & Tiffany (2002) highlight renewal as a very serious candidate mechanism undermining CET efficacy. This is because an AD individual acquires alcohol-related cue associations in an environmental context such as a home, friend's house or a public house to name a few and treatment/ extinction occurs in a clinical setting. Therefore when the AD individual leaves hospital and returns to the acquisition context(s), the individual is now vulnerable to renewal and by extension relapse. It seems unlikely that any of the threats to extinction in isolation are to account for the current effectiveness of CET for treating AD as these threats also apply to ANX and BE behaviour. However, this section will discuss the possibility that individual differences between AD/ heavy drinkers

and light drinkers and/or reinforcer type (alcohol US or non-drug US) could interact with these threats to extinction. First, the three studies listed in Martin et al., (2010) systematic review (Collins & Brandon, 2002; Mackillop & Lisman, 2008; Stasiewicz et al., 2007) will be discussed to familiarise the reader with their methodology so it can be discussed in the context of the wider extinction learning literature.

Collins & Brandon (2002) directly tested the effects of physical context renewal after extinction in an analogous sample of moderate to heavy social drinkers. 78 university students (53% female) were randomly assigned to three conditions: same context (SC), different context (DC) and different context + E-cue (DC+E). E-cue was a stimulus that was present in the extinction phase and used as an extinction reminder. First participants completed their baseline measurements. For this participants placed cotton balls in their mouth for three minutes to measure salivation and completed ratings of self-report urges to drink. Salivation and self-report urges were the cue reactivity measurements collected in every phase of this experiment. Next the participants completed the pretest which was similar to the baseline except participants were exposed to the sight and smell of beer without consumption. Some participants then had seven extinction trials while others had a maximum of ten extinction trials. The number of extinction trials varied depending on how long it took participant's reactivity measures to return to baseline. The extinction trials were identical to the pretest trials except the E-cue was present for all participants. After a 25 minute distraction phase where participants completed a crossword puzzle, participants completed the renewal test. The renewal test procedure was the same as the extinction trials except it only consisted of two trials and only the DC+E condition was exposed to the E-cue. The DC and DC+E condition did the baseline/pretest phase in one room (context A), went into a new room for the extinction phase (context B) and returned to the baseline/ pretest room for the renewal test phase. The SC condition stayed in the same room throughout every phase. Therefore this was an ABA vs ABA(E) vs AAA design. As hypothesised, the DC condition showed the most renewal in both self-report and salivation

cue reactivity, SC had the least renewal and DC+E had intermediate attenuated renewal. This study empirically demonstrated the importance of renewal alcohol-related cue reactivity in a non-AD population.

Stasiewicz et al. (2007) conducted a similar study investigating the effects of physical context renewal on cue reactivity, but this time in AD outpatients. 143 AD (56% male) participated. The design and procedure was very similar to Collins & Brandon (2002). Participants were randomly assigned to SC, DC and DC+E and a fourth group similar to DC+E, but where the E-cue had an increase in salience (DC+sE). In this experiment the DC, DC+E and DC+sE conditions did the pretest and extinction phase in one room (context A) and the renewal test in another room (context B). The SC condition did all phases in the same room. Therefore it was an AAB vs AAB(E) vs AAA design. The results show all groups equally decreased in cue reactivity (both saliva and self-report) during extinction and had equal cue reactivity renewal in the test phase.

These results are inconsistent with Collins & Brandon (2002) and with the wider, more theoretical learning theory research (Bouton, 2004; Nelson, 2002). The authors describe two possibilities why this could be the case: 1) the rooms were not dissimilar enough and extinction managed to generalise between them and 2) the present study compared an AAB to AAA design whereas Collins & Brandon (2002) compared an ABA to AAA design. Research has shown ABA renewal is stronger than AAB renewal (Üngör & Lachnit, 2008). Contemporary theory holds ABA renewal is superior to AAB because during acquisition both the cue and context A acquire both strong isolated and net associative strength. However, during extinction the cues original association does not weaken, but it rather acquires two competing memories of both predicting the US and not predicting the US. Context B however does acquire negative associative strength and which supresses the acquisition memory and therefore inhibits responding. This is called Protection-From-Extinction (Rescorla, 2003).

As Stasiewicz and colleagues highlight, ABA renewal experiment paradigms are not realistic in clinical populations because acquisition is not under the control of the experimenter and often happens in multiple contexts. Extinction has been shown to be very context dependent, however if extinction learning is conducted in multiple context it could theoretically help extinction learning generalise to more contexts such as the acquisition contexts (Glautier, Elgueta, & Nelson, 2013). Mackillop & Lisman (2008) tested renewal of cue reactivity after multiple context extinction. 73 university students who were heavy social drinkers (males who drank 20+ standard drinks a week and females who drank 14+ per week) were randomly allocated to three conditions: 1) SC where participants received three cue-exposure sessions in the same context, 2) multiple context (MC) where participants received one cue-exposure session in three different contexts and 3) neutral context (NC) where participants were exposed to neutral cues in neutral contexts. The participants' pre-experiment alcohol-related conditioning history was considered context A. The extinction rooms were context B and the testing room context C. Therefore, this study utilised an ABC design. The main dependent measures were cue reactivity (salivation and self-report urges).

The results showed all three conditions were equal in strength of extinction. Surprisingly, none of the conditions showed a renewal effect. This result is inconsistent with previous research; as the ABC design reliably produces strong renewal (Bouton, 2004; Üngör & Lachnit, 2008). One possible reason is because this study had fewer extinction sessions (three) and therefore the association was not extinguished thoroughly enough. However, this is unlikely because the results show cue reactivity diminished across all extinction sessions. The authors argued that it is possible a single day of sessions in Collins & Brandon (2002), as opposed to the multiple day sessions in Stasiewicz et al., (2007) and Mackillop & Lisman (2008), could potentially increase the distinction between contexts. This is supported by past research demonstrating extinction trials that are spaced

and not massed together increase the effectiveness of extinction training and therefore reduces ABA renewal of fear conditioning in rats (Urcelay, Wheeler, & Miller, 2009). The wider extinction literature effectively demonstrates extinction learning is context-dependent (Bouton, 2004; Nelson, 2002). Collins & Brandon (2002) are also consistent with the wider literature. While Stasiewicz et al., (2007) is inconsistent, the discrepancy could be explained due to using an AAB vs AAA design. The results of Mackillop & Lisman (2008) are not easily explained. What is certainly clear is more research is needed for human extinction of alcohol-related cues.

The human literature on extinction of alcohol-related cues can be developed in two ways. 1) It is necessary to investigate the differences in AAB, ABA and ABC designs. Unfortunately this would be difficult due to the Pavlovian conditioning occurring in extra-experimental settings. Thewissen, Snijders, Havermans, van den Hout, and Jansen (2006) investigated ABA renewal in smokers. In this study, ABA was controlled by creating an association between smoking and different coloured ashtrays. This methodology can be adapted to incorporate drinking. 2) All the current research predominantly focuses on physical spatial contexts. Contexts not only include physical environments, but temporal periods, drug states, emotions and cognitions. No doubt all these factors interact to determine the state of an individual's relapse. Conklin & Tiffany (2002) discussed spontaneous recovery and reinstatement as other threats to extinction. The passage of time may cause a gradual change in context and therefore a change in temporal context (i.e. a long gap post-CET) could spontaneously recover their cue reactivity. Spontaneous recovery could work on the same principles as renewal only on a temporal context (Bouton, Westbrook, Corcoran, & Maren, 2006). No research to date has empirically studied this. Likewise with reinstatement, drug states could act as a form of context and work on the same principles as renewal to trigger relapse. There has been some research that included drug states in the CET literature by using priming doses (Dawe et al., 2002;

Kavanagh et al., 2006; Rankin et al., 1983; Sitharthan et al., 1997), but more refined research is needed in this area.

Extinction in multiple contexts attempts to reduce the context-dependency of extinction by increasing the generalisability across contexts. The greater literature of multiple context extinction shows multiple context generally does increase extinction generalisability (Glautier et al., 2013; Gunther, Denniston, & Miller, 1998; Shiban, Pauli, & Muhlberger, 2013; Vansteenwegen et al., 2007), however the literature is still inconsistent (Neumann, Lipp, & Cory, 2007). The effects of multiple contexts on extinction of in humans could be taken in several future directions. While Mackillop & Lisman (2008) failed to demonstrate a suppression of cue reactivity in an ABC renewal design after multiple context extinction training, other research has demonstrated multiple contexts extinction training does enhance suppression of ABC renewal. For example, fear cue reactivity to images of spiders has been shown to be more greatly suppressed in a novel context after multiple context extinction training compared to single context extinction training in patients with arachnophobia (Shiban et al., 2013; Vansteenwegen et al., 2007). Glautier et al., (2013) demonstrated multiple context extinction training was better than single context extinction training for suppression of responding in the novel context of an ABC Pavlovian conditioning design for generic, non-biologically relevant CS-US pairings. Mackillop & Lisman (2008) had heavy social drinkers participate (Stasiewicz et al., 2007 had AD participants), whereas the other multiple context research discussed here had spider-phobic patients or a random sample of university students. Perhaps there is a difference between light social drinkers, heavy social drinkers and AD patients in their ability to generalise extinction learning across contexts as well as their potential impairments in their general extinction learning ability (see section 1.3.1 Resistance-to-extinction and impulsivity). Another important difference between these studies is reinforcer type. Maybe this is further evidence supporting a difference between people's ability or a difference between social drinkers and AD in how they acquire and

extinguish associations between alcohol rewards and non-drug rewards. Gunther et al., (1998) showed extinction learning generalised across context after multiple context extinction training in rats with an alcohol US. However, research with humans have not replicated this (Mackillop & Lisman, 2008; Stasiewicz et al., 2007) so more research is needed.

Collins & Brandon (2002) results also suggested a potential method for attenuating threats to extinction is to utilise an E (extinction reminder). E's are neutral cues that are present during extinction learning. As a result they become conditioned inhibitors. With the widespread use of ambulatory computer-based devices (i.e. mobile telephones) it is now extremely easy to test this empirically. It is now possible to conduct randomised control trials in which AD patients receive CET with neutral auditory cues during sessions. During and after treatment, when patients find themselves in high risk situations or experiencing intense cravings they can speed-dial a number or use an app to be exposed to the E auditory cues. Collecting consumption information at follow-up will allow the effectiveness of this modification to the treatment to be examined (Rosenthal & Kutlu, 2014). However, research into the use of E is currently limited and results are mixed. Collins & Brandon (2002) showed E attenuated renewal of alcohol cues. Experiment two of Culver, Stoyanova, & Craske (2011) showed E attenuated renewal of conditioned fear, but experiment three did not. Recent research has demonstrated E cues do not always modulate the expression of a CR through the strength of its direct associative link with the US, but rather through occasion setting mechanisms (Bustamante, Uengoer, & Lachnit, 2016). This will be discussed in more detail in the immediate next section 1.3.3.2 Occasion setting.

1.3.3.2 Occasion setting

Thus far this review has discussed extinction and context renewal with the implicit assumption that the mechanisms underpinning these phenomena have been under the

constraints of a Rescorla-Wagner (R-W) framework. That is to say the recovery of extinguished responding has been dependent on the sum of the associative strength of the context and all the stimuli involved. For example when the R-W is applied to AD and exposure treatment; when an individual consumes alcohol in the home context, both the stimuli present and the context itself acquire associative strength that maintains the CR. When the patient undergoes CET in the treatment context the associative strength of the CS(s) used decreases and the association is "unlearned". Simultaneously the treatment context becomes inhibitory. The home context retains its associative strength, which combined with the residual excitatory associative strength that remains in the CS, summates to renewal of the CR.

However, there are several lines of research that suggests response recovery does not rely on the direct excitatory and inhibitory associations between the context and US. Instead it has been theorised extinction training is "new learning" of an occasion-setting relationship (Bouton, 2004). According to this theory, once a CS-US link has been established, extinction training of the CS does not weaken the link, but instead a new inhibitory association is learned. This inhibitory association works on the associative link between the CS and the US rather than directly involving the US. Typically it is considered that contextual stimuli occasion-set the CS-US link so that the CS becomes ambiguous with two memories (associations) attached to it. This account holds that stimuli and contexts which become occasion-setters influence which memory is retrieved by setting the occasion (Bouton, 2004; Trask, Thrailkill, & Bouton, 2017).

Occasion setters are therefore stimuli (or context) that modulate responding to another CS which shares an association with the same US. A CS indicates when an US is coming and an occasion setter indicates whether an US is coming. The typical occasion setting paradigm in Pavlovian training has the target CS (A) followed by the US only if the occasion setting, feature stimulus (X) is also present (AX+) otherwise A is unreinforced (A-). This is called feature positive (FP) discrimination (A-, AX+). Feature negative (FN)

discrimination is the opposite where A is reinforced but the compound AX is not (A+, AX-). According to R-W, X should acquire excitatory and inhibitory associative strength for FP and FN training respectively. However, research shows this is not always the case. Experiments that have trained rats in FP discrimination have shown that when the AX compound are trained simultaneously (A-, AX+) then the X feature does elicit a CR (indicating direct excitatory input). As does A alone and AX together (Trask et al., 2017). Whereas when the AX compound is trained serially (i.e. X presentation after A has been terminated; A-, A→X+) then the X feature does not elicit a CR (Ramos, Siegel, & Bueno, 2002; Ross & Holland, 1981).

Latent inhibition adds to further support an occasion setting mechanism. Latent inhibition is robust phenomenon consisting of unreinforced preexpsoure to a CS prior to reinforced training of the CS. As a result the acquisition of the CS-US link is retarded potentially due to reduced salience of the CS (Rescorla, 1971). However, research has shown, when the occasion setter feature stimulus is preexposed prior to standard FP discrimination training (X -/ A-, A→X+) there is no evidence of latent inhibition for the acquisition of occasion setters (Oberling, Gunther, & Miller, 1999). Moreover, when a negative occasion setter is subsequently trained as an excitatory CS, the acquisition of associative strength is not retarded as you would expect due to latent inhibition. In addition to this, the new association as an exciter assigned to the stimulus does not interfere with its ability to attenuate a CR as a negative occasion setter (Bouton & Swartzentruber, 1986).

Simultaneous and serial training is not the only factor to influence whether a R-W mechanism or occasion setting mechanism will prevail. The differential salience between the target stimulus and feature stimulus impacts this as well; the larger the salience of the target stimulus and the smaller the salience of the feature stimulus, the greater the chance of occasion setting occurring (Holland, 1989). This makes contexts ideal occasion setters for addiction. When consuming alcohol, the context comes before consumption and often has periods of being unreinforced (not drinking). In addition to this, research has shown

AD patients (Field et al., 2004; Sinclair, Garner, Pasche, Wood, & Baldwin, 2016) and heavy drinkers, but not light drinkers show attentional bias towards alcohol-related cues (Field et al., 2004). Therefore, if an alcohol-related CSs (sight and smell of alcohol) are more salient and the context is less salient (merely the background and not attended to) contexts are likely to become occasion setters during alcohol consumption behaviour.

Contexts do not always summate with CSs to produce decreased CRs. Bouton & Swartzentruber (1986) conditioned light and tone to signal a foot shock in context A and successfully trained extinction of just tone in context B. However, when light (which did not undergo extinction training) was presented in context B, there was no suppression of the CR. In contrast to this Glautier et al., (2013) trained four cues: A, B, C, and G (randomly generated boxes of different, sizes, colours and shapes) to signal different colour light flashes in context A (red and green light flashes were randomly assigned as the cues US). Responding was measured with keyboard presses. Cue A and G were trained with the same US, but only cue A underwent extinction training in context B in which it was extinguished. When cue G was presented context B, responding was suppressed indicating the context acquired inhibitory strength and summated to attenuate responding across cues. An explanation for the discrepancy between these two studies could be due to the structure of the experiments. Bouton & Swartzentruber (1986) had delayed onset of the CS after subjects were exposed to the context and long inter-trial intervals (ITI), whereas Glautier et al., (2013) had almost immediate CS presentation after exposure to context and a very short ITI. Therefore, as discussed earlier, this creates conditions where contexts can take on an occasion setting role or become a compound CS with the target CS. Thirdly, it can be argued that summation tests are unfair measures of context inhibition because of the conditioning histories of the CSs. One CS has only had excitatory training while the other has inhibitory as well and therefore the CSs have differential sensitivities to inhibition. However, Rescorla (2008) (experiment one) trained CS X+ and Y- in context A and X- and Y+ in context B. Therefore the CSs had similar training histories and both contexts

received excitatory and inhibitory training. Response recovery was measured in ABA renewal. The results showed greater suppression of responding of Y in context A and X in context B indicating the contexts did not summate and therefore modulated responding like an occasion setter.

It should also be noted that occasion setters are immune to extinction. Ramos et al., (2002) produced conditioned hypothermia tolerance in rats. One group was conditioned simultaneously meaning they received ethanol injections (CS) while the light stimulus (feature stimulus) was present, while the other group were conditioned serially meaning they received their ethanol injections after the light had terminated. Half the subjects in both groups underwent extinction training (unreinforced light presentations) while the other half in both groups did not. There were also rats who received saline injections and underwent identical acquisition and extinction training as the ethanol groups. In the test phase, all subjects regardless of group received the light stimulus and ethanol injections. The results showed, within the simultaneously trained groups, that the saline extinction and control groups had the same amount of hypothermia as the ethanol extinction group. However, the ethanol non-extinction group remained tolerant to ethanol-induced hypothermia indicated by not reducing body temperature as much as the other three groups. Whereas, within subjects that were trained serially, there was no statistically significant difference in body temperature in all four groups. Meaning the ethanol group that underwent extinction did not demonstrate extinguished tolerance as their body temperature lowered as much as the other groups. These results support when compound stimuli are simultaneously trained, light (feature stimulus) acquires direct associative control over the US which can be attenuated with extinction. However, when serially trained, light becomes an occasion setter which was not affected by extinction training.

Viewing context renewal in terms of occasion setting and not feature excitation/inhibition poses important implications for CET as a treatment for addiction. Firstly, this review has proposed including as many cues as possible in the exposure

procedure in hope to extinguish them all because there is no way of knowing which stimuli have become CSs, which are most salient, and what their CRs are to optimise CET efficacy. However, it can be argued that the most proximal cues to alcohol use are CS and the distal ones are occasion setters (Ramos et al., 2002). Because occasion setters are immune to extinction it would be a waste of time to extinguish them. This review has also argued for performing extinction in alcohol-related contexts. While smoking research has suggested this has been beneficial in boosting the efficacy of CET (McClernon et al., 2007), said research has also included sham smoking so it is unclear how much drug use context and sham drug use both contributed to this. However, while the current method of CET may not be useful for treating AD occasion setters cannot be reverse through extinction, maybe an adapted CET could work. Research has shown feature positive and feature negative occasion setters can be reversed (Pace, McCoy & Nallan, 1980). Perhaps a modified form of CET which includes CS extinction in a clinical setting and alcohol-related setting. In both setting the patient can also consume dealcoholised beverages in an attempt to extinguish both S-O and R-O contingencies. In addition to this, in a clinical setting, stimuli can be trained as inhibitory occasion setters. Likewise, in the alcohol-related setting, stimuli and maybe the context can be trained to become inhibitory occasional setters too.

1.4 Conclusion

In conclusion, addiction and other psychiatric disorders (e.g. anxiety disorders and binge eating disorder) develop and are maintained, at least in part, by the interaction of Pavlovian and instrumental conditioning processes. CET attempts to treat these disorders by extinguishing the Pavlovian CS-US associations. CET has been demonstrated to be effective for anxiety disorders and binge eating disorder, but not so much for addiction. This discrepancy is referred to in this paper as the alcohol cue exposure therapy paradox (ACETP). The explanation for ACETP may be due to individual differences between

addicted and non-addicted populations. These differences could be expressed in multiple ways that may interact. Firstly, differences may be expressed in impairments during Pavlovian learning. The limited research suggests a history of heavy alcohol use and learning with an alcohol US (but not other rewards) could result in resistance-to-extinction. Moreover, drinking status and reinforcer type may modulate an individual's ability to generalise extinction learning across contexts. Secondly, individual differences between these groups may also be expressed the development of habitual behaviour. Drinking status and reinforcer type has also been shown to bias in favour of the development of habitual learning, as shown in Pavlovian-instrumental transfer research. Finally, drinking status has been shown to bias attention to alcohol-related stimuli which facilitates stimuli becoming occasion setters which has implantations for the CET procedure. Therefore, this thesis will directly investigate the effects of drinking status and reinforcer type on extinction of CS-US pairings for generic US, biologically relevant USs (i.e. food and alcohol), and the effects of Pavlovian-instrumental transfer.

Chapter 2

General Methods

This chapter contains materials, apparatus, methods, and shared general procedures common across many chapters in this thesis. Specific methods are described within chapters to which they are unique. The three questionnaires described in this chapter are utilised in all experiments. The Pavlovian learning computer task described in this chapter was utilised in Chapter 3 and Chapter 4. The apparatus described that runs all computer tasks (tasks described in this chapter and elsewhere) were utilised for every experiment except for the experiment presented in Chapter 4. Details of the apparatus used in Chapter 4 are described there.

2.1 Ethical approval

All experiments were approved by the University of Southampton's psychology department Ethics Committee and Research Governance Office. The experiment presented in Chapter 4 specifically, had an additional NHS REC committee (16/SW/0343 17/EM/0111 East Midlands-Nottingham1) and Health Research Authority approval.

2.2 Informed consent and debriefing

All experiments were advertised on the University of Southampton's psychology experiment advertisement forum eFolio, with paper posters placed around the University of Southampton campuses, and by word of mouth and personal solicitation. All advertisements gave the experimenter's contact details. See Chapter 4 for details of additional advertisement, recruitment and consent unique to that experiment. For the experiment presented in Chapter 3, participants either signed up directly to the experiments on eFolio or contacted the experimenter to request to take part. If they contacted the experimenter they were given a participant information sheet, asked if they had any questions, and asked to consider this information before booking in time at the lab. As the

experiments reported in Chapter 5 and Chapter 6 were over several days, regardless of whether the participant signed up on eFolio or contacted the experimenter, the participant were contacted and given the participant information sheet, asked if they had any questions to consider this information before booking in lab time for every day the experiment took place. For these experiments, participants were made aware before they booked lab time, that they were free to withdraw at any time, for any reason, but payment for participation was dependent on completion of the experiments. For all experiments, once participants arrived at the lab, they were given the participant information sheet and asked if they had any questions. The core procedural components of the experiment and participants right to withdraw were verbally reiterated. Written informed consent was given by participants signing consent forms.

At the end of every experiment participants were thanked for taking part and asked what they thought of the experiment. Participants were then give a brief verbal summary of the experiments purpose, aims, and hypotheses. They were also handed a debriefing statement which detailed this information and also included references apposite to the experiment and safe drinking guidelines and details for useful resources to receive help if they had concerns about their alcohol consumption. Participants were then asked if they had any further questions. Once all questions had been answered participants were asked if they felt satisfactorily debriefed. If the participants answered in the affirmative they were offered to take the debriefing statement with them and the experimenter highlighted the relevant contact details for further questions or concerns.

See Appendix 1 for experiment specific participant information sheet, consent forms, and debriefing statements.

2.3 Sample size calculations

All sample sizes were calculated with G*Power 3.1.9.2. The statistical test selected for every experiment was a repeated measures ANOVA between factors. α was set to 0.05.

β set to .8. For Chapter 3 the sample size was 78, Chapter 4 102, Chapter 5 60, and Chapter 6 40.

2.4 Materials

2.4.1 Alcohol use disorder identification test

The Alcohol Use Disorder Identification Test (AUDIT, Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) was used to measure severity of alcohol consumption in the last six months. The full AUDIT is a 10-item questionnaire that has a maximum score of 40 and is used to screen for hazardous and harmful drinking behaviour. AUDIT scores may be analysed as a continuous variable, but can be categorised into levels of alcohol consumption. A score of < 8 is not considered hazardous or harmful drinking behaviour. A score of $\geq$ 20 indicates possible dependence on alcohol. Its reliability, validity, sensitivity and specificity are well documented in the literature for a range of clinical populations worldwide (Daeppen, Yersin, Landry, Pe, & Decrey, 2000; Gache et al., 2005; Moussas et al., 2009; Saunders et al., 1993; Zavar, Jarahi, Alimoradi, & Khosravi, 2015). The AUDIT-C only contains a subset (first three consumption items) of the full AUDIT scale, and is used for screening for levels of alcohol consumption in clinical and non-clinical populations. Every experiment except for Chapter 4 only used the AUDIT-C. The full AUDIT was used in Chapter 4 within the alcohol-dependent sample to measure the severity of alcohol consumption six months prior to when their abstinence commenced. AUDIT-C was used for the control sample of Chapter 4 to screen participants for eligibility and measure severity of alcohol consumption in the last six months.

2.4.2 Timeline followback

Timeline Followback (TLFB, Sobell & Sobell, 1992) was used for a measure of recent alcohol consumption. The TLFB method is a self-report drinking assessment that obtains estimates of alcohol consumption over a specific period. The period of self-report

for the TLFB varies anywhere between one year to one week. The TLFB allows for fine-grain detailed measurements of alcohol consumption to allow the analysis of variability, pattern and extent of consumption. The alcohol TLFB has been shown to have good psychometric properties, reliability and validity (Hoeppner, Stout, Jackson & Barnett, 2010; Rueger, Trela, Palmeri, & King, 2012). All experiments used a seven day TLFB as seven days has been shown to have greater accuracy than 30 days (Hoeppner et al., 2010).

2.4.3 Why use both AUDIT and TLFB?

Both the AUDIT and TLFB were used to increase reliability of self-reported alcohol consumption. The TLFB is a more direct self-report of specific alcohol consumption which allows for an analysis of variability and pattern. However, the TLFB used in the experiments of this thesis covers a very small time period and is therefore susceptible of miss-representing an individual's normal alcohol consumption. Therefore AUDIT(-C) was also used as it indirectly measures alcohol consumption frequency and quantity over a longer period of time.

2.4.4 Barratt impulsiveness scale 11th ed

Barratt Impulsivness Scale 11th Ed (BIS-11, Patton, Stanford, & Barratt, 1995) was used to measure and control for impulsivity; high impulsivity is a trait common in alcohol dependence (see Chapter 1 section 1.3.1 Resistance-to-extinction and impulsivity). The BIS-11 is a 30-item questionnaire. The BIS has been the most widely used impulsivity questionnaire for over half a century; it is considered the gold standard of impulsivity questionnaires. Despite its extensive use, analysis of its psychometric properties are rare, but available literature supports its psychometric properties, internal consistency and convergent validity (Stanford et al., 2009). The BIS-11 was the only impulsivity measurement utilised to preliminarily probe if individual differences in disinhbition influences Pavlovian extinction. As the main focus of this thesis is on alcohol consumption in relation to associative learning, no further impulsivity measures were used.

Copies of questionnaires can be found in Appendix 2.

2.5 Pavlovian conditioning computer task

The Pavlovian conditioning computer task was used Chapter 3 and Chapter 4. See the Appendix 3 for the computer task on-monitor instructions. The computer task was designed to study causal-judgement Pavlovian conditioning. In other words, participants had to learn the associative relationship between which generic neutral cues triggered different coloured flashes from a sensor located on the computer screen. The unconditioned stimuli were not biologically relevant. The general procedure of the task consists of participants viewing a computer monitor. The visual of the monitor displayed one of four rooms with its own unique and discrete visual texture. The sensor, a pyramidal shape, is located at the bottom of the screen. Participants observe one of four different objects/cues enter from the top of the screen, fall down through the room and exit out past the sensor. As the cue passes the sensor it can trigger it to flash. It may flash red, flash green or remain inactive. Only one cue is presented per trial and each object consistently triggered one of those outcomes. Participants must learn and remember which cue triggered which outcome. As they see the cue enter the room they must make a prediction of what the sensor outcome will be. They make a prediction by pressing a key before the cue has reached the sensor (key press while the cue is in the designated prediction window). Different outcomes are designated different keys. In the early trials of the experiment participants must guess the predicted outcome, but as the experiment progresses they learn from their error and make correct predictions based on past trials. The computers and programme used were identical to and have been described in detail previously in (Glautier et al., 2013). A summary of this procedure follows.

2.5.1 Apparatus

For Chapter 3, three personal computers were used with screens measuring 41 cm x 26 cm (W x H). The display used 32 bit colour mode and pixel resolutions of 1440 x 900 and were controlled by a computer program written in Microsoft Visual Studio 2008 C# language, and XNA Game Studio Version 3.1 for 3-D rendering of the experimental scenario was used. Auditory information was presented via speakers located on both sides of the screens. The machine used to run this programme in experiment three is described in Chapter 4.

2.5.2 Computer task design

The computer task was designed to study the learning of associations between objects and sensor outcome allowing measurements of acquisition, extinction, response recovery, and context inhibition (see Chapter 1 for a detailed explanation of these phenomena and a discussion about ABC design in Pavlovian learning). Prior to the learning task participants had to read the instructions displayed on the screen and begin by pressing the C key (see Appendix 3 for on screen instructions). This action removed the text and triggered an animation where four context boxes arranged in the 2 x 2 grid are seen from a distance. The four boxes are markedly different from each other in visual texture and colour so that experimental manipulations could be carried out e.g. implementing a recovery experiment using an ABC design. One of these boxes is chosen at random to serve as the context for the acquisition phase. Stage 0 consisted of the eight practice trials. In the practice trials there were two cues, one triggered a blue flash outcome from the sensor and the other had no effect on the sensor. Stage 0 was followed by stage 1 which consisted of the acquisition phase. In this phase the critical cues were reinforced with the outcome, which happened in context A. Stage 2 consisted of the extinction phase (including the summation test [stage 2a]) where cue A and G were no longer reinforced,

which happens in context B. Stage 3 consisted of the recovery test phase where cue A was presented in novel context (context C).

Within the onscreen box a pyramidal "sensor" is located at the bottom centre of the screen. Directly above the sensor was a translucent band forming the prediction window. When dictated by the experimental protocol a 3D object would enter from the top of the screen and fall at a constant speed where it would exit at the bottom of the screen. From when the object enters the screen to its exit is one trial. One trial lasted approximately 4.8 s with an inter-trial interval of 5.2 s. The object always entered the screen at a random location that was contained within the parameters of the prediction window. The object would take 1.2 s to pass behind the prediction window. The object is always visible throughout the entirety of the trial. Participants had to make predictions by pressing the relevant keys when the object was within the parameters of the prediction window. When the object left the prediction window, if it triggered a sensor response, the sensor changed colour. Figure 2.1 illustrates the visual display of the boxes set up with a selection of different objects that were the cues.

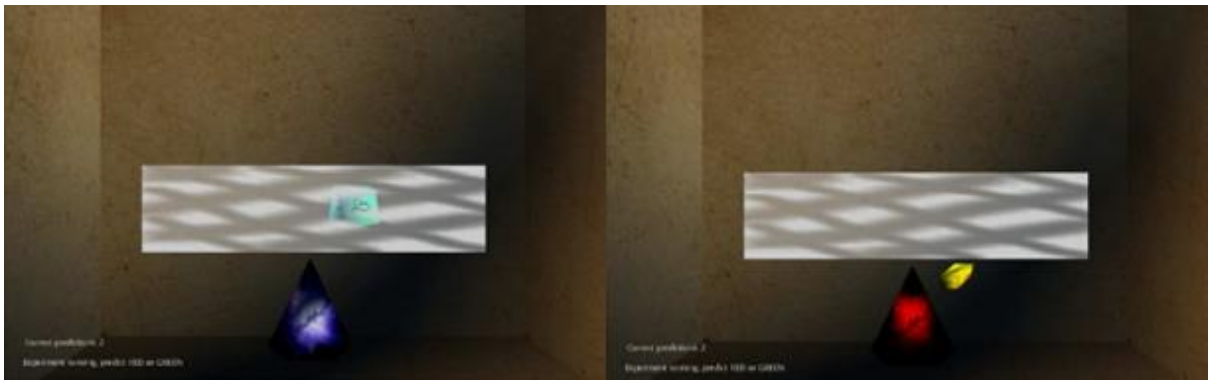


Figure 2.1. Visual depiction of the computer task cited in (Glautier et al., 2013): screen shot illustrating the general features of the screen display, examples of different cues and a red outcome.

A total of four objects (cue A, cue B, cue C and cue G) were randomly selected for each participant from a possible 16 objects that can be generated from combinations of four binary-valued features. The objects can vary on size; small (1cm) or large (2cm), distortion: (twisted or flat surface), colour: (yellow or turquoise) and pattern: (zigzag lines

or a jug [Wingdings symbols 98 and 104 respectively]). Cue A and G (critical cues) always predicted an X outcome, cue B (filler cue) a Y outcome and cue C (filler cue) was a Z outcome. The red and green flashes were randomly assigned to represent the X and Y responses for each participant. Z outcome was always an inactive sensor. Participants had to press the R key if they predicted the cue would trigger a red outcome, the G key for a green outcome or withhold response for no outcome.

Stage 0 took place in context A and had with eight practice trials in which an object had four trials of predicting a blue response and another object had four trials of no response. All trials were randomised. Participants had to press the B key or do nothing. Without an interval after the practice trials stage 1 started. Here participants acquired associations between cues A, B, C, and G with outcomes X, Y, Z and X respectively. There were 10 trials for cue A and G and 20 for cue B and C. Stage 2 consisted of the extinction phase where A & G-X associations were non-reinforced. There was eight trials for every cue. There was also the summation test (stage 2a) to test whether context B became inhibitory by having two presentations of cue G. Stage 3 consisted of the recovery test phase where a non-reinforced cue A is presented twice in context C (a novel context). This design is displayed in .

Table *2.1*.

Table 2.1. Summary of Experimental Design

Stage 1	Stage 2	Stage 2a	Stage 3
A: A → X (x10)	B: A → Z (x8)		C: A → Z (x2)
A: B → Y (x20)	B: B → Y (x8)		
A: C → Z (x20)	B: C → Z (x8)		
A: G → X (x10)		B: G → Z (x2)	

Note. A: A → X (x10) indicates context A, cue A, outcome X present on 10 trials. Outcomes X and Y randomised as X=red and Y=green or vice versa and outcome Z indicates no outcome. Trial orders are randomised within blocks.

2.6 Statistical analysis

The raw data from the experiments presented in Chapter 3 and Chapter 4 were separated by cue and aggregated into blocks. Each block consists of two trials. Therefore cue A block one is the average of the first two cue A trials. Cue A block two is the average

of the third and fourth cue A trials etc. The conditioning experiment presented in Chapter 5 was treated the same to generate blocks that are the average of five trials. The data of all experiments in Chapter 3 to Chapter 5 was analysed with mixed Analysis of Variances (ANOVA) in block x group (drinking status) tests. In some instances additional analyses were conducted for these experiments which are described in the specific chapters to which they are unique. Unless stated otherwise, the ANOVA's assumption of sphericity were violated and Greenhouse-Geisser corrections were applied. See Chapter 5 and Chapter 6 for the analysis techniques applied to the pilot study and the Pavlovian-instrumental transfer study respectively.

Chapter 3

Individual Differences in Acquisition and Extinction of Pavlovian Learned Responses for Generic Stimuli in Light and Heavy Social Drinkers

3.1 Abstract

The Rescorla-Wagner model makes several predictions about association learning rates when contexts and cues are different saliences. Alcohol-dependent patients and individuals with high impulsivity trait have been shown to have attentional biases towards alcohol-related cues when they know alcohol is available. Therefore, alcohol-related cues could have differing saliences in drinking contexts and nondrinking contexts (i.e. clinical setting). These differences in salience could have an effect on extinction learning and therefore could explain the alcohol cue exposure treatment paradox (ACETP). This study investigated the effects of levels alcohol consumption and impulsivity on Pavlovian conditioning ability. In this experiment, participants were social drinkers from the University of Southampton categorised as light or heavy drinkers and low and high impulsiveness. The results showed no difference between drinking groups at any stage of the Pavlovian task. However, a block*group interaction was found in the recovery data for the impulsiveness groups. Further research is needed to explore this result. In conclusion in social drinkers, drinking status and impulsivity trait had no effect on associative learning of neutral cues, however future research is needed to explore the effect in a clinical sample and the effect of reinforcer type.

3.2 Introduction

In Chapter 1 it was discussed that CET is not as effective at treating AD as it is for anxiety disorders and binge eating, we called this discrepancy the Alcohol Cue-Exposure Therapy Paradox (ACETP). It was concluded that individual differences between AD and non-dependent people is likely to explain the ACETP. These differences could be

expressed through differences in the acquisition, extinction and response recovery of learned CS-US pairings that may be influenced by differences in alcohol-related attentional processing (and therefore salience of) stimuli. This chapter will focus on differences in general conditioning ability between light and heavy social drinking groups.

In Chapter 1 it was suggested that levels of alcohol consumption and impulsivity may explain the ACETP through resistance-to-extinction (REX). REX is an impairment in extinguishing CS-US associations. The ACETP suggests REX may be association with levels of alcohol consumption. High levels of impulsivity have also been associated with REX (Broos et al., 2012). Impulsivity is defined as persistent behaviours and an inability to consider outcomes or stop a behaviour that has negative consequences, preference for immediate gratification and an increased propensity to engage in risky behaviours (Perry & Carroll, 2008). Impulsivity is both a risk factor for drug abuse and is exacerbated as a consequence of drug abuse in all drug classes (Crews & Boettiger, 2009). Impulsivity is a trait also associated with an impairment of the prefrontal cortex (Crews & Boettiger, 2009). Impulsivity is not a unidimensional concept and response inhibition is one facet of impulsivity (Perry & Carroll, 2008). Extinction is a form of response inhibition; an individual learns to withhold the CR when the CS is trained in extinction. It is possible therefore that the capacity for extinction is linked to capacity of response inhibition. Research has shown that people with AD and high trait impulsiveness have greater attentional bias towards alcohol-related cues when they know alcohol is available, but this bias is attenuated when it is not (Field & Cox, 2008; Papachristou et al., 2012). The R-W model predicts more rapid and stronger CS-US pairings when a cue has large salience, but during extinction when the salience of the cue has reduced, extinction learning would be slower compared to an individual who had small cue salience throughout acquisition and extinction learning (this is explained in more detail in Chapter 5).

As this study is a preliminary study, non-drug CS-US pairings were used to see if REX generalises across to generic Pavlovian learning. It also used an analogous sample of light

and heavy drinking groups based on an assumption of alcohol-related effects on Pavlovian learning being on a spectrum from light social drinkers (largely unaffected) to heavy social drinkers to AD (most affected). The aim of this study is to investigate the effects of drinking history and impulsivity on classical conditioning mechanisms, with particular focus on extinction. The primary aim is to determine whether there is a difference in rates and strength of extinction between participants with a high and low levels of alcohol consumption. The secondary aim is to investigate the role impulsivity has in Pavlovian learning. The following hypotheses were tested:

1) The heavy drinking group compared to the light drinking group will have equivalent rates of acquisition learning.
2) The high impulsivity group compared to the low impulsivity group will have equivalent rates of acquisition learning.
3) The heavy drinking group would have slower a rate of extinction of the CS-US pairings compared to the light drinking.
4) The high impulsivity group would have slower a rate of extinction of the CS-US pairings compared to the low impulsivity group.
5) The heavy drinking group would have greater response recovery of the CS-US pairings compared to the light drinking group.
6) The high impulsivity group would have greater response recovery of the CS-US pairings compared to the low impulsivity group.
7) Levels of alcohol consumption will be positively correlated with impulsivity.

3.3 Methods

3.3.1 Participants

74 participants (20 male, 54 female) with a mean age of 20.4 years (SD = 2.9, range = 18 – 38) took part. All but one participant were students at University of Southampton. 85.2% were psychology students, the remainder were from a variety of other disciplines.

94.7% were undergraduates and the remainder were postgraduates; a single participant was a postdoc at Southampton. Participants received six course credits or were entered into a prize draw for a chance to win a £50 Amazon voucher upon completion of the experiment.

3.3.2 Materials

Participants completed the AUDIT-C, TLFB and BIS-11 questionnaires and the Pavlovian conditioning computer task described in Chapter 2.

3.3.3 Design

A between subjects design was used with two independent variables (level of drinking and inhibition) each with two levels: light and heavy drinking; low and high inhibition. Participants were allocated to their condition by a median split of the questionnaires. There were 37 participants in each condition.

3.3.4 Procedure

Participants came to the lab individually and completed the AUDIT-C, TLFB and BIS-11 questionnaires in that order after giving informed consent (see Chapter 2). They then went into a cubicle in which they completed the Pavlovian conditioning computer task. The experiment took 30 minutes in total.

3.4 Results

3.4.1 Questionnaires

Table 3.1 displays the mean total score of number of units consumed for the full TLFB week and on each of the individual days, comparing light and heavy drinkers. Not a single participant reported drinking alcohol on the day of testing. The median total number of units consumed was 10.95 (SD = 23.8, range = 0-118.7). Participants were divided into light and heavy drinking groups based on a median split of the total score. The mean total units consumed for the light drinking group was 4.74 (SD = 3.79, range = 0 -10.9) and the

heavy drinking group 31.3 (SD = 27.8, range = 11-118.7). A t-test revealed the light and heavy drinking groups total scores were significantly different t (37.3) = -5.75, $p < .001$.

Table 3.1. Mean number of alcohol units consumed for the total week and on each individual day.

	Light Drinking Mean (SD)	Heavy Drinking Mean (SD)
Total	4.74 (3.79)	31.3 (27.8)
0	0 (0)	0 (0)
-1	.32 (.94)	2.67 (5.97)
-2	.56 (1.46)	3.5 (5.58)
-3	.76 (1.87)	7.25 (10.8)
-4	.39 (1.38)	4.85 (8.41)
-5	1.93 (3.28)	7.29 (9.1)
-6	.78 (2.54)	5.68 (8.37)

Note. 0 = day of testing, -1 = the day previous to the day of test, -2 = the day previous to -1 etc.

Table 3.2 displays the mean total score of the AUDIT-C and the mean score of each of the individual questions, comparing light and heavy drinkers. The mean total score of the AUDIT-C for the light drinking group was 5.2 (SD = 2.4, range = 1-9) and 7.9 (SD = 2, range 3-12) for the heavy drinking group. A t-test revealed the light and heavy drinking groups total scores were significantly different t (72) = -5.16, $p < .001$.

Table 3.2. Mean total score and individual questions of AUDIT-C.

	Light Drinking Mean (SD)	Heavy Drinking Mean (SD)
Total	5.2 (2.4)	7.9 (2)
Question 1	2.2 (.8)	3 (.81)
Question 2	1.5 (.1)	2.3 (.1)
Question 3	1.5 (.99)	2.6 (.65)

Table 3.3 displays the mean total score and the six subscales of the BIS-11 comparing light and heavy drinking groups and low and high impulsiveness groups. The mean total BIS-11 score for the light drinking group was 64.6 (SD = 1, range = 47-86) and 65.8 (SD= 8.3, range = 49-84) for the light drinking group. A Mann-Whitney U test indicated there was no difference between light and heavy drinking groups on total BIS-11 score U = 637, p = 607.

The median of the total BIS-11 score collapsed across participants was 65.5 (SD = 9.1, range = 47-86). Participants were also divided into high and low impulsiveness groups based on a median split of the total score. The low impulsiveness group had a mean total BIS-11 score of 57. 6 (SD = 5.1, range = 47-65) and the high impulsiveness group had a mean of 72.8 (SD = 4.9, range = 66-86). Research suggests a total score of > 71 equates to a classification of high impulsivity, a score ranging 52-71 is within the normal range and a score < 52 classifies participants as extremely over-controlled or did not complete the questionnaire honestly (Stanford et al., 2009). 13 of out the 37 high impulsive group had a total score lower than 71. Four of the 37 low impulsive group had a total score lower than 52. Therefore, 77% of participants scored within normal range. A t-test revealed the high and low impulsive groups total scores were significantly different t (72) = -13.5, $p < .001$.

Table 3.3. Mean for the total score and the six sub scale scores of BIS-11 by drinking groups and impulsiveness groups.

	Drinking		Impulsiveness	
	Light Mean (SD)	Heavy Mean (SD)	Low Mean (SD)	High Mean (SD)
Total	65.5 (1)	65.8 (8.3)	57.6 (5.1)	72.8 (4.9)
Attention	10.5 (2.7)	10.8 (2.4)	9.1 (2)	12.2 (2)
Cognitive Instability	6.4 (1.7)	6 (1.6)	5.6 (1.4)	6.9 (1.6)
Motor	14.9 (3.8)	16.3 (2.8)	14 (3.1)	17.2 (2.9)
Perseverance	7.4 (1.8)	7.2 (1.6)	6.3 (1.3)	8.3 (1.5)
Self-Control	13.5 (2.7)	13.7 (3)	12 (2)	15.1 (2.8)
Cognitive Complexity	11.9 (2.3)	11.8 (2.5)	10.8 (2)	13.9 (1.3)

Spearman's Rho tests were conducted to see if the total scores from each questionnaire correlated with each other. The correlations results are summarised in Table *3.4*. BIS-11 was not significantly correlated with TLFB. BIS-11 was weakly positively correlated with AUDIT-C and AUDIT-C was moderately positively correlated with TLFB.

Table 3.4. Spearman's Rho correlations between AUDIT-C, TLFB and BIS-11

	AUDIT-C	TLFB	BIS-11
AUDIT-C	-		
TLFB	.58**	-	
BIS-11	.34*	.09	-

Note. AUDIT-C = Alcohol Use Disorder Identification Test – C, TLFB = Time Line Follow Back, BIS-11 = *Barratt Impulsivness Scale 11th Ed.* * = $p < .01$. ** = $p < .001$.

3.4.2 Behavioural data

3.4.2.1 Drinking Status

Cue A

Figure 3.1 displays the mean proportion of X responses to cue A across the acquisition phase (blocks 1 - 5), extinction phase (blocks 6 – 9) and the recovery test phase (blocks 10 and 11) between light and heavy drinkers. Inspection of Figure 3.1 suggests the two groups increased their X responses equivalently during the acquisition phase, decreased their X responses equivalently during the extinction phase and increased their X responses equivalently during the recovery test. This indicates the participants successfully learned the CS-US association, learned to extinguish said association during extinction training, and demonstrated an ABC renewal effect. The results of Figure 3.1 also suggests there was no difference between the two drinking groups in their performance at any stage of the task. The extinction data shows an absolute difference between light and heavy drinking groups with the heavy group having impaired extinction, but this difference does not look significant. Three mixed ANOVAs were conducted. The acquisition data was tested in a 2 (drinking status; light vs heavy) x 5 (block; 1-5) mixed ANOVA. The extinction data was tested in a similar 2 x 5 (block; 5-9) mixed ANOVA. The recovery test data was tested in a similar 2 x 2 (blocks 9 & 10) mixed ANOVA. All ANOVAs for cue A by drinking groups are reported in

Table *3.5*. The results of the ANOVAs support this as there was a significant main effect of block for the acquisition, extinction and recovery test data, but no main effect of group or block*group interaction for any ANOVA. This supports the notion that participants successfully learned the CS-US pairing and demonstrated an ABC renewal effect for cue A, but drinking groups did not perform significantly differently.

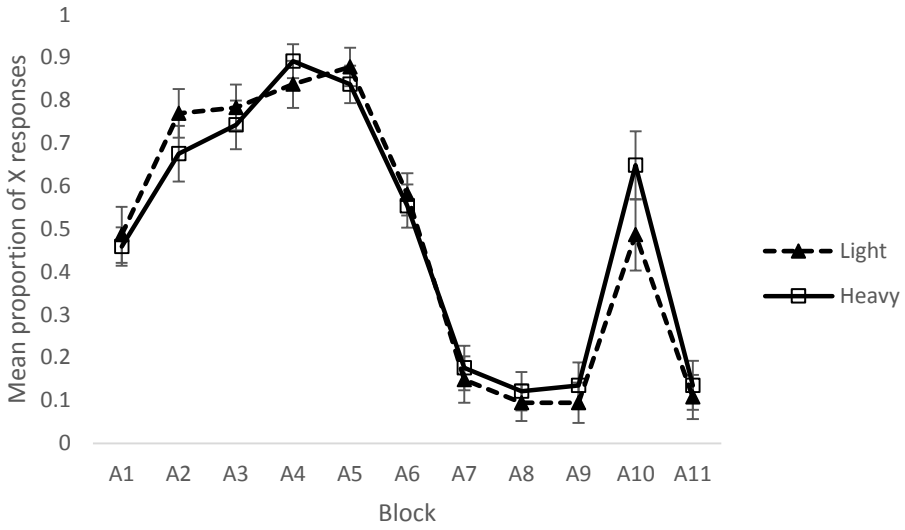


Figure 3.1. A line graph displaying the mean proportion of X responses to cue A across the acquisition phase (blocks 1 - 5), extinction phase (blocks 6 – 9) and the recovery test phase (blocks 10 and 11) between light and heavy drinkers. Error bars represent the standard error.

Table 3.5. Repeated Measures Analysis of Variance for Cue A for drinking data

Stage	Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Acquisition	Between-Subjects						
	Drinking	.016	1	.016	.341	.561	.005
	Error	3.46	72	.048			
	Within-Subjects						
	Block	7.52	3.13	2.4	26.46	.001*	.269
	Block x Drinking	.212	3.13	.068	.746	.531	.01
	Error	20.47	225.6	.091			
Extinction	Between-Subjects						
	Drinking	.001	1	.001	.017	.896	.000
	Error	2.25	72	.031			
	Within-Subjects						
	Block	33.59	2.65	12.68	120.8	.001*	.627
	Block x Drinking	.099	2.65	.037	.355	.761	.005
	Error	20.16	190.7	.105			
Recovery Test	Between-Subjects						
	Drinking	.190	1	.190	1.99	.163	.027
	Error	6.88	72	.096			
	Within-Subjects						
	Block	7.58	1	7.58	51.24	.001*	.416
	Block x Drinking	.137	1	.137	.925	.340	.013
	Error	10.66	72	.148			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
*$p < .001$

Cue G

Figure 3.2 displays the mean proportion of X responses to cue G across the acquisition phase (blocks 1 - 5) and the summation test phase (block 6) between light and heavy drinkers. Inspection of Figure 3.2 suggests the two groups increased their X responses equivalently during the acquisition phase and decreased their X responses equivalently during the summation test. This indicates acquisition learning and response suppression during summation was successful and equivalent between groups. An identical ANOVA as the one conducted with cue A's acquisition data was conducted on the acquisition data of cue G. The cue G summation test data was tested with a 2 (drinking group; light vs heavy) x 2 (blocks 5 & 6) mixed ANOVA. All ANOVAs for cue G by drinking groups are reported in Table 3.6. The results of the ANOVAs showed there was a significant main effect of block for the acquisition and summation test data, but no main effect of group or block*group interaction for any ANOVA. This supports the notion that the participants in both drinking groups were comparable in learning the CS-US association for cue G and the extinction context became equivalently inhibitory for both groups. The results of cue A ABC renewal and cue G response suppression in the summation test have demonstrated Protection-from-extinction (P-F-E).

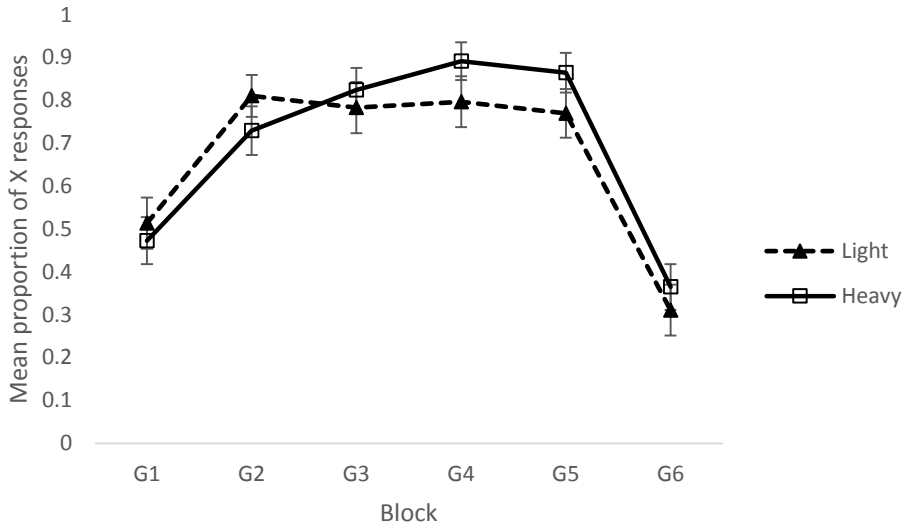


Figure 3.2. A line graph displaying the mean proportion of X responses to cue G across the acquisition phase (blocks 1 - 5) and the summation test phase (block 6) between light and heavy drinkers. Error bars represent the standard error.

Table 3.6. Repeated Measures Analysis of Variance for Cue G for drinking data

Stage	Source	*SS*	*df*	*MS*	*F*	*P*	η^2
Acquisition	Between-Subjects						
	Group	.009	1	.009	.167	.684	.002
	Error	3.74	72	.052			
	Within-Subjects						
	Block	6.12	3.26	1.88	21.69	.001*	.232
	Block x Group	.470	3.26	.144	1.67	.171	.023
	Error	20.31	234.5	.087			
Summation Test	Between-Subjects						
	Group	.102	1	.102	1.89	.173	.026
	Error	3.89	72	.054			
	Within-Subjects						
	Block	8.52	1	8.52	78.16	.001*	.52
	Block x Group	.015	1	.015	.140	.710	.002
	Error	7.85	72	.109			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared. *$p < .001$

3.4.2.2 Impulsivity

Cue A

Identical statistical analyses to those conducted with cue A for the drinking groups were conducted on the acquisition, extinction, and recovery test data for cue A, but between low and high impulsiveness groups. All ANOVAs for cue A by impulsiveness group are summarised in

Table *3.7*. Figure 3.3 displays the mean proportion of X responses to cue A across the acquisition, extinction and recovery test phases between low and high impulsivity. Inspection of Figure 3.3 suggest there was an absolute difference between low and high impulsiveness groups with low impulsiveness groups having greater X responses (and therefore strong associative learning), however, this difference is likely to be non-significant. Likewise, there was an absolute difference between low and high impulsiveness groups on extinction performance with the high impulsiveness group having impaired extinction performance increasingly by block nine. The data also suggests there is an absolute difference between the two groups in the response recovery data.

The ANOVA results showed there was a main effect of block for the acquisition, extinction, and recovery tests data indicating successful learning and ABC renewal. The results showed a non-significant main effect of group and block*group interaction for the acquisition and extinction data indicating equivalent learning between groups. However, while there was no main effect of group for the response recovery data, there was a block*group interaction indicating the high impulsiveness group demonstrated stronger ABC renewal.

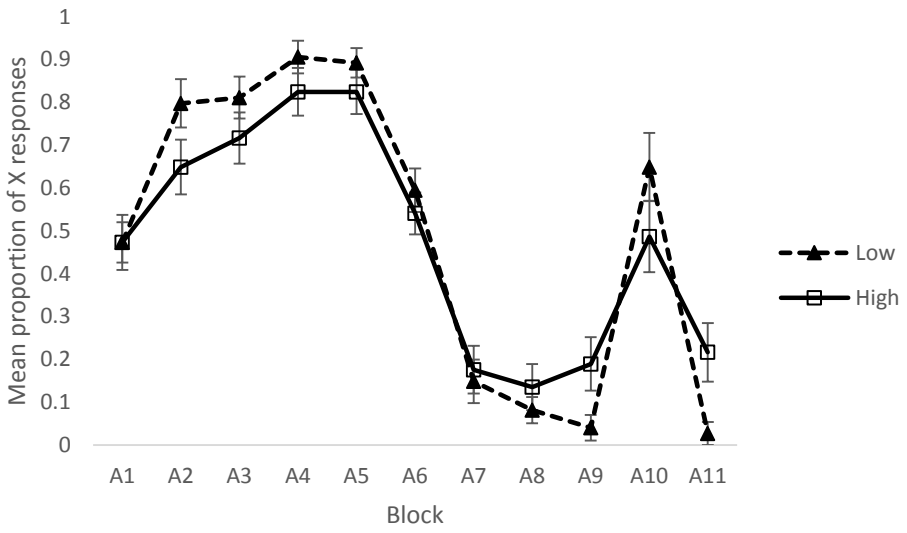


Figure 3.3. A line graph displaying the mean proportion of X responses to cue A across the acquisition phase (blocks 1 - 5), extinction phase (blocks 6 – 9) and the recovery test phase

(blocks 10 and 11) between low and high impulsiveness groups. Error bars represent the standard error.

Table 3.7 Repeated Measures Analysis of Variance for Cue A for impulsivity data

Stage	Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Acquisition	Between-Subjects						
	Impulsivity	.114	1	.114	2.44	.123	.033
	Error	3.36	72	.047			
	Within-Subjects						
	Block	7.52	3.13	2.4	26.46	.001*	.269
	Block x	.212	3.13	.068	.746	.531	.01
	Impulsivity						
	Error	20.47	225.4	.091			
Extinction	Between-Subjects						
	Impulsivity	.009	1	.009	.227	.600	.004
	Error	2.25	72	.031			
	Within-Subjects						
	Block	33.59	2.65	12.67	123.7	.001*	.632
	Block x	.572	2.65	.216	2.11	.109	.028
	Impulsivity						
	Error	19.54	190.9	.102			
Recovery Test	Between-Subjects						
	Impulsivity	.001	1	.001	.009	.926	.000
	Error	7.07	72	.098			
	Within-Subjects						
	Block	7.58	1	7.58	55.16	.001**	.434
	Block x	8.94	1	8.94	6.5	.013*	.083
	Impulsivity						
	Error	9.9	72	.137			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
* $p < .05$, ** $p < .001$

Cue G

Identical statistical analyses to those conducted with cue G for the drinking groups were conducted for the impulsiveness groups. All cue G by impulsiveness group ANOVAs are reported in Table 3.8. Figure 3.4 displays the mean proportion of X responses to cue G across the acquisition phase and the summation test phase between low and high impulsiveness groups. Inspection of Figure 3.4 suggests the two groups increased their X responses equivalently during the acquisition phase, decreased their X responses equivalently during the summation test. This indicates acquisition learning and response

suppression during summation was successful and equal between groups. The results of the ANOVAs support this as there was a significant main effect of block for the acquisition and summation test data, but no main effect of group or block*group interaction for any ANOVA.

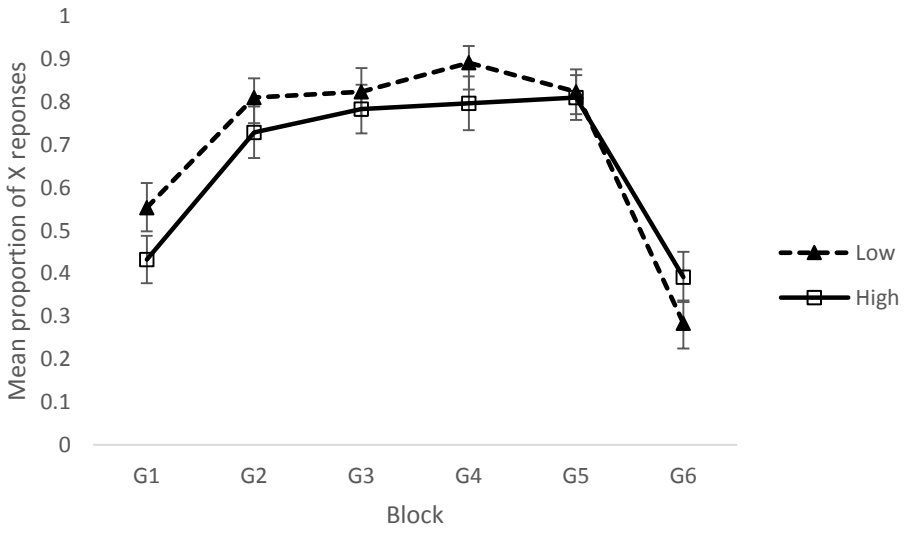


Figure 3.4. A line graph displaying the mean proportion of X responses to cue G across the acquisition phase (blocks 1 - 5) and the summation test phase (block 6) between low and high impulsivity groups. Error bars represent the standard error.

Table 3.8 Repeated Measures Analysis of Variance for Cue G for impulsivity data

Stage	Source	*SS*	*df*	*MS*	*F*	*P*	η^2
Acquisition	Between-Subjects						
	Impulsivity	.091	1	.091	1.8	.184	.024
	Error	3.65	72	.051			
	Within-Subjects						
	Block	6.12	3.28	1.87	21.34	.001*	.229
	Block x Impulsivity	.138	3.28	.042	.481	.713	.007
	Error	20.64	235.8	.088			
Summation Test	Between-Subjects						
	Impulsivity	.041	1	.041	.754	.388	.01
	Error	3.95	72	.055			
	Within-Subjects						
	Block	8.52	1	8.52	79.39	.001*	.524
	Block x Impulsivity	.137	1	.137	1.28	.262	.017
	Error	7.72	72	.107			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
*$p < .001$

3.4.2.3 Supplementary analysis

As no difference was found between drinking groups at any stage of learning task for any cue Spearman's Rho correlations were conducted between the TLFB data and the acquisition and extinction data for cue A and cue G. The results presented in Table *3.9* revealed there was non-existent correlations (all p-values > .4) between drinking data and task performance indicating task performance has no relationship with alcohol consumption behaviour.

Table 3.9 A table displaying correlations between TLFB data and task performance

	Cue A Acquisition	Cue A Extinction	Cue G Acquisition
TLFB	-.04	-.09	-.09

3.5 Discussion

The results showed the participants successfully learned the CS-US associations for both cue A and G. The light and heavy drinkers and low and high impulsivity conditions learned the CS-US associations for cue A and G at equivalent rates and strengths. This is to be expected for equally salient stimuli. This supports the first two hypotheses that both groups in the dimension of drinking status and impulsivity would learn the CS-US pairings similarly. The results show both groups in levels of alcohol consumption and impulsivity were equivalent at suppressing responding for cue G in the summation test indicating context B became inhibitory. All participants successfully extinguished cue A X responses during the extinction phase. The rate and strength of extinction between light and heavy drinkers were equivalent, as were the low and high impulsiveness groups. This does not support the hypotheses that heavy drinkers and high impulsiveness groups would have impaired extinction compared to the light drinkers and low impulsiveness groups respectively. Finally, all participants demonstrated a recovery of cue A X responses in a novel context. The recovery paired with the suppression of cue G in the summation test indicates P-F-E. There was no difference between light and heavy drinkers in response

recovery. This does not support the hypothesis that the heavy drinking group would have greater recovery compared to the light group. There was however, a significant interaction between response recovery and impulsivity.

The results show that the low impulsivity condition had a stronger recovery compared to the high impulsivity. The R-W predicts that greater response recovery occurs when there is greater CS-US acquisition and when there is greater context inhibition due to the P-F-E effect. The present studies data showed an absolute difference between the low and high impulsiveness groups at the end of the acquisition stage with the low impulsivity group having greater X responses and at during the summation test with the low impulsivity group having reduced X responses. This absolute difference however, was small and was not statistically significant. Therefore, the interaction of block*group, but not the main effect of group found in the recovery data could reflect a small magnitude of P-F-E. In addition to this the high impulsivity group had a non-significant impaired extinction performance. Previous research that has shown high trait impulsivity being associated with REX (Broos et al., 2012). The impulsivity result may be a unique anomaly present in the sample or be suggestive of something that needs further research.

It was predicted drinking behaviour would be positively correlated with impulsivity. This hypothesis was partially supported. The AUDIT-C and not TLFB was significantly correlated with BIS-11. This could be because the TLFB used in this study covered a small time frame (one week) which could misrepresent an individual's usual level of alcohol consumption. Whereas the AUDIT-C captured more generalised consumption behaviour over a longer period (six months). Higher drinking levels may correlate with impulsivity scores because they are not independent constructs, and the BIS-11 captures something of the underlying maladaptations related to heavy drinking (either as an antecedent or cause of).

A limitation of the study is the use of a median split to determine groups. As the sample consisted only of social drinkers, it is possible no difference was found between the

groups due to the limited variation in drinking data which is supported by the results in the supplementary analysis which revealed no correlation between the drinking data and task performance. Alternatively, it is possible alcohol consumption only affects Pavlovian conditioning in the most severe cases of alcohol consumption (i.e. clinical and subclinical populations). Likewise, impulsivity may only affect Pavlovian conditioning in AD populations. Another reason why there was no difference between groups could be due to the cues and US used. The present study used generic, neutral cues and US. However, as past research has shown, AD and high impulsiveness groups have an attentional bias towards alcohol-related cues (Field & Cox, 2008; Papachristou et al., 2012). Therefore, differences in Pavlovian conditioning may be detected in groups with differences in levels of alcohol consumption and impulsivity traits for learning with biologically relevant stimuli. Future research is needed to 1) replicate this experiment with an AD sample and 2) investigate the effects of drinking history on the associative learning properties of alcohol-related cues.

In conclusion, this experimental paradigm successfully demonstrated ABC renewal and context inhibition that resulted in cue P-F-E. However, there was no difference between drinking groups and impulsivity groups in this sample in CS-US acquisition and extinction learning. There may be a difference between impulsivity groups, but not drinking groups in response recovery. More research is needed to investigate this. Future research needs to study this phenomena in a clinical sample and with alcohol-related cues.

Chapter 4

Individual Differences in Acquisition and Extinction of Pavlovian Learned Responses for Generic Stimuli in Alcohol-Dependence

4.1 Abstract

The previous chapter reported no difference between differing levels of alcohol consumption within a social drinking sample in any aspect of Pavlovian conditioning processes. It was theorised differences may only be observed between alcohol-dependent and non-dependent groups. The present study used the same Pavlovian conditioning task as the previous chapter with a sample of alcohol-dependent patients and age and sex matched controls of light drinkers ($\leq$ 5 on AUDIT-C). Participants also completed personality questionnaires to control for variables such as impulsivity, negative affect, and Big Five Inventory personality subscales. The results showed evidence of impaired learning for the alcohol-dependent group as compared to the controls but no differences were observed on context inhibition. However, whilst the group difference on extinction learning was clear-cut, involving a block by group interaction, the difference on acquisition learning only appeared as a main effect of group, the block by group interaction fell short of significance. Differences in learning were not mediated by personality traits and may therefore arise from their drinking history. In conclusion the results suggest that AD patients have impaired extinction learning related to their alcohol use.

4.2 Introduction

It was demonstrated in Chapter 3 that there was no difference between light and heavy social drinkers in their rates of acquiring or extinguishing (via extinction) learned associations of generic cues. It has been assumed that variances in Pavlovian conditioning, resulting from differences in levels of alcohol consumption, are on a continuum ranging from people with low levels of alcohol consumption to AD. Therefore, the quantity of alcohol consumption typical of social drinkers may not affect Pavlovian conditioning,

however there may be a discernible difference between clinical and non-clinical populations. Therefore the present study is a replication of Chapter 3, but with a sample of AD patients and age and sex matched controls. The following hypotheses were tested:

1) The alcohol-dependent group compared to the control group will have equivalent rates of acquisition learning which would be apparent in a signficiant block*group interaction in the analysis of cue A acquistion data.
2) The alcohol-dependent group would have slower a rate of extinction of the CS-US pairings compared to the control group which would be apparent in a signficiant block*group interaction in the analysis of cue A extinction data.
3) The alcohol-dependent group would have greater response recovery of the CS-US pairings compared to the control group.

4.3 Methods

4.3.1 Participants

102 participants (62 male, 40 female) with a mean age of 41.3 years (SD = 11.9, range = 21 – 81) completed the experiment. 51 people in the alcohol-dependent group were recruited from two Southampton treatment services (the Manor Clinic [MC] and the Society of St. James [SSJ]). There were also 51 participants in the control group who were age and sex matched to experimental group who were recruited from the University of Southampton and the general public of Southampton through personal solicitation, poster advertisements and word of mouth. The inclusion criteria for all participants were: 1) 18 years or over, 2) not taking benzodiazepines, 3) No self-declared learning difficulties, 4) No head injury resulting in an overnight hospital stay in the last year, 5) no physical impairment making keyboard use difficult or impossible (e.g. arthritis), and 6) sufficient understanding of English to give full informed consent and comprehend the questionnaires/ computer task instructions. Specific inclusion criteria for the alcohol-dependent group were: a diagnosis of alcohol dependence; abstinent for a minimum of 14 days, but less than

one year. In contrast, the specific inclusion criterion for the control group was scoring ≤ 5 on the AUDIT-C.

Overall, 21.6% of participants were unemployed, 5.9% were in volunteer work, 58.9% were in employment, 8.8% were students, and 4.9% were retired. Participants received £10 upon completion of the experiment.

4.3.2 Materials

4.3.2.1 Questionnaires

The three questionnaires that were described in Chapter 2 were used plus three additional questionnaires (see the Appendix 2 for copies of all questionnaires). These additional questionnaires were:

1. Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) is a 14 item, four point likert scale, self-rating questionnaire. There are seven questions for depression and seven questions for anxiety symptoms. It has been shown to have very good sensitivity, specificity, reliability, validity and internal consistency in general and AD populations (Al Aseri et al., 2015; Bjelland, Dahl, Tangen, & Neckelmann, 2002; Djukanovic, Carlsson, & Årestedt, 2017; Mcpherson & Martin, 2011; Mykletun, Stordal, & Dahl, 2001). Depression is highly comorbid with alcohol dependence and can influence associative learning. Therefore, this questionnaire was selected in order to measure and to control for depression and anxiety symptomology.

2. 44-item Big Five Inventory (44-BFI; John, Donahue and Kentle, 1991) is a 44 item, five point likert scale, self-rating questionnaire which measures five broad bidimensional personality traits: openness, conscientiousness, extraversion, agreeableness and neuroticism. Typically questionnaires of this nature are lengthy (240 items taking 45 minutes to complete), however the 44-BFI is designed for brevity. The 44-BFI has been shown to have good psychometric properties and to be reliable and valid. Even shorter 5

item and 10 item BFIs have been developed and have been shown to be psychometrically sound, reliable, and valid. However, the 44 item BFI was chosen for its superior psychometric properties over the briefer versions (Arterberry, Martens, Cadigan, & Rohrer, 2014; Gosling, Rentfrow, & Swann, 2003; Ong, 2014). The 44-BFI was necessary to measure and control for personality traits that can influence associative learning mechanism e.g. extraversion and neurotiscm.

3. author-made checklist of other drug use to measure polysubstance use. This questionnaire asks participants if they have used tobacco, cannabis, stimulants, opioids, benzodiazapines, hallucinogens, ketamine or any other drugs (recreational or medicinal) in the last six months and in the last week. Participants respond by indicating never, infrequently or regularly.

4.3.2.2 Apparatus and computer task

The computer task used was identical to the task used in Chapter 3. The programme was run on a laptop computer with a screen measuring 30.5 cm x 19.2 cm (W x H) running at 60 Hz. The display used and programme language were identical to the machines described in Chapter 2.

4.3.3 Design

A between subjects design was used with an independent variable (level of drinking) each with two levels: alcohol dependent and control. There were 51 participants in each condition.

4.3.4 Procedure

After participants gave informed consent (see Chapter 2 for details on recruitment and consent) they completed the six questionnaires. All participants completed the BIS-11, HADS, 44-BFI, and drug use checklist. The alcohol-dependent sample completed the full

AUDIT in addition to these. The control sample completed the AUDIT-C and TLFB. For each questionnaire the participants were given a sheet of paper with the questionnaire's likert scale responses printed on. The experimenter read the questions out loud and participants gave the number of the likert scale representing their answer. Participants then completed the computer task. The experiment took 45 minutes in total.

4.4 Results

4.4.1 Sample characteristics

There were 51 participants (31 male and 20 female) in each group. The alcohol dependent group had a mean age of 41.5 years (SD = 11.5, range = 21 – 81) and the control group had a mean age of 41.1 years (SD = 12.3, range = 21 – 73). There was not a statistically significant difference between the two groups ages t (100) = .165, p = .869. The alcohol dependent group were recruited from MC (N = 24) and SSJ (N = 27) and had an overall mean of 78.4 days abstinent (SD = 69.5, range = 15 – 300). The mean number of days the MC and SSJ patients were abstinent was 73.5 (SD = 35.7, range = 35 – 186) and 82.8 (SD = 90.1, range = 15 – 300) respectively, which was not statistically significant t (34. 8) = -.493, p = .625.

The mean AUDIT score for the alcohol-dependent group was 30.7 (SD = 5.6, range = 20 - 40). The mean AUDIT-C score for the control group was 2.3 (SD = 1.7, range = 0 - 5). 98% of the control sample scored $\leq$ 3 on question one of the AUDIT, meaning they drink a maximum of 2-3 times per week. 21.6% of the control group abstained from alcohol entirely. The TLFB data showed that 37.3% of the control group reported not consuming any alcohol in the week before taking part in the experiment. The TLFB also showed that the mean number of units reported in the last week was 4.5 (SD = 6.1, range = 0 – 25.4). 94.1% of the control group participants consumed less than 14 units per week, within the Chief Medical Officers' Low Risk Drinking Guidelines (CMO, 2016).

A summary of the participant's recreational and prescribed drug use categorised by time period and group is presented in Table 4.1.

Of the AD patients, in the six month period prior to the experiment five (9.8%) reported no other substance use (except prescribed medication – see table 4.1). 16 (31.4%) reported only smoking tobacco in the six months prior to taking part in the experiment, meaning 58.8% use one or more substances in addition to alcohol and tobacco. Of the AD group who reported using stimulants (N=24), one participant reported using crack cocaine, one participant reported meth-amphetamine use, and the rest (N=22) were using cocaine, amphetamines, and ecstasy. Of the AD group who reported using opioids six months prior to the experiment (N= 19), four were prescribed codeine or tramadol, the remaining 15 participants were a mixture using heroin and abusing prescribed pain killers. The six AD who reported using opioids one week prior were taking prescribed codeine or tramadol. Of the AD patients who reported using benzodiazepines six months prior (N=8), only one reported it was specifically for their detoxification from alcohol.

Within the control group, 44 (86.3%), reported using no other drugs (except medication) in the six months prior to the experiment. Two (3.9%) of the control group reported only smoking tobacco. Therefore, 9.8% of the control group reported using one or more substances in addition to alcohol and tobacco. One control group participant reported using amphetamines and ecstasy, one reported prescribed diazepam, one reported using ketamine, and two reported being prescribed codeine.

Within the AD group, 74.5% (N=38) of participants reported taking no additional drugs beyond the non-prescribed drugs listed above in the six months prior to the experiment. This had increased to 84.3% (N=43) one week prior. Out of the prescribed drugs used six months prior to the experiment, 11 of the AD group reported using psychotropic drugs including antidepressants (N=9), one participant reported Zopiclone and one participant reported Modafinil. In addition to the psychotropic drugs, one participant reported using Flecainide. Out of the prescribed drugs used one week prior to

the experiment, nine of the AD group reported using psychotropic drugs including antidepressants (N=5), one participant reported Pregabalin, one participant reported Zopiclone, one participant reported Aripiprazole and Procyclidine. In addition to these psychotropic drugs one participant reported Naproxen, one reported Viagra, and one reported Flecainide.

Within the control group, 68.5% (N=35) of participants reported taking no additional drugs beyond the non-prescribed drugs listed above in the six months prior to the experiment. This increased to 75.4% (N=39) at one week. Four of the control group reported using prescribed psychotropic drugs six months prior to the experiment including antidepressants (N=2) and antipsychotics (N=2). In addition to these 19 participants reported using non-psychotropic drugs. One week prior the experiment only three of the control group were taking prescribed psychotropic drugs including antidepressants (N=2) and antipsychotic (N=1). In addition to this, 18 participants reported using prescribed drugs that were non-psychotropic.

Table 4.1. A summary of the number (and percentage) of participants in the AD and control groups who used recreational and prescribed drugs within 6 months and 1 week prior to the experiment.

		1 week		6 months	
		AD N (%)	Control N (%)	AD N (%)	Control N (%)
Non- prescribed Drugs					
	Tobacco	37 (72.5)	2 (3.9)	42 (82.3)	4 (7.9)
	Cannabis	1 (2)	1 (2)	15 (29.4)	3 (5.9)
	Stimulants	3 (5.9)	0	24 (47)	1 (2)
	Opioids (including prescribed)	6 (11.7)	0	19 (37.3)	2 (3.9)
	Hallucinogens	0	0	4 (7.8)	0
	Benzodiazepines	0	0	8 (15.7)	1 (2)
	Ketamine	0	0	5 (9.8)	1 (2)
	Tobacco only	34 (66.7)	3 (5.9)	16 (31.4)	2 (3.9)
	Alcohol only (or nothing)	15 (29.4)	45 (88.2)	5 (9.8)	44 (86.3)
Prescribed Medications					
	Psychotropic	8 (15.7)	3 (5.9)	11 (21.5)	4 (7.8)
	Other	3 (5.9)	18 (35.3)	1 (1.9)	19 (37.3)

4.4.2 Questionnaires

4.4.2.1 Impulsivity

The mean total BIS-11 score of the alcohol-dependent and control groups were 74.7 (SD = 15.7, range = 40 – 106) and 56.6 (SD = 7.5, range = 42 – 77) respectively. The overall median of the BIS-11 scores was 63. A Mann-Whitney U test showed the alcohol-dependent group scored significantly higher than the control group on the BIS-11 $U = 443$, $p < .001$ indicating the alcohol dependent group were more impulsive.

4.4.2.2 Depression and anxiety

The mean total depression subscale of the HADS was 10.4 (SD = 4, range = 0 – 17) and 5.4 (SD= 2.6, range = 0 – 13) for the alcohol-dependent and control group respectively. Likewise, the mean total anxiety subscale of the HADS was 5.7 (SD = 4, range = 1 – 20) and 2.7 (SD= 3.1, range = 0 – 13) for the alcohol-dependent and control group respectively. Two Mann-Whitney U tests were conducted to compare the alcohol-dependent and control group on these two subscales. The results showed the alcohol-dependent group scored significantly higher than the control group on depression subscale of the HADS [$U = 650.5$, $p < .001$] and anxiety subscale [$U = 548.5$, $p < .001$] indicating the alcohol-dependent group experienced a higher degree of depression and anxiety symptoms in the week before testing.

4.4.2.3 Personality traits

Table 4.2 summarises the 44-BFI subscale means, standard deviations, ranges, and Mann-Whitney U results. Mann-Whitney U tests were conducted on the subscale data to see if the alcohol-dependent and control group differ. Only the neuroticism and conscientiousness subscales were significant. This indicates the AD group were more neurotic and less conscientious than the control group.

Table 4.2 Summary of mean 44-BFI for each subscale for alcohol-dependent and control groups

	Alcohol-dependent M (SD, range)	Controls M (SD, range)	*U*	*p*
Extroversion	27.9 (7.2, 11-38)	25.8 (6, 13-38)	1038	.078
Neuroticism	27.6 (6.4, 16-40)	19.8 (5.4, 9-33)	478.5	.001**
Agreeableness	34.1 (6.4, 17-45)	36.6 (4.4, 25-45)	1023	.063
Conscientiousness	30.6 (8.6, 12-45)	35.9 (5.1, 21-45)	839	.002*
Openness	36.6 (6.6, 19-48)	36.9 (5.4, 22-45)	1297.5	.984

Note. $^{**}p < .001$, $^{*}p < .01$.

4.4.3 Behavioural data

4.4.3.1 Cue A

Acquisition

Figure 4.1 displays the mean proportion of X responses to cue A across the acquisition phase (blocks 1 - 5), extinction phase (blocks 6 – 9) and the recovery test phase (blocks 10 and 11) between both groups. Inspection of the acquisition phase of Figure 4.1 shows both groups X responses increasing across the 5 blocks indicating cue A's CS-US association was learned. The graph suggests the control group learned the associations much more rapidly than the alcohol-dependent group. To test the difference in acquisition rates between groups a 5 (blocks 1 - 5) x 2 (alcohol-dependent vs control) repeated measures ANOVA was carried out on acquisition data. All cue A ANOVAs are reported in Table 4.3.

The results showed a main effect of block was significant, showing a significant increase in X responses in later blocks indicating increments in associative strength and therefore successful learning. However, there was a non-significant block*group interaction revealing the main effect of block was the same for both groups. The main effect of group was also non-significant with both groups responding equally throughout the acquisition phase.

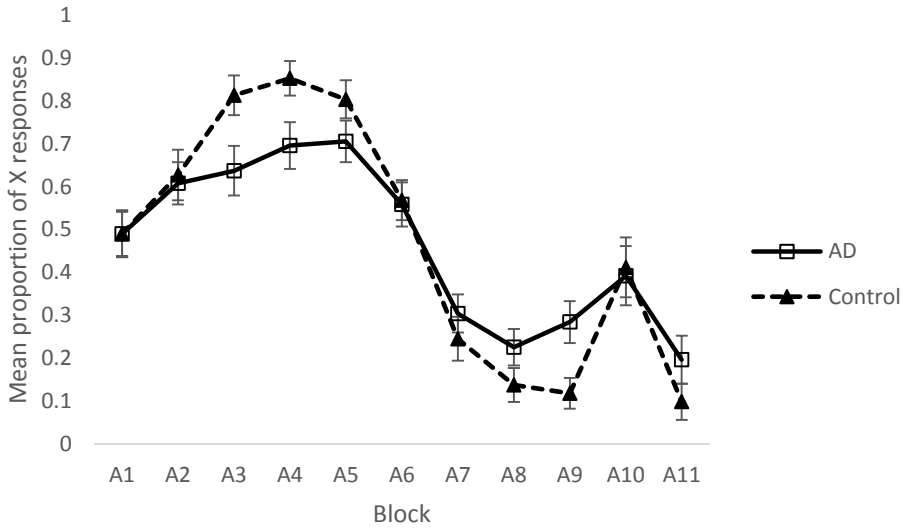


Figure 4.1. A line graph displaying the mean proportion of X responses to cue A across the acquisition phase (blocks 1 - 5), extinction phase (blocks 6 – 9) and the recovery test phase (blocks 10 and 11) between both groups. Error bars represent the standard error.

Extinction

As can be seen in Figure 4.1 the proportion of X responses decreases across blocks 6 – 9 indicating decrements in associative strength and therefore successful extinction of acquisition appropriate responses. Inspection of the figure suggest the control group displayed more rapid and stronger extinction learning. A 5 (blocks 5 - 9) x 2 (alcohol-dependent vs control) repeated measures ANOVA was conducted to test the difference between groups in extinction data.

Like the acquisition data, there was a main effect of block on the extinction data showing a significant reduction in acquisition appropriate responses and therefore successful extinction was achieved. While there was not a main effect of group there was a significant block*group interaction. This indicates that main effect of block was influenced by drinking status factor. For the final extinction block (A9), the mean number of X responses were .28 (SD = .35) and .12 (SD = 2.6) for the alcohol-dependent and controls respectively. The high standard deviations for the alcohol-dependent group revealed that average group differences are reduced by large group variance in performance. As such, the significant interaction indicates extinction is stronger in the control group.

Recovery

As can be seen in Figure 4.1 there is an increase in X responses in the recovery test phase showing acquisition appropriate responses returned. Recovery strength does not appear to be different between groups. A 2 (block: 9 and 10) x 2 (alcohol-dependent vs control) repeated measures ANOVA was conducted to test the differences between groups on their recovery effect in a novel context. There was a significant main effect of block showing X responses were recovered. However, the block*group interaction was not significant showing the block effect was the same in both groups. Likewise there was no significant main effect of group showing recovery of X responses was equal in both groups.

Table 4.3 Repeated Measures Analysis of Variance for Cue A for drinking data

Stage	Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Acquisition	Between-Subjects						
	Drinking	.207	1	.207	3.23	.075	.031
	Error	6.42	100	.064			
	Within-Subjects						
	Block	5.74	3.47	1.65	16.7	.001**	.143
	Block x Drinking	.639	3.47	.184	1.86	.126	.018
	Error	34.3	347	.099			
Extinction	Between-Subjects						
	Drinking	.043	1	.043	1.03	.312	.01
	Error	4.18	100	.042			
	Within-Subjects						
	Block	26.1	3.09	8.44	80.6	.001**	.446
	Block x Drinking	1.03	3.09	.332	3.17	.023*	.031
	Error	32.4	309.1	.105			
Recovery Test	Between-Subjects						
	Drinking	.138	1	.138	1.43	.235	.014
	Error	9.65	100	.097			
	Within-Subjects						
	Block	2.06	1	2.06	14.1	.001**	.123
	Block x Drinking	.442	1	.442	3.03	.085	.029
	Error	14.6	100	.146			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
**$p < .001$, *$p < .05$

4.4.3.2 Cue G

Acquisition

Figure 4.2 displays the mean proportion of X responses to cue G across the acquisition phase (blocks 1 - 5) and the summation test phase (block 6) between both groups. Inspection of the acquisition phase of Figure 4.2 shows both groups X responses increasing across the 5 blocks indicating the cue G CS-US association was learned. The graph also suggest that while the control participants learned the association more quickly, there was no difference between groups by the final acquisition trials. To test the difference in acquisition rates between groups a 5 (blocks 1 - 5) x 2 (alcohol-dependent vs control) repeated measures ANOVA was carried out on acquisition data. All ANOVAs for cue G are summarised in Table 4.4. The results showed cue G had a significant main effect of block and a significant main effect of group, but not a significant block*group. This shows that there was indeed a significant increase in X responses to cue G over blocks, and that the two groups learned at unequal rates, but learning was comparable by the final block. The alcohol-dependent group learned more slowly than the controls, but by the end of the acquisition learning phase both groups were comparable in the CS-US association.

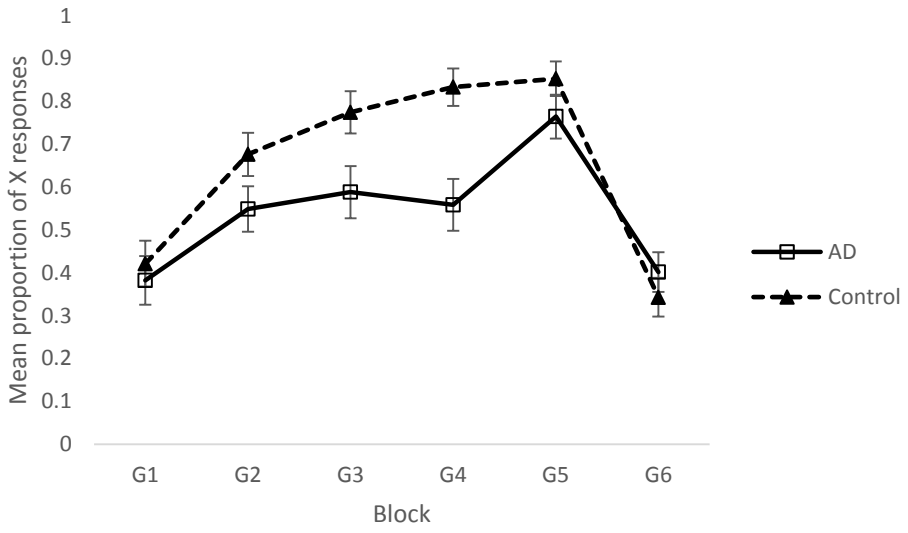


Figure 4.2. A line graph displaying the mean proportion of X responses to cue G across the acquisition phase (blocks 1 - 5) and the summation test phase (block 6) between both groups. Error bars represent the standard error.

Summation

Figure 4.2 shows a decrease in X responses in block 6. This is a suppression of X responses while cue G is presented in the extinction context. A 2 (blocks) x 2 (alcohol-dependent vs control) repeated measures ANOVA was conducted to test the difference between groups on the summation test. There was a significant main effect of block showing that X responses were significantly decreased when cue G was presented in the extinction context. However, there was not a significant block*group interaction, nor a significant main effect of group indicating that both groups supressed X responses equally.

Table 4.4 Repeated Measures Analysis of Variance for Cue G for drinking data

Stage	Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Acquisition	Between-Subjects						
	Group	.522	1	.522	7.44	.008*	.069
	Error	7.02	100	.07			
	Within-Subjects						
	Block	9.26	3.56	2.61	26.9	.001**	.212
	Block x Group	.846	3.56	.238	2.46	.052	.024
	Error	34.4	355.2	.097			
Summation Test	Between-Subjects						
	Group	.006	1	.006	.089	.766	.001
	Error	6.22	100	.062			
	Within-Subjects						
	Block	9.71	1	9.71	106.2	.001**	.515
	Block x Group	.276	1	.276	3.02	.086	.029
	Error	9.14	100	.091			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
**$p < .001$, *$p < .01$

4.4.4 Mediation analysis

The results presented above showed that the extinction performance of the control (light drinkers) and experimental (AD) differed with extinction proceeding more slowly in the AD than in the light drinkers. The *a priori* objective of this experiment was to look specifically at the effect of AD on performance in the learning task, but it was reported above that the light and dependent drinker groups differed on a number of personality traits which have been shown to influence associative learning performance. There exists, therefore, the possibility that the observed effect of AD on extinction performance could be mediated through these personality traits. In order to determine whether or not AD had a direct effect on extinction and to see whether or not there were any indirect effects of AD on extinction mediated by personality we carried out a mediation analysis (Hayes, 2013). In this analysis, all variables with a significant difference between experimental and control group differences (BIS11, HADS-A, HADS-D, 44BFI-C, and 44BFI-N) were standardised and entered as parallel mediators (Model 4 PROCESS version 3.1) and group (AD vs light drinkers) was entered as a direct effect variable. The dependent variable was obtained from a regression of X responses on block (from the end of acquisition, block 5,

to the end of extinction, block 9). A linear regression coefficient was calculated separately for each participant to summarise their performance over the extinction phase and served as the dependent variable. The results of this analysis indicated a direct effect of group on extinction (effect = -.08, SE= .029, t= -2.75, $p < .01$) but that there were no indirect effects (smallest $p = .2$, effect = .02, SE = .02 for 44BFI-C) confirming that the observed effect of dependence on extinction learning was not mediated by group difference on personality traits.

4.5 Discussion

The results showed participants successfully learned the CS-US pairings of both cue A and cue G. Moreover, the participants displayed successful extinction and response recovery for cue A and successful response suppression for cue G during the summation test. This indicates the entire sample on average displayed ABC recovery and context inhibition of the extinction context.

It was hypothesised that the AD group and control group would have equivalent rates of CS-US acquisition. The results showed this hypothesis was supported. The statistical tests revealed the AD group learned the CS-US association for cue A and cue G at the same rate as the control group. It should be noted, for cue G, the main effect of group was significant and the block*group interaction became close to significant ($p = .052$). However, as an interaction significance was not met caution is needed in overstating the group differences.

The mediation analysis eliminated personality differences as an explanation of the results. It is possible one or more of the following reasons could contribute to this outcome. Firstly, the AD participants may have alcohol-related impairment of associative learning processes. In addition to this or alternatively, the AD participants may have some form of cognitive impairment, such as they may have failed to sustain attention throughout the task. This is indirectly supported by previous research which suggests cocaine users are

impaired in learning generally. Ersche et al. (2016) showed cocaine users were slower at acquiring instrumental discrimination. Perhaps AD patients are slower at other forms of associative learning? The extinction result (discussed below) coupled with the acquisition data nearing significance suggests in future research in which Pavlovian conditioning is measured differently may show general learning impairment.

The final, less likely, explanation proposed is the AD participants could have had greater reward incentive. Participants were informed they were to be paid £10 upon completion of the experiment during the recruitment and giving of informed consent. A greater number of the AD participants were non in full time employment compared to the control group. The AD participants may also have heightened reward sensitivity in comparison to the controls. Therefore, even though both groups received identical procedural instructions and the experimenter tried to establish that each participant fully understood the task before participating, the AD participants may have become impatient and lied about understanding the task to more quickly receive the payment. Whereas the control group, who could be less motivated by the payment incentive, could have taken time to fully understand the task and complete it properly. It remains uncertain to what extent the latter explanation contributes to the findings as a lot of the AD participants seemed genuinely interested in the experiment and helpful once they were told the wider background of the research is related to relapse behaviour, cue-exposure and recovery.

The AD group, when compared to the control group, also demonstrated impaired extinction learning as shown by the significant block*group interaction on the extinction data. This supports the hypothesis that the AD group would have slower extinction of the previously acquired CS-US pairings. However, it is unclear why this is the case. It was theorised the AD participants would display inferior extinction performance due to alcohol-related REX. However, the REX displayed by the current AD sample may be augmented the potential confounding variables described in the previous paragraph. Alternatively the extinction result may be explained solely by the other factors outlined in

the previous paragraph and may have nothing to do with the effects of alcohol use on associative learning processes. It may be possible that the slower extinction rate can be explained by the acquisition data. The R-W model predicts the weaker the CS-US associative strength, the weaker the extinction learning. The cue A data shows an absolute difference between AD and control groups in which the AD displayed less X responses by the end of the final acquisition block. However, there was no statistically significant difference on the acquisition data. Therefore, this suggests that the two groups had comparable understanding of what outcome cue A predicts by the end of the acquisition phase.

The results displayed equivalent acquisition performance between the two groups and impaired extinction performance for the AD group, which demonstrated clear REX in an AD sample. In addition, the present study's results suggest AD related impaired extinction is not mediated by personality traits; suggesting a direct influence of alcohol consumption. Therefore, these results warrant further investigation. Several experiments are needed. Firstly, by investigating reinforcer type. The present study (and all experiments presented in this thesis thus far) have used the same Pavlovian conditioning task in which participants learn pairings of generic stimuli. As discussed in previous chapters, the R-W model predicts differences in cue salience would result in different rates of learning. Past research has shown AD patients who relapsed displayed greater attentional bias to alcohol-related cues compared to non-dependent individuals (Cox, Hogan, Kristian, & Race, 2002). The experiments presented thus far in this thesis have shown there is no difference between light and heavy social drinkers in their Pavlovian performance, but this is between AD and light drinkers. Therefore, it is possible that differences in Pavlovian performance may emerge within a social drinking sample for alcohol-related stimuli, but not non-drug related biologically relevant stimuli (e.g. food) or generic stimuli such as those used in this study. Future research is needed to determine whether incentivised rewards (e.g. alcohol, food & money) and levels of alcohol consumption play a role in the development of REX.

Secondly, it is unclear whether the alcohol-related differences in extinction performance were present before chronic alcohol use or a consequence of. Future research is needed to disentangle that.

In conclusion, the study presented here suggests that AD patients have impaired extinction learning which is related to their chronic and severe alcohol use and not mediated by personality traits that are commonly related to addiction and which have been shown to influence associative learning processes (i.e. impulsivity, depression symptomology, and BFI constructs). More research is needed to determine whether this difference in extinction learning is a consequence of AD pathology and whether reinforcer type interacts with alcohol consumption.

Chapter 5

Individual Differences and Reinforcer Type in Acquisition and Extinction of Learned Pavlovian Responses in Light and Heavy Social Drinkers

5.1 Abstract

As a result of their conditioning history, alcohol and non-alcohol related cues acquire different motivational properties. Alcohol-related cues have strong influences on alcohol seeking and consumption. Individuals with a high levels of alcohol consumption and individuals with high trait impulsiveness have been shown to strengthen the influence of alcohol-related cues on motivation. The aim of the present study is to investigate the effect of drinking history and impulsivity on Pavlovian conditioning of reinforcer type in human social drinkers. This study required participants to drink alcohol and placebo (non-alcohol) drinks in which they could not determine which drink contained alcohol based on smell and taste. A pilot study was undertaken to determine the most effective drinks to use. The present study had participants learn associations between generic neutral cues with alcohol and food rewards and undergo extinction and renewal in an ABA and ABC design. The results showed successful ABA, but not ABC renewal for both alcohol and food cues. They also revealed there was no difference between light and heavy drinkers at any stage of the Pavlovian conditioning task to either reinforcer type. In addition to this there was no difference between high and low impulsivity groups at any stage of the conditioning task. There was however, greater spontaneous recovery mid-extinction training in the low impulsivity group. In summary, the present study's paradigm can be successfully used to investigate ABA renewal, but social drinkers do not demonstrate a difference in Pavlovian conditioning between alcohol and non-drug cues.

5.2 General Introduction

The previous experiments presented in this thesis have demonstrated there is no difference between light and heavy social drinkers in Pavlovian acquisition, extinction, and

response recovery for the learning of generic neutral cues. However, when the study was replicated in an AD sample, the results showed the AD group had impaired extinction learning compared to age and sex matched healthy controls. In previous chapters it was discussed that AD patients react differently and give greater levels of attention to alcohol-related cues compared to non-drug cues. This difference could explain the ACETP. Therefore, the aim of the present study is to test the effects of reinforcer type on Pavlovian mechanisms. The conditioning experiment described in this chapter will use alcohol and non-alcohol placebo as unconditioned stimuli. The conditioning experiment requires participants to discriminate between the alcohol and placebo beverages only by experiencing the subjective feelings of alcohol intoxication to attempt to create Pavlovian associations between the conditioned stimuli and intoxication effect, so it was imperative that the beverages used in the conditioning experiment be perceptually identical. Therefore, before the conditioning experiment, a pilot study was conducted to determine the most effective beverages to use to deceive participants in their ability to distinguish between alcohol and placebo drinks.

5.3 Pilot study

5.3.1 Introduction

Alcohol is commonly used in psychopharmacology research. Alcohol has been administered to participants in a range of research studies including: 1) investigating the effects of alcohol on cognitive and psychomotor performance (Liguori, D'Agostino, Dworkin, Edwards, & Robinson, 1999; Weissenborn & Duka, 2003), 2) investigating facets of alcohol dependence e.g. cue reactivity and consumption (Davidson et al., 2003; Kaplan et al., 1984; Marlatt, Demming, & Reid, 1973; Stockwell, Hodgson, Rankin, & Taylor, 1982), 3) investigating the effects of alcohol on emotional processing and social interaction (Stappenbeck & Fromme, 2014), 4) investigating the effects of alcohol on risky and social behaviours (Abbey, Saenz, & Buck, 2005), and 5) designing effective alcohol-

placebos and administration methodologies (Corcoran & Segrist, 1993; Glautier, Taylor, & Remington, 1992; Lachenmeier, Kanteres, & Rehm, 2014; Lachenmeier, Pflaum, Nieborowsky, Mayer, & Rehm, 2016) to name a few.

The latter type of research is perhaps the most important for alcohol-placebo research in which deception of participants, in regards to knowledge of what they are consuming, is vital. If research that utilises an alcohol-placebo is ineffective in deceiving participants, this can have a profound effect on task performance, therefore confounding results and limiting the data's interpretation and usefulness. One method of deceiving participants into becoming unaware of which type of drink they are being administered is beverage manipulation (Rohsenow & Marlatt, 1981). The alcohol and placebo beverages need to be identical on visual, tactile, olfactory and taste perception, however, this has proved challenging of researchers due to the potency of olfactory and taste properties of alcohol which are hallmarks that experienced drinkers have learned to expect when consuming alcohol.

Past research has attempted to overcome this challenge by adding the smell of alcohol to the placebo drink either by adding an alcohol floater to the drink or lining the rim of the glass with alcohol (Assefi & Garry, 2003; Bernstein, Wood, & Colby, 2016; Davidson et al., 2003; Liguori et al., 1999). A limitation to this approach of beverage manipulation is both the alcohol and placebo drinks contain alcohol and therefore both beverages can have the pharmacological effects that are supposed to be isolated to alcohol alone. Another method of beverage manipulation is using elaborate maskers such as lime juice (Knight, Barbaree, & Boland, 1986; Newlin, 1986), Tabasco (Weissenborn & Duka, 2003) and peppermint (Bombeke, Schouppe, Duthoo, & Notebaert, 2013; Glautier, Drummond, & Remington, 1994; Glautier et al., 1992).

The alcohol-placebos utilised are not always entirely effective. In a recent study involving administering placebo drinks in a bar setting, it was reported 11% of the participants were not deceived into thinking they had consumed alcohol (Bernstein, et al.,

2016). In addition to this Corcoran & Segrist (1993) tested whether participants could tell the difference of alcohol content between non-alcoholic, light and regular beers. There were two non-alcoholic beers used and participants could successfully identify one non-alcoholic beer as having less alcohol content than the other beers. The other non-alcoholic beer was estimated to have the same amount of alcohol content as the light and regular beer. This indicates that some people are able to distinguish between alcoholic and non-alcoholic drinks. This is supported by a meta-analysis on the effectiveness of placebos that concluded participants in the placebo condition estimate they consumed less alcohol and report lower levels of intoxication than their alcohol condition counterparts (Schlauch et al., 2010). This meta-analysis revealed that type of mixer moderates estimates of number of alcoholic drinks consumed highlighting the importance of beverage manipulation. Past research has shown one reason why some people are able to distinguish between placebo and alcohol drinks better than others. Individuals with greater alcohol consumption levels are better than those which consume less alcohol at detecting the difference between non-alcoholic and regular beer (Martin, Earleywine and Young, 1990), however, to our knowledge, similar research has not been conducted with other types of alcohol.

Spirits, in particular vodka, is the most widely used in research. The placebos for vodka are often just the mixer with a small amount of alcohol or masker added to attempt to make the taste and olfactory properties of the drinks identical. Beer has also been used to a lesser extent (Corcoran & Segrist, 1993; Kaplan et al., 1984; Martin et al., 1990) and to our knowledge only one study has used wine (Davidson et al., 2003). Beer has been a useful beverage of choice in research due to its popularity and widespread availability of regular, light and non-alcoholic brands. Until recently, non-alcoholic alternatives to alcohol have contained small doses of alcohol; non-alcoholic beer is typically .5% ABV and wine came in either low alcohol around 5-7% ABV or more recently alcohol free at .05 or .5% ABV. The non-alcoholic beer used in past research have all been commercially available brands with ABVs of .5% and .4% (Corcoran & Segrist, 1993), .05%, .3% and

.5% (Martin et al., 1990). Kaplan et al., (1984) did not report the brand, but being commercially available it can be assumed it is .5% ABV. Only very recently have dealcoholized alternatives become widespread commercially available in both beer and wine at 0% ABV. 0% ABV spirits are now commercially available where the burning taste of alcohol is mimicked with capsaicinoids. Manufacturers claim the taste is identical to regular spirits, however peer reviewed research showed all the participants could distinguish between regular and dealcoholized spirits and concluded the burning taste was more reminiscent of chili than ethanol (Lachenmeier et al., 2016).

Similar claims of the 0% ABV beers and wines have been made by manufactures that taste has improved from non-alcoholic beverages from decades ago and they are harder to distinguish from their alcohol counterparts. If these claims are true, it has implications for treatment of AD. Using non-alcoholic beverages as substitute drinks for abstaining AD patients is not a novel idea. It has been theorised that allowing the consumption of non-alcoholic beverages could potentially improve the efficacy of CET in treating alcohol dependence by increasing the number of exteroceptive cues being extinguished (taste as well as visual and olfactory cues) and putting the operant behaviour of physically lifting the bottle/ glass and swallowing/drinking under extinction, therefore extinguishing both stimulus-outcome (S-O) and response-outcome (R-O) associations simultaneously and not just the S-O of traditional CET (Conklin & Tiffany, 2002; Troisi II, 2013). Therefore if the newer 0% ABV dealcoholized alternatives to regular alcohol are similar to regular alcohol, it could have potential therapeutic effects.

Therefore the primary aim of the pilot study is to see how well people can distinguish between placebo and alcohol beverages using commercially available 0% ABV beers and wine. Because 0% ABV spirits have already been scrutinised in previous research a vodka placebo will be created in-line with previous research techniques. The secondary aim of the pilot study is to see if elaborate maskers such as peppermint are still necessary with the allegedly improved dealcoholized options. The pilot study was

conducted to determine the best method of beverage manipulation to help determine which beverages are most suitable to use for the associative learning experiment described later in this chapter which utilised an alcohol unconditioned stimulus.

Based on the results of (Corcoran & Segrist, 1993) and Lachenmeier et al. (2016) the following hypotheses were tested:

1) Participants will be able to distinguish between dealcoholized and regular beer without a peppermint masker.
2) Participants will be able to distinguish between dealcoholized and regular wine without a peppermint masker.
3) Participants will not be able to distinguish between the alcohol and placebo vodka options with and without peppermint.
4) Participants will be better at distinguishing between all alcohol and placebo options without peppermint compared to with peppermint.
5) Participants with a history of greater alcohol consumption will be better at distinguishing between all types of alcohol and placebo drinks with and without peppermint compared to those with a history of less alcohol consumption.

5.3.2 Methods

5.3.2.1 Participants

48 participants (38 female) with a mean age of 19.4 years (SD = 1.2, range = 18 – 22) took part. All participants were undergraduate students at University of Southampton. 85.4% were psychology students, the remainder were evenly distributed between, biology, mathematics, history, computer science and medicine. The vast majority of participants received 3 course credits, while a minority received £2 for completion of the experiment.

5.3.2.2 Materials

AUDIT-C described in Chapter 2 was the only questionnaire used.

Alcolmeter

The Lion Alcolmeter S-D2 was used to estimate of blood alcohol level (BAL) by measuring the concentration of alcohol vapour in expired breath.

Drinks and food

The alcohol room choice phase was set up identically to the conditioning experiment described later. Therefore, for this phase there was 10 x 50 ml 5% ABV beer (Heineken) and 10 dried fruit snacks (five of apricot bites and five of cranberries) arranged on a tray in one room. The other room had an identical set up except the drinks were 0% ABV beer (Bavaria).

For the alcohol taste phase, overall there were 12 x 10ml drinks all presented in 25ml shot glasses. There were four glasses of beer. Two of which were 5% ABV (Heineken) and two 0% ABV (Bavaria). Four of the drinks were red wine, two of which were 12% ABV (Mondelli Merlot) and two 0% ABV (Eisberg Alcohol Free Wine). The final four drinks were vodka and orange juice or tonic water and orange juice. Two of the drinks 40% ABV vodka (Russian Standard) mixed with Sainsbury's Pure Orange Juice, the remaining two were Sainsbury's Indian Tonic Water. The drinks were 2ml of vodka or tonic water and 8 ml of orange juice. One alcohol and one non-alcoholic beverage of each drink type also had 1ml peppermint extract added as a masking agent. The peppermint used was Dr. Oetker American Peppermint Extract because it was the only available option that does not contain ethanol.

5.3.2.3 Design

A between subjects design with one independent variable that has two levels: light and heavy drinkers. There are seven dependent measure: one is the forced choice of room alcohol vs non-alcohol and six are the forced choice of drink pairs of alcohol versus non-alcohol.

5.3.2.4 Procedure

All participants were tested individually in the lab in between 12:00-17:00. First, participants were then breathalysed to ensure they did not have alcohol in their system. All participants BAL = 0 at the start of the experiment. Next participants completed the AUDIT-C questionnaire. After the questionnaire participants completed the room choice phase. For this phase, room A and room B both contained drinks. One room contained alcohol containing beer and the other contained a non-alcoholic counterpart. Rooms A and B were counterbalanced in regards to which room contained alcohol and which room participants visited first. The rooms were cubicles with a desk, chair and computer with a plain white tray next to the computer. The tray contains ten 50ml drinks of 5% ABV beer or 0% ABV beer next to an array of 10 fruit snacks. Plastic cups containing small amounts of vodka was hidden on the window seal, behind the blinds of each cubicle. In addition, small vodka soaked tissues were taped to the underside of the desk and chair. This was to attempt to make both cubicles smell identically of alcohol. During this phase participants went into one room and sat in the chair for 30 seconds and inspected the environment without drinking or eating and then immediately did the same thing for 30 seconds in the other room. After both rooms have been inspected participants had to make a decision on which room contains the alcohol containing drinks. Finally, participants completed the taste choice phase. This phase was set in a third novel cubicle identical to the other two except on the tray were 12 10 ml drinks arranged in six pairs. The pairs were an alcohol containing drink with a non-alcoholic counterpart. These were 5% ABV beer and 0% ABV beer, 12% ABV red wine and 0% ABV red wine and 40% ABV vodka and orange juice or tonic water and orange juice. There were another three pairs identical to these, but each had 1ml of peppermint extract in. For this phase all drinks without peppermint were consumed before the drinks with peppermint; this sequential ordering was to ensure a lingering peppermint taste did not confound the results. The order of drink type and the order of drinking the alcohol or non-alcoholic drink first was completely randomised.

During this phase participants consumed one drink first, waited two seconds and then consumed the other drink. There was a 60 second interval before participants consumed the next drink pair. During this interval participants made a decision on which of the two drinks contained alcohol and rinsed their mouth out with water. This process was complete when all six drink pairs were consumed. At the end of the experiment participants were breathalysed to show they had consumed alcohol. Participants were advised to remain in the lab until BAL=0 or they could sign a disclaimer saying we advise them to stay, but they are leaving against our advice. They were also advised to stay safe and not to drive or operate heavy machinery for up to three hours after the experiment and they understood the advice (see Appendix 1). All participants signed the disclaimer and left immediately.

5.3.3 Results

5.3.3.1 *AUDIT*-C

The sample was categorised into light and heavy drinking groups based on a median split of the AUDIT-C data. The results showed a median of 6 (SD = 2.2, range = 1 – 12). The light drinking group mean was 4.9 (SD = 1.2, range = 1 – 6). The high drinking group mean was 8.6 (SD = 1.2, range = 7 – 12). A t-test was conducted to see if the two groups differ in AUDIT-C score. The results revealed a significant difference t (46) = -10.5, $p < .001$.

5.3.3.2 Room choice

Overall, 79.2% of participants correctly identified the room that contained the alcoholic drinks in. Table 5.1 summarises the observed count of light and heavy drinkers that correctly or incorrectly identified the room that contains alcohol. A chi-square test was calculated comparing the frequencies of correct choices in light and heavy drinking groups. The results showed there was no difference between groups in identifying the alcoholic room. All chi-square test results are presented in Table 5.4.

Table 5.1 Crosstab of correct and incorrect alcohol room choice by light and heavy drinking groups

	Correct	Incorrect	Total
Light	18	6	24
Heavy	20	4	24
Total	38	10	48

5.3.3.3 Taste test

Overall, when tasting the non-peppermint drinks, 68.8%, 83.3%, and 83.3% correctly identified the alcoholic versions of beer, wine and vodka drinks respectively. Table 5.2 summarises the observed count of light and heavy drinkers that correctly identified which drinks contained alcohol. A chi-square test was conducted to compare light and heavy drinking groups on selecting the alcohol version of beer, wine, and vodka drinks. All results showed there was no difference between groups in identifying which drink was alcohol and which was the placebo without and peppermint masking agent. Overall, when tasting the drink options with a peppermint masking agent, 66.7% 70.8%, and 56.3% could accurately identify the alcohol version of beer, wine and vodka respectively. Likewise, results are summarised in Table 5.2. Three identical chi-square tests were calculated. Likewise, the results showed there was no difference between groups in identifying beer, wine, or vodka.

Table 5.2 Crosstab of correct and incorrect taste test choice by light and heavy drinking groups for beer, wine and vodka drink types with and without peppermint

	Drink	Group	Correct	Incorrect	Total
Non-peppermint	Beer	Light	16	8	24
		Heavy	17	7	24
		Total	33	15	48
	Wine	Light	20	4	24
		Heavy	20	4	24
		Total	40	8	48
	Vodka	Light	18	6	24
		Heavy	22	2	24
		Total	40	8	48
Peppermint	Beer	Light	17	7	24
		Heavy	15	9	24
		Total	32	16	48
	Wine	Light	14	10	24
		Heavy	20	4	24
		Total	34	14	48
	Vodka	Light	13	11	24
		Heavy	14	10	24
		Total	27	21	48

Three McNemar tests were conducted to compare the presence of peppermint vs no peppermint on selecting the alcohol version of beer, wine and vodka. Table 5.3 summarises the crosstabs of with and without a peppermint masking agent. In Table 5.3, the columns contain the number of participants that responded correctly or incorrectly when the drinks had a peppermint masking agent and the rows are the same without the peppermint. As can been seen with identifying alcohol beer, 24 participants could correctly, identify the alcohol beverage consistently with and without peppermint. Likewise, seven participants were consistently incorrect. Eight participants incorrectly identified the drink that contained beer without peppermint, but could identify the alcohol beer when there was peppermint. Similarly, when there was peppermint, nine participants could not identify the alcohol beer, but could without peppermint. The results of the McNemar test showed there was no difference between the presence of absence of a peppermint masking agent in determining which beer contained alcohol ($p = 1$).

For the participants' identification of the alcohol containing wine, 30 participants consistently were correct in identifying the alcohol wine with and without peppermint and four were consistently incorrect. Four participants incorrectly identified the alcohol wine

when there was no peppermint, but correctly identified it with and 16 were incorrect with peppermint, but correct without. The McNemar results also showed no difference between the presence and absence of peppermint (p = .18). These results suggest that participants were quite accurate at identifying the alcohol containing drink regardless of a peppermint masking agent being used for both the beer and wine beverages.

For the participants identification of vodka beverages, 19 participants were consistently correct in identifying which drink contained vodka and not tonic water regardless of whether peppermint was present or not. Not a single participant was consistently incorrect. 21 participants incorrectly identified the vodka drink when peppermint was presence, but were correct when it was absent and eight were correct when peppermint was present, but incorrect when absent. The results of the McNemar test revealed a significant difference for participants' ability to identify the vodka drink between beverages with a peppermint masking agent and those without (p < .05). These results suggest that for vodka drinks compared to tonic water placebo drinks, participants are impaired at identifying the alcohol containing beverage when a peppermint masking agent has been applied.

Table 5.3 Crosstab of correct and incorrect taste test choice for beer, wine, and vodka by drinks with and without peppermint.

Drinks without Peppermint		Drinks with Peppermint		
		Correct	Incorrect	Total
Beer	Correct	24	9	33
	Incorrect	8	7	15
	Total	32	16	48
Wine	Correct	30	10	40
	Incorrect	4	4	8
	Total	34	14	48
Vodka	Correct	19	21	40
	Incorrect	8	0	8
	Total	27	21	48

Table 5.4 Summary of chi square tests results

		χ^2	*df*	*p*
	Room Choice	.505	1	.362
No Peppermint	Beer	.097	1	.5
	Wine	0	1	.65
	Vodka	2.4	1	.122
Peppermint	Beer	.375	1	.38
	Wine	3.63	1	.055
	Vodka	.085	1	.5

Note. χ^2 = chi square, *df* = degrees of freedom, *p* = exact sig.

5.3.4 Discussion

As this experiment is a pilot study to determine the most effective way to conduct an alcohol based Pavlovian conditioning experiment, participants were first asked to sit in a room, set up identically to how the conditioning experiment would be for 30 seconds. Participants spent 30 seconds in one cubicle that contained a tray with glasses of alcohol containing beer, and 30 seconds in a different, but identical room with a tray with 0% dealcoholized beer. Participants overwhelmingly (79%) could identify the room that contained alcohol. This was not affected by drinking status. Informal chats between the experimenter and participants revealed that that alcohol containing room smelled strongly of alcohol and the dealcoholized room smell strongly of fruit; smell coming from the glasses more strongly than the fruit snacks. Participants could identify the cubicle that contained alcohol despite the attempts to make both cubicles smell of alcohol. The smell of the dealcoholized beer, which participants described as fruity, was noticeable. As participants were in the cubicle for 35 minutes in the Pavlovian conditioning experiment, it was this result that made the decision to have both alcohol and placebo drinks present throughout the conditioning experiment in an attempt to eliminate the smell confounder.

As the Pavlovian conditioning experiment involved participants consuming alcohol and placebo drinks, and being unable perceptually to identify the alcoholic beverage, participants in the pilot study were asked to consume a variety of alcohol and dealcoholized drinks. Participants consumed beer, wine and vodka/orange juice drinks and 0% ABV equivalences; vodka placebo achieved with tonic water replacement. Participants

consumed these drinks describe as they are above and again with peppermint extract added as a masking agent. It was hypothesised heavy drinkers would be better at identifying the drinks that contained alcohol compared to light drinkers regardless of drink type or the presence/ absence of peppermint. This hypothesis was not supported as the results showed no difference in any drink variable. It was also hypothesised that, for beer and wine drinks, participants would be able to distinguish between the versions without peppermint, but not with peppermint. This hypothesis was not supported as the results showed participants could identify the alcohol containing version of these two drinks despite a peppermint masking agent being used. Finally, it was hypothesised participants would not be able to correctly identify the alcohol version of the vodka and mixer beverages regardless of the use of a peppermint masking agent. This hypothesis was also not supported as the results showed participants could correctly identify the vodka drink without peppermint more accurately (83.3%) than with peppermint (56.3%). As the presence of peppermint made a significant difference in participants' accuracy, and achieved an accuracy as close to 50% as possible, the vodka/ tonic water and orange juice drinks with peppermint was the drink used in the Pavlovian conditioning experiment.

A strength of the present study was the placebo drinks were 100% alcohol-free. There was no alcohol added to the drink or glass rim to infuse the smell of alcohol into the placebo drinks to deceive the participants. In addition, a natural peppermint extract was selected that did not contain any ethanol at all, as most peppermint extract are 95% ethanol. The pilot study's results showed that participants were able to correctly identify with high accuracy the alcohol versions of beer and wine. This casts doubt on the effectiveness of modern dealcoholized beverages being used for sham consumption during a modified CET procedure. CET effectiveness is maximised when the cues are idiosyncratic to the patient. Therefore, it seems very unlikely that modern dealcoholized wine as placebo consumption can augment CET efficacy as 83% of the participants could correctly identify the wine. 69% of participants could correctly identify beer so perhaps

there is a subset of patients drinking dealcoholized beer could help, but that seems unlikely when one considers drinking history severity.

A weakness of the present study was the limited variation in drinking status. All the participants were social drinking students. The majority of students were clustered around the median of the AUDIT-C and therefore variability of scores was limited which compromises the ability to classify a sample of homogenous drinkers as light and heavy. Future research would benefit from using more extreme methods of categorising participants, such as recruiting social drinkers who consume very little in their day to day life (e.g. < 5 units a week) and who drink a lot (e.g. > 14 units a week). Alternatively future research could recruit moderate social drinkers and problematic binge drinkers. The pilot study found no difference between light and heavy drinking groups in their accuracy in detecting alcohol in the beer and wine beverages, potentially because the lack of variability in AUDIT-C scores and clustering around the mean indicates the present sample consists mainly of light drinkers. Maybe a difference will emerge in actual heavy or problematic drinkers. If this is the case, then it seems unlikely that current dealcoholized beverages are suitable for increasing the efficacy of CET by modifying the traditional CET procedure with placebo consumption. It is unlikely because past research has shown heavy drinkers are better at detecting fake alcohol (Martin et al, 1990).

In conclusion, the present study suggests that light and heavy drinkers are equal in their ability to tell the difference between alcohol and commercially available 0% ABV dealcoholized versions of beer and wine. Light and heavy drinkers are also equally able to tell the difference between vodka and orange juice and tonic water placebo alternatives. The only alcohol-placebo beverage that could successfully deceive participants was the vodka/tonic water and orange juice beverages that had peppermint extract as a masking agent added to it; the most commonly used drink manipulation method of alcohol-placebo literature.

5.4 Main Experiment

5.4.1 Introduction

Thus far, the experiments presented in this thesis have studied the effects of the levels of alcohol consumption on one's ability to acquire and extinguish Pavlovian conditioning. The experiments have used the same generic CS-US pairings to measure this. To what extent do these finding generalise to biologically relevant USs? There is evidence supporting the idea that cues associated with alcohol reinforcers and non-alcohol reinforcers acquire different motivational properties. For example, alcohol-related, but not non-alcohol (e.g. water/soft drink) cues have been shown to increase subjective cravings in social drinkers (Field & Jones, 2017) and AD patients (Witteman et al., 2015) and elevate alcohol consumption in social drinkers (Field & Jones, 2017; Van Dyke & Fillmore, 2015). Moreover, alcohol-related cues have been shown to bias in favour of habitual behaviour which can be a predictor of relapse in AD patients (Garbusow et al., 2016).

Dickinson et al. (2002) demonstrated that reinforcer type, independent of levels of alcohol consumption influences the development of habitual learning. In this study, rats were trained to lever press for either ethanol or food pellets. The amount of ethanol administered per session did not exceed .3ml of 10% ethanol solution which the authors argued would not have a significant pharmacological impact or lead to the development of alcohol-dependence. After instrumental training the rats underwent devaluation by receiving ethanol or food pellets with lithium chloride injections. In the test phase rats had the choice to press both levers in extinction. The results showed the pellet devaluation group pressed the pellet lever less than the ethanol devaluation group. In contrast the ethanol devaluation group did not decrease their ethanol lever pressing. The rats were insensitive to ethanol devaluation and therefore responded in a habitual manner. While reinforcer type can independently affect motivation, reinforcer type and level of alcohol consumption interact to affect motivation.

Research has shown drug-related cues to be powerful motivators. Preclinical research on alcohol drinking baboons has shown when subjects were trained to lever press for alcohol or soft-drink in a between subjects design (USs were paired with light CSs; CSs later underwent extinction) they worked harder to consume alcohol in the presence of the alcohol-related CS. Furthermore, the alcohol-related CS compared to the soft-drink CS, had greater REX both within session and between sessions (Holtyn, Kaminski, Wand and Weerts, 2014). To our knowledge there are no published experiments that study REX of alcohol-related cues in a human sample.

Alcohol-related cues are also cognitively processed differently from non-alcohol cues dependent on participant's levels of alcohol consumption. Field et al. (2004) demonstrated heavy social drinkers have a larger attentional bias to alcohol-related cues (when their presentation duration was long) and rated alcohol-related cues more pleasantly than did light drinkers. The results also showed a weak positive correlation between attentional bias and subjective cravings. This is supported by a meta-analysis which revealed a weak (r = .19), but significant positive correlation between attentional bias to drug-related cues and subjective cravings (Field, Munafo, & Franken, 2009). The results of this meta-analysis also revealed the correlation was weaker for alcohol-related cues compared to cannabis, heroin, and cocaine, but the correlation for alcohol-related cues and cravings was stronger if cravings were experimentally manipulated to be higher. This was empirically demonstrated by Ramirez et al. (2014), the results of which were consistent with Field et al. (2004; 2009), and showed that in vivo exposure to alcohol, but not water, increased subjective cravings and the correlation between attentional bias to alcohol-related cues and cravings.

As discussed in Chapter 3, trait impulsivity can influence attentional bias towards alcohol-related cues. The results of Chapter 3 showed that increasing the salience of the extinction context did not yield greater context extinction or context inhibition. In addition to this the results showed there was no difference between light and heavy social drinking

groups in their acquisition, extinction or response recovery of neutral CS-US pairings. There was however a significant response recovery interaction with impulsiveness group, but it remains unclear why this was.

Papachristou et al. (2012) found participants with impaired response inhibition perceive alcohol-related cues as more salient and were more reactive to their environment when they consider alcohol to be available compared to when it is unavailable. The R-W model predicts that when cue salience is increased during CS-US acquisition, associative learning is acquired more rapidly and to a stronger degree. As AD and high impulsiveness individuals perceive alcohol-related cues as more salient, which is attenuated when the alcohol US is unavailable (i.e. in treatment/ extinction context) then there would be different salience of the alcohol-related cues during CS-US acquisition and extinction and therefore different learning patterns.

In a hypothetical example, in a non-dependent and/ or low impulsive person, the alcohol-related cue salience would be consistently low through acquisition and extinction learning. Whereas, the AD and/ or high impulsive person would have a greater cue salience α during acquisition compared to the cue α of the extinction training. Using arbitrarily chosen values for non-dependent/ low impulsiveness: context A $\alpha = .25$, context B $\alpha = .25$, cue $\alpha = .3$ throughout all learning trials. In contrast, the AD/ high impulsiveness have the same context αs as the other group, but when alcohol is expected: context A cue $\alpha = .7$, and not expected: context B cue $\alpha = .3$.

Figure 5.1 displays a line graph of hypothetical acquisition and extinction rates of a cue when the α is increased for the acquisition phase for AD/ high impulsiveness only; all α parameters are defined above.

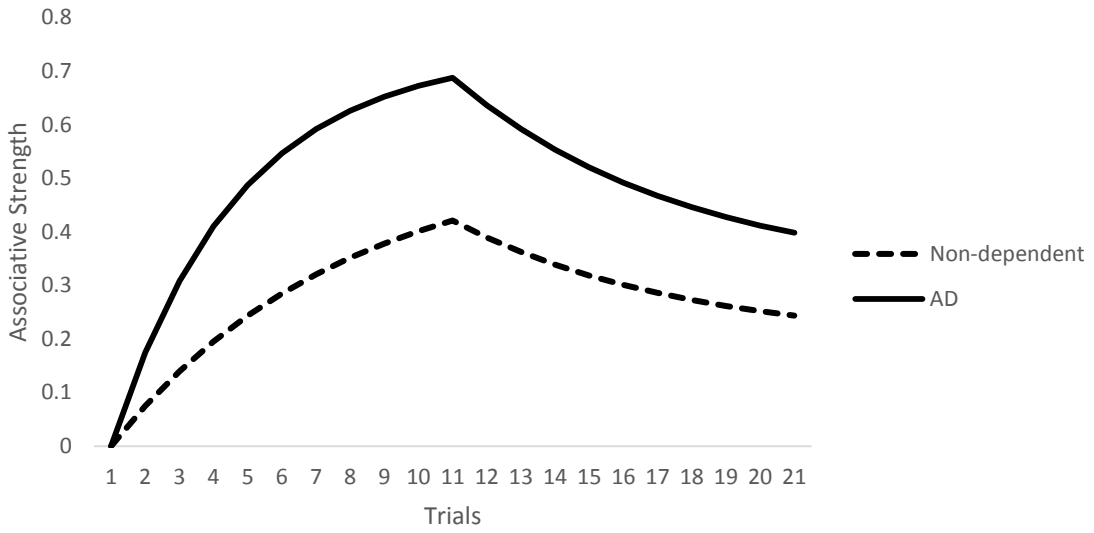


Figure 5.1. A hypothetical example of the rate and strength of a CS-US acquisition and extinction between individual with AD/ high impulsivity and non-dependent/ low impulsivity. The non-dependent/ low impulsivity condition have low and constant cue salience throughout all trials and the AD/ high impulsivity condition have increased cue salience for the acquistion trials and identical salience to the non-dependent/ low impulsiveness condition for the extinction trials. *Note.* Trial 1 = pre-conditioning strength, trial 2-11 = acquisition and trials 12-21 = extinction.

As can be seen in Figure 5.1, the AD/ high impulsiveness group has greater acquisition and weaker extinction compared to the non-dependent/ low impulsiveness group. Therefore, the combination of greater associative strength and attenuated extinction learning indicates the cues associative properties is protected in the P-F-E effect and therefore may explain ACETP.

Therefore, the aim of this study was to investigate the effects of drinking history, reinforcer type, and impulsivity on acquisition, extinction and response recovery for alcohol-related and food-related cues. As the present study administered alcohol to the participants, an analogous sample of social drinking students participated. Drinking status (light versus heavy) was retained as a variable despite Chapter 3 showing no difference between groups because it allowed investigation into how drinking status and reinforcer type interact. This allowed the present study's results to be added to Chapter 3 and either support or be incongruent with the conclusion that there are no differences in Pavlovian mechanism in social drinkers. A flaw of previous extinction research on alcohol-related

cues (and cue reactivity research more generally) is cue acquisition tends to be extra-experimental and therefore not under the experimenters control. The present research paired various, distinct neutral coloured shapes with the alcohol and food rewards to control for conditioned stimuli acquisition. The present study also tested acquisition, extinction and recovery in an ABA and ABC design to yield insight into the robustness of the design and procedure, as past research clearly demonstrates while ABA recovery is stronger than ABC, both types of recovery are reliably generated (Bouton, 2004; Polack, Laborda, & Miller, 2012).

The following hypotheses were tested:

1) The heavy social drinking group compared to the light social drinking group will have quicker mean acquisition rates for the alcohol US, but equal for the food US.
2) The high impulsiveness group compared to the low impulsiveness group will have quicker mean acquisition rates for the alcohol US, but equal for the food US.
3) The heavy drinkers will have slower mean extinction rates for the alcohol CS-US association compared to the light drinkers, but no difference for the extinction of the food US.
4) The high impulsiveness group compared to the low impulsiveness group will have slower mean extinction rates for the alcohol US, but equal for the food US.
5) The heavy drinkers will have greater mean response recovery for the alcohol CS-US association compared to the light drinkers, but no difference in response recovery for the food US.
6) The high impulsiveness group will have greater mean response recovery for the alcohol CS-US association compared to the low impulsiveness group, but no difference in response recovery for the food US.
7) Response recovery will be greater in ABA renewal compared to ABC renewal for both alcohol and food USs.

5.4.2 Methods

5.4.2.1 Participants

68 participants took part, but eight withdrew within the first three days due to either the drinks being too unpleasant to consume in such great volume or no longer being able to fulfil the agreed commitment to five days (see Chapter 2 for details of recruitment and informed consent). Therefore, 60 participants (27 male, 33 female) with a mean age of 20.9 years (SD = 2.4, range = 18 – 31) completed the experiment. All but five participants were students at the University of Southampton. Three participants were visiting students from other universities (Portsmouth, Kent, and Wroclaw) and two participants were university graduates in employment. 43% of the students were psychology students, the remainder in a variety of other disciplines. The vast majority of participants received full cash payment for completion of the experiment. The minimum cash payment was £112.5, but could reach a maximum of £132 for remaining in the lab after the computer tasks were done for that day for their BAL to reach a reading of 0 on the Alcolmeter. Some participants received a minimum of 225 course credits which could reach a maximum of 264 course credits or a mixture of cash and credits.

5.4.2.2 Materials

The questionnaires used and apparatus that ran the computer task were the same as those described in Chapter 2.

Alcolmeter

The same Alcolmeter as the Pilot study was used.

Drinks

The alcohol containing drinks were 10 x 50ml of 40% ABV Russian Standard Vodka and Sainsbury's Pure Orange Juice with a peppermint floater. There were six ml of vodka in the 50 ml drink therefore there were .24 of a unit in each drink and because ten

drinks were used per session of the computer task; 2.4 units per alcohol session in total. The non-alcoholic drinks were 10 x 50ml of non-alcoholic (0% ABV) Sainsbury's Indian Tonic Water and orange juice with a peppermint floater. There were six ml of tonic water in the 50 ml drink. The peppermint floater was achieved by adding ½ ml of Dr. Oetker American Peppermint Natural Extract. This particular peppermint extract was chosen because it was the only commercially available peppermint that did not contain ethanol to ensure there was no ethanol at all in the non-alcoholic placebo drinks.

Food

The food samples used were Sainsbury's Ready to Eat Dried Apricots and Sainsbury's Sultanas, Basic. Five of each food type were present in every session.

Computer Task

The experiment took place over five days with three sessions a day. Therefore, there was a total of 15 sessions (summarised in Table 5.5). The first 10 sessions were the acquisition sessions. Five of the acquisition sessions involved learning the association between cue A and alcohol and five involved learning association between cue C and soft drink. In the acquisition phase, cue B (associated with food1), D (associated with food2), E, and F (both associated with wait) were present in every session. There were also four sessions in the extinction phase of which two extinguished the alcohol-related cue and one of the food-related cues (Cue D) separately and two where these cues were extinguished together. Cue B and cue C were present and remained reinforced throughout the extinction phase. The final phase is a single session of the recovery test in which only cue A and cue D were presented in extinction. The contexts represented by the backgrounds displayed on the computer monitor during the computer task changes as such to account for ABA and ABC renewal.

Table 5.5 Summary of overall experiment structure

Table 1	Session 1	Session 2	Session 3
Day 1:	Acquisition A1	Acquisition S1	Acquisition A2
Day 2:	Acquisition S2	Acquisition S3	Acquisition A3
Day 3:	Acquisition S4	Acquisition A4	Acquisition S5
Day 4:	Acquisition A5	Extinction 1	Extinction 2
Day 5:	Extinction 3	Extinction 4	Recovery Test

The computer program was written in Microsoft Visual Studio 2013 C# language. The structure of the task starts with a fixation cross on the computer monitor with a duration of two seconds. Next, one of the distinct cues is presented superimposed on a distinct background for four seconds. Within this four second window participants had to press a key that indicated which outcome they predicted. The outcomes were: drink, eat or wait; the A key was to indicate a prediction of drink, the G key a prediction of food and the L key a prediction of wait. After the key is pressed, or after four seconds, the outcome (and therefore correct response) appears on the screen for two seconds. The outcome screen was a black screen with white text in the centre of the screen saying: “Drink”, “Food1”, “Food2” or “Wait”. Next, a countdown screen appeared for 45 seconds. This screen had a white background with instructions of “Drink”, “Eat” or “Wait” written in black with a black circle representing a countdown timer in the middle of the screen. The circle starts off incomplete and slowly fills up to form a complete circle over the 45 second period. A correct predictions counter was present throughout the task (see Figure 5.2 for a visual representation of the task). During the 45 second period participants had to complete the reward presented on the correct response screen, regardless of whether their button press was correct or not. Therefore, if the correct response screen said: “Drink” participants would do one of the 50 ml drinks, if it said: “Food1” they would have to eat the food that was allocated as food1, if it said: “Wait” they would have to sit inactive for 45 seconds to start the next trial. All drinks and food were presented to the left hand side of the computer on a white plastic tray. After 45 seconds participants had to start the next trial by pressing the spacebar. The cues association with the outcomes, the background for each phase of the

experiment, the order the cues were presented and whether apricots or sultanas were food1 or food2 were randomised. The order of the alcohol and soft-drink sessions were presented in Table 5.5.

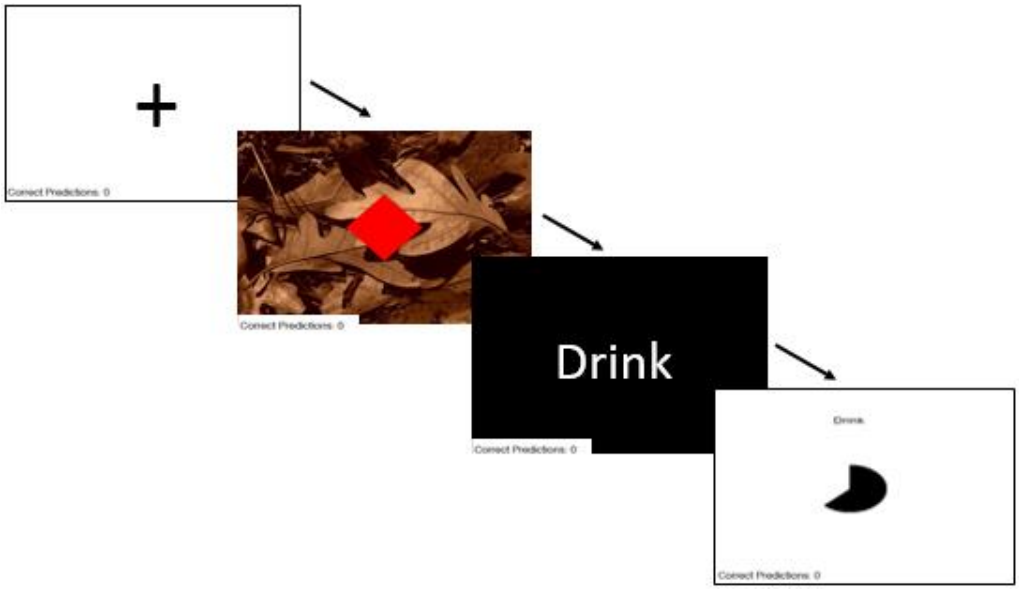


Figure 5.2. Visual representation of each component of the computer task. Presented is the red diamond cue on brown leaf background with correct response "Drink" and the countdown timer.

The cues and backgrounds were carefully selected as to minimise any confusion or confounding associations. For instance, coloured shapes were chosen for cues as they are generally neutral and contain little significance to most people. All the shapes and colours were chosen to be as distinct from each other as possible. Natural backgrounds were chosen to not be confounded with the shapes. For example, natural backgrounds were chosen over geometric shapes as to prevent associations being formed between cue shapes and background shapes. Likewise, background colours and cue colours were selected so cues could stand out. For example, a starry background was used, therefore a yellow star shaped cue could not be used. Likewise, a blue circle shaped cue was used so a blue sky background was not chosen. Finally, backgrounds were selected to have equal visual salience between and within the backgrounds. See Appendix 3 to see the full list of cues and backgrounds.

Table 5.6 summarises the protocol within each session. Cue A was associated with the alcohol drink. Cue C = soft-drink. Cue B and D = $Food_1$ and $Food_2$ respectively. Cue E and F = wait (Φ). Every acquisition session consisted of 40 trials. There were 10 trials for cues A, C, E and F. There were five trials for cues B and D. This was to ensure there were equal number of trials for all cues. Because there are five acquisition sessions for alcohol and five for soft-drink cues A, B, C and D had 50 trials each. Each trial lasted 53 seconds with 40 trials a session therefore each session lasted 35 minutes. The first two extinction session consisted of 40 trials each. There were 10 trials for cues A, D, E and F and five trials for cues B and C per session. In the final two extinction sessions there were 40 trials; 10 trials for each cue. Therefore all cues get 30 trials each in the extinction phase. The extinction sessions lasted 35 minutes each. In the final phase cue A and D were present in extinction for the recovery test. They were presented in both context W and context Y to measure ABA and ABC renewal. There were four trials overall: one for cue A and one for cue D in context W and one for cue A and one for cue D in context Y. The recovery test lasted 2.5 minutes. The order of W and Y context presentation was counterbalanced. Due to a technical error the order of cue A and cue D within both contexts were not counterbalanced. When context W was presented first the order of cue presentation was always ADDA. When Y context was presented first the cue order was always DAAD.

Table 5.6 Summary of the protocol within each session.

Acquisition sessions		Extinction sessions			
Alcohol	Soft	Alcohol CS	Food CS	Both (x2)	Recovery test
W: A->Alcohol (x10)	**W**: C->Soft (x10)	**X**: A->Φ (x10)	**X**: D->Φ (x10)	**X**: A->Φ (x10)	**W**: A->Φ (x1), **Y**: A->Φ (x1)
W: B->Food1 (x5)	**W**: D->Food2 (x5)	**X**: B->Food1 (x5)	**X**: B->Food1 (x5)	**X**: D->Φ (x10)	**W**: D->Φ (x1), **Y**: D->Φ(x1)
W: D->Food2 (x5)	**W**: B->Food1 (x5)	**X**: C->Soft (x5)	**X**: C->Soft (x5)	**X**: C->Soft (x10)	
W: E->Φ (x10)	**W**: E->Φ (x10)	**X**: E->Φ (x10)	**X**: E->Φ (x10)	**X**: B->Food1 (x10)	
W: F->Φ (x10)	**W**: F->Φ (x10)	**X**: F->Φ (x10)	**X**: F->Φ (x10)		

Note. **W:** A → Alcohol (x10) indicates context W, cue A, outcome present on 10 trials. Φ = wait. Trial orders are randomised within blocks.

Every session after the first ended with onscreen questions in which participants had to answer questions to demonstrate their conscious awareness knowledge of the CS-US relationships of the task. This was to ensure participants had learned cue A is paired with the alcohol drink and cue C is paired with the soft-drink as participants had to gradually determine which was which by pairing the cue with the subjective feeling if mild intoxication and not be able to identify alcohol through smell and taste of the drink.

5.4.2.3 Design

A mixed design with one between subjects independent variable with two levels: light vs heavy social drinkers and one within subjects independent variable with two levels: alcohol or food reinforcers. The dependent variables are the stages of the computer task: 1) acquisition (end of phase responding), 2) extinction (end of phase minus final acquisition) and 3) recovery (recovery test minus extinction).

5.4.2.4 Procedure

Participants had to arrive at the lab for five days. The days did not have to be consecutive, but completed within a 14 day period. Participants were asked to arrive at the lab having fasted for two hours beforehand. Only once a participant had a breathalyser reading above 0 because of binge drinking the previous night and rescheduled to return another day. After breathalysing on day one participants completed the AUDIT, TLFB and BIS-11 questionnaires. Participants then started their first computer session. There was a 60 minute break in between each session. As there were three sessions per day the day was structured: 35 minute task – one hour break – task – break – task. Therefore, participants were in the lab for three hours and 45 minutes. Participants were not allowed to leave the lab during the breaks except to use the toilet and spent their time studying or watching television on BBC iPlayer, Netflix or YouTube ad libitum. The experimenter would also supply the participants with water if they did not bring their own. This was repeated for five days except the final day's third session was 2.5 minutes in duration and therefore the

final day lasted three hours only. At the start of each day, 20 minutes after the end of every session, at the start of every session and at the end of each day participants were breathalysed. At the end of days one and two participants still had a breathalyser reading over 0. The rest of the days were structured to avoid this. Participants could opt to sign a disclaimer stating they have been offered the chance to stay in the lab until their BAL reached 0, but they have chosen to leave and have been advised not to drive or operate heavy machinery for up to three hours and to stay vigilant and safe. They were informed they can earn more money/ credits by staying in the lab, but for BAL to reach 0 would take approximately two hours. The majority of participants opted to sign the disclaimer and leave early.

5.4.3 Results

5.4.3.1 Questionnaires

Drinking Data

The participants were categorised into light and heavy drinking groups based on a median split of the TLFB data. Participants reported a median of 7.15 units (SD = 21.4, range = 0 – 108) consumed in the week prior to the experiment commencement in the TLFB questionnaire. For the AUDIT-C, the light drinking group reported a mean of 4.8 (SD = 2, range = 0 – 8), whereas the heavy drinking group reported a mean of 7.5 (SD = 2, range = 3 – 10). For the TLFB, the light drinking group reported a mean of 2.2 units consumed (SD = 2.4, range = 0 – 7.1), whereas the heavy drinking group reported a mean of 28.4 units consumed (SD = 23.8, range = 7.2 – 108). T-tests to compare light and heavy drinking groups were performed on the total AUDIT-C and TLFB data. The results showed there was a significant difference between light and heavy groups on AUDIT-C reported scores t (58) = -5.2, $p < .001$ and on the TLFB data t (29.6) = -6, p < .001. Therefore, the AUDIT-C results suggest that the heavy drinkers reported more hazardous drinking behaviour over the six months prior to the commencement of the experiment, indicated by

their significantly higher average scoring on the questionnaire. Likewise, the same is true for the TLFB, as participants in the heavy drinking group reported a significantly greater amount of average units consumed compared to the light drinking group in the week prior to the experiment. However, as the sample collected were social drinkers, there is a lot of overlap between the two groups in the AUDIT-C data meaning that on average, the heavy drinkers reported more hazardous drinking behaviour, but overall the sample scored within a non-hazardous range. For the TLFB data, the heavy drinking group were less homogenous than the light drinking group and reported greater variance on units consumed. While the greater units consumed at the tail end of the distribution does vary greatly from the median, the majority of participants were concentrated around the median indicating that the sample as a whole consumed very little indicating some of the heavy drinking group participants would not meet the criteria for heavy drinkers.

Impulsivity

The reported mean total score of the BIS-11 for the light drinking group was 60.5 (SD = 7.3, range = 47 – 76) and 62.6 (SD = 10.6, range = 48 – 91) for the heavy drinking group. A t-test was conducted to compare light and heavy drinking groups on their total BIS-11 scores. Results revealed there was no statistical difference between groups t (58) = -.87, p = .39. The median of the total BIS-11 score was 58.5. Participants were allocated to low and high impulsiveness groups based on a median split. The mean total BIS-11 score was 54.4 (SD = 3.4, range = 47-58) for the low impulsiveness group and 68.7 (SD = 7, range = 58-91) for the high impulsiveness group. A t-test revealed there was a significant difference between high and low impulsiveness groups t (41.5) = -10.1, $p < .001$.

5.4.3.2 Behavioural Data

Drinking Cue A: Acquisition

Figure 5.3 displays the mean proportion of acquisition-appropriate responses for cue A across the acquisition phase (blocks 1 - 10), extinction phase (blocks 11 – 16) and

the recovery test phase (blocks 17 and 18) between light and heavy drinkers. Inspection of the acquisition phase of Figure 5.3 shows both groups acquisition-appropriate responses increased across the 10 blocks indicating they equally learned the associations between cue A and the outcome. The graph suggests there was no difference between groups in acquisition strength, which is supported by an ANOVA. All ANOVAs for cue A are reported in detail in Table 5.7.

To test the difference in acquisition strength between groups a 10 (block) x 2 (light or heavy drinking) repeated measures ANOVA was carried out on the acquisition data. The main effect of block was significant, showing a significant increase in acquisition-appropriate responses in later blocks indicating increments in associative strength and therefore successful learning. However, there was no-significant block*drinking interaction indicating that the main effect of block was the same for both groups. The main effect of drinking was also non-significant with both groups responding equally throughout the acquisition phase.

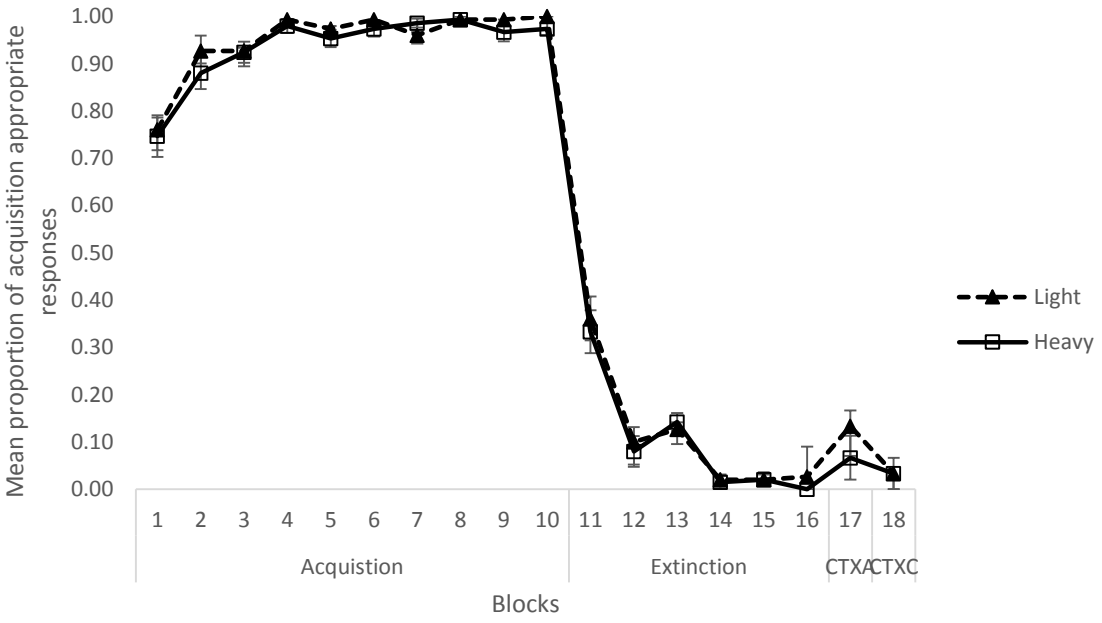


Figure 5.3. A line graph displaying the mean proportion of acquisition-appropriate responses to cue A across the acquisition phase (blocks 1 - 10), extinction phase (blocks 11 – 16) and the recovery test phase (blocks 17 and 18) between light and heavy drinkers. Error bars represent the standard error.

Drinking Cue A: Extinction

As can be seen in Figure 5.3 the proportion of acquisition-appropriate responses decreases across blocks 11 – 16 indicating decrements in associative strength and therefore successful extinction of responding. Inspection of the figure suggest there was no difference between heavy and light drinking conditions at any stage of extinction. The non-significance is confirmed by a repeated measures ANOVA. In block 13 there was a weak spontaneous recovery of acquisition appropriate responding. This is most likely because block 13 is the start of the final day of testing; a suppression of correct responses was quickly restored.

A 7 (block) x 2 (light or heavy drinking) repeated measures ANOVA was conducted to test the difference between groups in extinction data. Blocks 10 – 16 were included in the ANOVA to compare the end of the acquisition phase to the extinction phase. Like the acquisition data there was a main effect of block on the extinction data showing a significant reduction in acquisition-appropriate responses and therefore successful extinction was achieved. There was not a significant block*drinking interaction revealing the main effect of block was equal for both groups. There was also a non-significant main effect of drinking meaning both groups did not differ on their extinction performance.

Drinking Cue A: Recovery Test

As can be seen in Figure 5.3 there is a small increase of acquisition-appropriate responses in the recovery test phase for both context A (ABA) and context C (ABC). ABA and ABC recovery were both quite small. ABA recovery was stronger than ABC; ABC recovery appears to be negligible. Two ANOVA's were conducted, one for ABA recovery and one for ABC recovery. ABA recovery was conducted with a 2 (block: 16 and 17) x 2 (light or heavy drinking) repeated measures ANOVA and a 2 (block: 16 and 18) x 2 (light or heavy drinking) repeated measures ANOVA was conducted for ABC recovery. Significance

outcomes for ABA recovery mirrors all other cue A ANOVAs reported. There was a significant main effect of block showing acquisition-appropriate responses were recovered. However, the block*drinking interaction was not significant showing the block effect was the same in both groups. Likewise there was no significant main effect of drinking showing recovery of acquisition-appropriate responses were equal in both groups. There was not a significant main effect of block, block*drinking interaction or main effect of group for ABC recovery. This indicates that a small amount of participants had ABA recovery, but not ABC recovery.

As there were such small amounts of response recovery no statistical test has been conducted to see if there was a difference between ABA and ABC response recovery when context A or context C came first. Instead the responses were summarised in Table *5.8*. As can be seen in Table *5.8* ABA recovery was stronger than ABC recovery regardless of which one came first. This is not surprising as ABA recovery is more robust than ABC. Not only was ABA recovery larger than ABC, but ABC recovery was non-existent when ABC preceded ABA. This could be because ABA recovery primed the participants for recovery type behaviour.

Table 5.7 Repeated Measures Analysis of Variance for Cue A for drinking data

Stage	Source	*SS*	*df*	*MS*	*F*	*P*	η^2
Acquisition	Between-Subjects						
	Drinking	.003	1	.003	1.14	.289	.019
	Error	.158	58	.003			
	Within-Subjects						
	Block	2.91	3.48	.836	25.8	.001**	.308
	Block x	.05	3.48	.015	.448	.909	.308
	Drinking						
	Error	6.53	201.6	.032			
Extinction	Between-Subjects						
	Drinking	.002	1	.002	.457	.502	.008
	Error	.314	58	.005			
	Within-Subjects						
	Block	45.1	2.35	19.2	411.4	.001**	.876
	Block x	.025	2.35	.011	.227	.831	.004
	Drinking						
	Error	6.35	136.2	.047			
Recovery Test							
CTXA							
	Between-Subjects						
	Drinking	.033	1	.033	1.42	.238	.024
	Error	1.36	58	.023			
	Within-Subjects						
	Block	.225	1	.225	4.53	.037*	.073
	Block x	.012	1	.012	.241	.625	.004
	Drinking						
	Error	2.88	58	.05			
CTXC							
	Between-Subjects						
	Drinking	.033	1	.033	3.61	.062	.059
	Error	.525	58	.009			
	Within-Subjects						
	Block	.012	1	.012	.631	.430	.011
	Block x	.005	1	.005	.281	.598	.005
	Drinking						
	Error	1.1	58	.019			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
**$p < .001$, *$p<.05$

Table 5.8 Table to show the total number of recovery responses for ABA and ABC recovery when context A is first or when context C is first

		Context A	Context C
Context A First			
	Cue A	4	2
	Cue D	4	2
Context C First			
	Cue A	2	0
	Cue D	2	0

Drinking Cue D

An identical set of statistical analysis that were applied to cue A were applied to cue D.

Table *5.9* summarises the results of the ANOVAs that were tested for the acquisition, extinction, context A recovery, and context C recovery data. Figure 5.4 displays the mean proportion of acquisition-appropriate responses to cue D across the acquisition phase (blocks 1 - 10), extinction phase (blocks 11 – 16) and the recovery test phase (blocks 17 and 18) between light and heavy drinkers. The pattern of data displayed in Figure 5.4 and the results of the ANOVAs show cue D was identical to cue A. Participants successfully learned the acquisition and extinction and showed ABA renewal. However, there was no ABC renewal and there was no difference at any stage between groups. One noticeable difference between cue A and cue D data is the spontaneous recovery of block 13 had a greater magnitude.

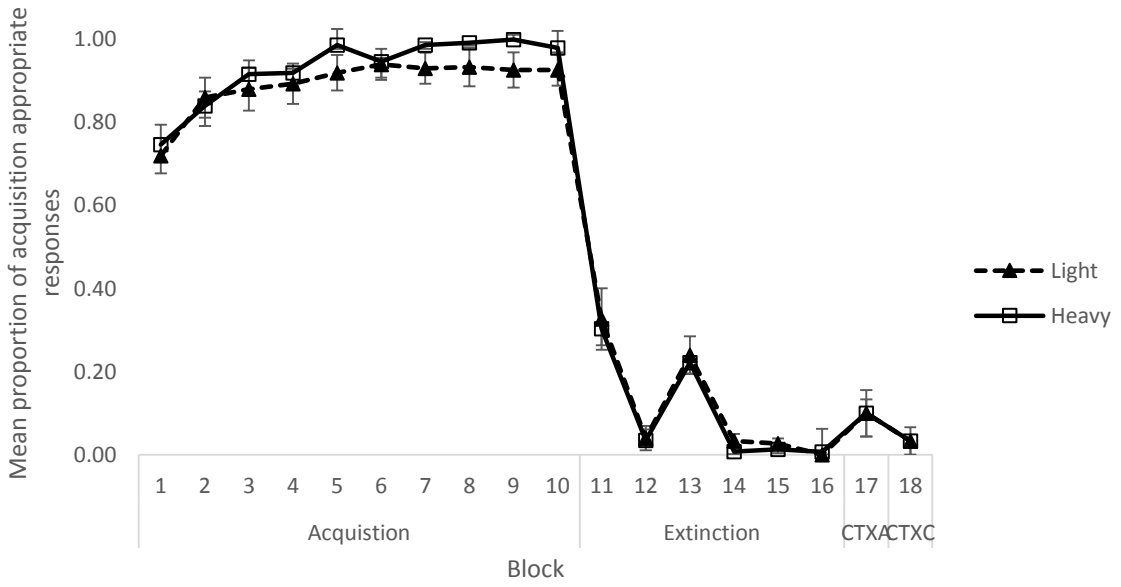


Figure 5.4. A line graph displaying the mean proportion of acquisition-appropriate responses to cue D across the acquisition phase (blocks 1 - 10), extinction phase (blocks 11 – 16) and the recovery test phase (blocks 17 and 18) between light and heavy drinkers. Error bars represent the standard error.

Table 5.9 Repeated Measures Analysis of Variance for Cue D for drinking data

Stage	Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Acquisition	Between-Subjects						
	Drinking	.022	1	.022	.94	.336	.016
	Error	1.37	58	.024			
	Within-Subjects						
	Block	2.87	4.38	.655	16.9	.001**	.225
	Block x	.115	4.38	.026	.677	.622	.012
	Drinking						
	Error	9.86	253.9	.039			
Extinction	Between-Subjects						
	Drinking	0	1	0	.028	.869	0
	Error	.397	58	.007			
	Within-Subjects						
	Block	42.4	2.43	17.5	287	.001**	.832
	Block x	.067	2.49	.028	.456	.456	.008
	Drinking						
	Error	8.57	140.8	.061			
Recovery Test CTXA							
	Between-Subjects						
	Drinking	0	1	0	.007	.993	0
	Error	1.35	58				
	Within-Subjects						
	Block	.28	1	.28	5.94	.018*	.093
	Block x	0	1	0	.007	.933	0
	Drinking						
	Error	2.74	58	.047			
CTXC							
	Between-Subjects						
	Drinking	0	1	0	.02	.889	0
	Error	.490	58	.008			
	Within-Subjects						
	Block	.027	1	.027	1.58	.214	.026
	Block x	0	1	0	.019	.889	0
	Drinking						
	Error	.993	58	.017			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
**$p < .001$, *$p < .05$.

Impulsivity

An identical set of statistical analysis that were applied to cue A and cue D with drinking groups were applied to these cues with the low and high impulsiveness groups.

Table *5.10* summarises the results of the ANOVAs that were tested for the acquisition, extinction, context A recovery, and context C recovery data for cue A and

Table *5.11* summarises the ANOVAs for cue D. Figure *5.5* displays the mean proportion of acquisition-appropriate responses to cue A across the acquisition phase (blocks 1 - 10), extinction phase (blocks 11 – 16) and the recovery test phase (blocks 17 and 18) between low and high impulsiveness groups. Likewise, Figure 5.6 displays the same for cue D. The pattern of data displayed in Figure 5.5 and the results of the ANOVAs show cue A were identical to the cue A analysis with the drinking groups. Participants successfully learned the acquisition and extinction and showed ABA renewal. However, there was no ABC renewal and there was no difference at any stage between groups. There was also spontaneous recovery at block 13.

The pattern of results displayed in Figure 5.6 and statistical analysis revealed cue D were identical to the cue D analysis with the drinking groups. Participants successfully learned the acquisition and extinction and showed ABA renewal. However, there was no ABC renewal. The only ANOVA result that deviates from the rest was, for the extinction data. The extinction data showed a main effect of block indicating successful extinction learning, but also showed a main effect of group. There was no block*group interaction. Post hoc tests reveal this difference lies in the difference between low and high groups in the spontaneous recovery of block 13. The low impulsivity group demonstrated greater spontaneous recovery. Both cue A and cue D demonstrated spontaneous recovery at block 13, but the effect was larger for cue D. There was no difference between drinking groups in the spontaneous recovery effect for cue A and D, but the impulsivity data suggests there is something unique about cue D for the low impulsiveness group.

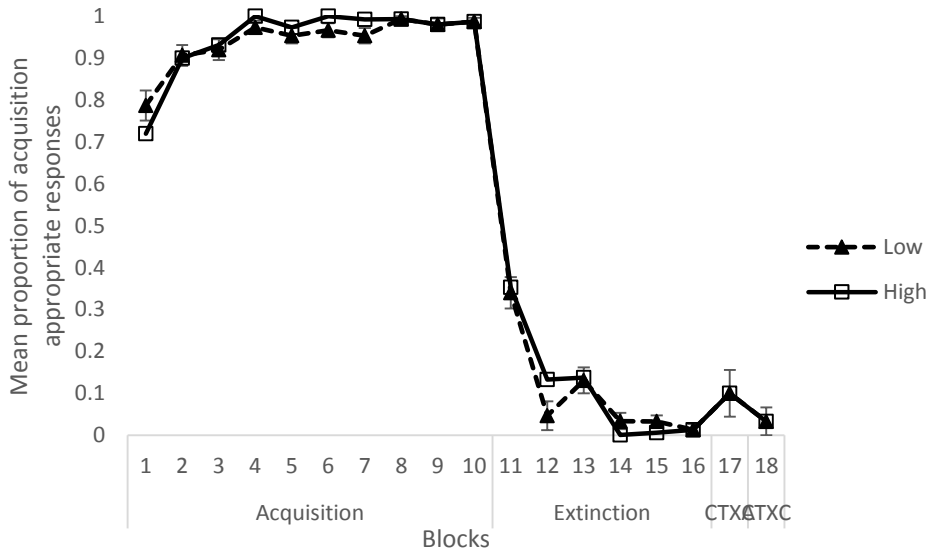


Figure 5.5. A line graph displaying the mean proportion of acquisition-appropriate responses to cue A across the acquisition phase (blocks 1 - 10), extinction phase (blocks 11 – 16) and the recovery test phase (blocks 17 and 18) between low and high impulsiveness groups. Error bars represent standard error.

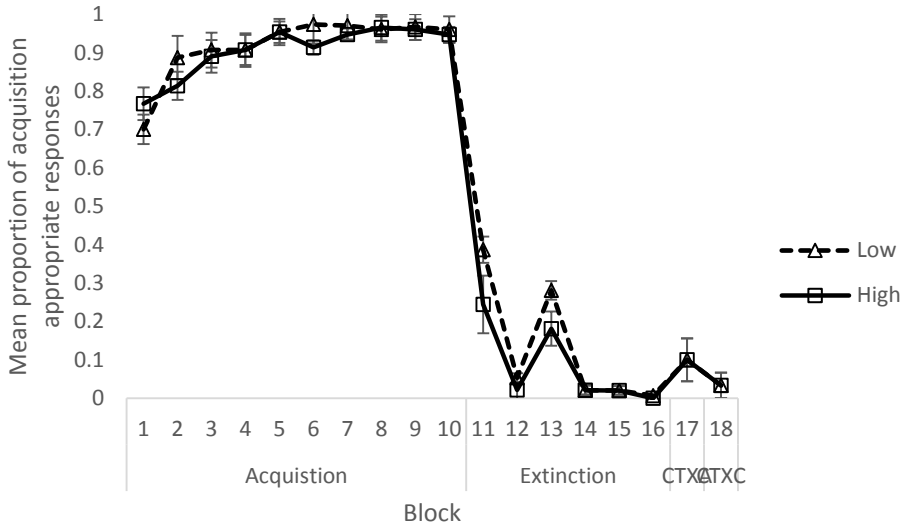


Figure 5.6. A line graph displaying the mean proportion of acquisition-appropriate responses to cue D across the acquisition phase (blocks 1 - 10), extinction phase (blocks 11 – 16) and the recovery test phase (blocks 17 and 18) between low and high impulsiveness groups. Error bars represent standard error.

Table 5.10 Repeated Measures Analysis of Variance for Cue A for impulsivity data

Stage	Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Acquisition	Between-Subjects						
	Impulsiveness	0	1	0	.17	.682	.003
	Error	.16	58	.003			
	Within-Subjects						
	Block	2.91	3.55	.818	26.1	.001*	.31
	Block x Impulsiveness	.12	3.55	.034	1.08	.364	.018
	Error	6.46	206	.031			
Extinction	Between-Subjects						
	Impulsiveness	.001	1	.001	.122	.728	.002
	Error	.316	58	.005			
	Within-Subjects						
	Block	45.1	2.35	19.19	419	.001*	.878
	Block x Impulsiveness	.139	2.35	.059	1.29	.281	.022
	Error	6.24	136.3	.043			
Recovery Test							
CTXA							
	Between-Subjects						
	Impulsiveness	0	1	0	0	1	0
	Error	1.37	58	.024			
	Within-Subjects						
	Block	.225	1	.225	4.52	.038**	.072
	Block x Impulsiveness	0	1	0	0	1	0
	Error	2.9	58	.05			
CTXC							
	Between-Subjects						
	Impulsiveness	0	1	0	0	1	0
	Error	.527	58	.009			
	Within-Subjects						
	Block	.012	1	.012	.628	.431	.011
	Block x Impulsiveness	0	1	0	0	1	0
	Error	1.11	58	.019			

Note. SS = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.

**$p < .001$, *$p < .05$

Table 5.11 Repeated Measures Analysis of Variance for Cue D for impulsivity data

Stage	Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Acquisition	Between-Subjects						
	Impulsiveness	.002	1	.002	.093	.762	.002
	Error	1.39	58	.024			
	Within-Subjects						
	Block	2.87	4.39	.653	17	.001**	.227
	Block x Impulsiveness	.196	4.39	.045	1.16	.329	.02
	Error	9.78	254.4	.038			
Extinction	Between-Subjects						
	Impulsiveness	.027	1	.027	4.17	.046*	.067
	Error	.371	58	.006			
	Within-Subjects						
	Block	42.4	2.51	16.9	294.6	.001**	.836
	Block x Impulsiveness	.288	2.51	.115	2	.127	.033
	Error	8.35	145.6	.057			
Recovery Test							
CTXA							
	Between-Subjects						
	Impulsiveness	0	1	0	.007	.933	0
	Error	1.35	58	.023			
	Within-Subjects						
	Block	.28	1	.28	5.94	.018*	.093
	Block x Impulsiveness	0	1	0	.007	.933	0
	Error	2.74	58	.047			
CTXC							
	Between-Subjects						
	Impulsiveness	0	1	0	.02	.889	0
	Error	.49	58	.008			
	Within-Subjects						
	Block	.027	1	.027	1.58	.214	.026
	Block x Impulsiveness	0	1	0	.019	.889	0
	Error	.993	58	.017			

Note. SS = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
**$p < .001$, *$p < .05$

5.4.3.3 Questions

The behavioural data clearly showed participants learned which cue was drink and which cue is food. However, it still remains unclear whether participants learned the specific drink (alcohol or soft) or specific food (food1 or food2). Figure 5.7 summarises the percentage of correct answers to the questions for each cues final acquisition block and final extinction block. For the acquisition phase 93% and 90% of participants were correct for cue B and cue D respectively. This is unsurprising as the foods were very discrete from each other. Likewise, at the end of the extinction phase 3% of participants responded with

a Y response belief that cue D predicted the onset of food2 and therefore, 97% were correct that cue D predicted no outcome in context B. For the acquisition phase 88% and 65% of participants were correct for cue A and cue C respectively. This is also unsurprising because it demonstrates the success of the drinks masking technique from the Pilot study. Participants were close to chance when deciding whether cue C was for soft drink or alcohol, but very accurately detected alcohol when cue A was presented. This might be because participants could not perceive alcohol by taste or smell and could rely on mild intoxication to make a decision for cue A. However with no alcohol in cue C drinks they had to rely only on their lack of mild intoxication and were therefore unsure which drink they were consuming. Alternatively it might be because the participant experienced a placebo effect of mild intoxication due to expecting alcohol.

This latter explanation does not seem to be very likely as, seen in Figure 5.8, both cue A and cue C showed learning overtime. Initial percentage of correct answers were around 60% for cue A and just under 30% for cue C. This indicated alcohol was not immediately obvious, which it would be if the smell or taste was strong, but rather learned through repeated exposure to mild intoxication. Likewise, as percentage of correct answers for cue C increased overtime from 30%-65%, this indicated if participants were experiencing placebo intoxication to start with, the majority of them were not by the end as they were close to guessing. Finally, at the end of the extinction phase, only 10% of participants responded with an acquisition-appropriate response belief that cue predicted the onset of alcohol reward and therefore 90% were corrected by holding the belief cue predicts no outcome in context B. Two repeated measures t-tests were conducted to compare answers to the questions between the end of the acquisition phase and extinction phase for cue A and the same for cue D. Results showed a significant difference between number of correct answers at the end of each stage for cue A t (59) = 12.4, $p < .001$ and cue D t (59) = 33.5, $p < .001$.

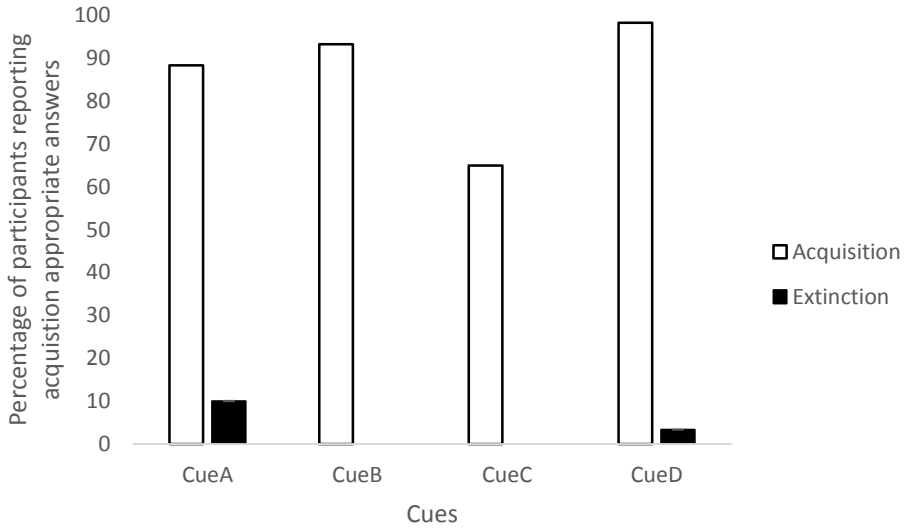


Figure 5.7. Bar graph showing the percentage of which reported acquisition-appropriate answers to the questions. The acquisition phase of each cue is the percentage of correct answers in the respective cues final acquisition block. The extinction phase of cue A and D and the final extinction block.

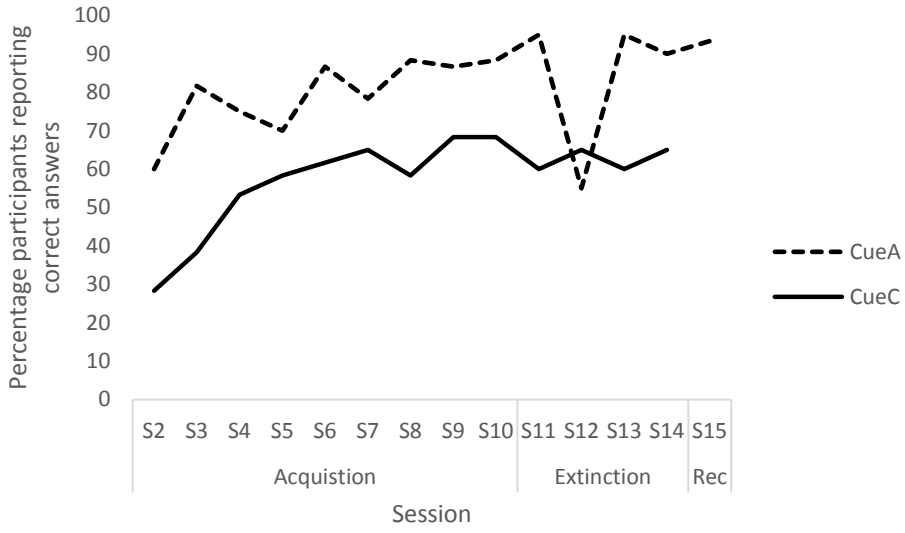


Figure 5.8. Line graph showing the percentage of participants who reported a correct answer for cue A and cue C for every session.

5.4.3.4 Supplementary analysis

As no difference was found between drinking groups at any stage of learning task for any cue, Spearman's Rho correlations were conducted between the TLFB data and the acquisition and extinction data for cue A and cue D. The results presented in Table 5.12 revealed there was non-existent correlations (all p-values > .5) between drinking data and

task performance indicating task performance has no relationship with alcohol consumption behaviour.

Table 5.12 A table displaying correlations between TLFB data and task performance

	Cue A Acquisition	Cue A Extinction	Cue D Acquisition	Cue D Acquisition
TLFB	.05	-.05	-.001	.08

5.4.4 Discussion

The results showed successful acquisition of alcohol, soft drink and food classical conditioning. They also showed successful extinction of alcohol and food related cues. The results showed a weak recovery of alcohol and food related cues in an ABA, but not ABC paradigm. Therefore, the results indicate that the present study's conditioning paradigm was a success for ABA renewal. This supports the hypothesis tested that ABA recovery will be stronger than ABC. It is surprising that ABC recovery was not elicited as previous research has clearly demonstrated that ABC recovery is a reliable occurrence (Bouton, 2004). It is not surprising that an ABA renewal effect was displayed as ABA has been demonstrated to be more robust than ABC (Polack et al., 2012). However, the experiments design may explain the lack of ABC. In this experiment the cue and context were always presented together. Typically experimental paradigms present the context constantly (presented and unreinforced between trials in the absence of the cue) and the cue intermittently; usually with a delayed onset after context is presented. In this study the cue and context were presented together and discontinued together every trial. It is therefore possible that the cues and context were trained as a compound stimuli which both acquired associative strength with the US. When one feature of the compound stimulus (i.e. the cue) was presented in a novel context, the excitatory strength of the cue in isolation was insufficient to elicit a renewal response. This seems to be supported by (Polack et al., 2012) which showed that extinction contexts can become inhibitory when the onset of cue after context is reduced as the cue and context are trained simultaneously, but context

becomes an occasion setter when the onset of delayed as the two features are trained sequentially. This supports the notion that ABA, but not ABC renewal was observed because the cue and context A were trained simultaneously, facilitating context-excitatory properties. The reason why the ABA renewal was so weak may be due to over training in the extinction phase. Both cue A and cue D's acquisition-appropriate response suppression reached floor level early on in the training. Perhaps less training would produce weaker extinction and stronger recovery.

The results also showed that there was no difference at any stage of the procedure, for any cue between light and heavy drinkers. This is consistent with Chapter 3. Therefore, the results support the hypotheses that there will be no difference between light and heavy drinkers on the acquisition, extinction, or recovery of the food-related cues. However, the hypotheses that there would be a difference between these two groups in acquisition, extinction and recovery of the alcohol-related cues was not supported. It is very likely there is no difference between light and heavy social drinkers in Pavlovian conditioning or their responses to alcohol and food USs is simply because their levels of alcohol consumption has been too little to be of any consequence in this domain (this will be discussed later during the study's limitations). Research has also shown that reinforcer type can influence motivational behaviour independent of alcohol consumption (Dickinson et al., 2002). Past research suggest alcohol-related cues and not food-related cues would generate greater response recovery because of the habitual type responding that develops for alcohol and not non-drug cues. It is unclear why the present study found no difference between alcohol and food cues at any stage of the task. It might simply be due to the extensive training during acquisition and extinction. A ceiling and flooring effect of these stages was reached early on in training, which would attenuate any recovery effect. However, this explanation seems unlikely as participants in both groups were equivalent in performance throughout every block of the task.

In addition to this, the results also showed there was no difference between low and high impulsiveness groups in acquisition, extinction, and recovery data for alcohol and food related cues. The cue D (food) results did however, show a significant block*group interaction during the extinction data. This result was a difference between groups on the spontaneous recovery of block 13. Block 13 is the first session of the final day. At this stage in the experiment structure participants would have had limited extinction training and acquisition-appropriate responses recovered overnight. Spontaneous recovery was observed for both cue A and cue D. The spontaneous recovery effect of cue D was overall stronger than cue A. While, there was no difference between drinking groups in the spontaneous recovery effect, the low impulsiveness group displayed stronger spontaneous recovery than the high impulsiveness group. It is unclear why these result were found. It is interesting to note that the recovery effect found in experiment two of Chapter 3 had a block*impulsiveness interaction and the spontaneous recovery effect on the present study replicated this result. Whereas, the recovery effect of the present study found no difference between groups. This is likely because of the strong extinction training produced. Whereas, the extinction training was weaker by block 13. There was no difference between low and high impulsiveness groups at the end of acquisition or by block 12 so it remains unclear as to why there is a difference between these groups in a recovery effect. However, the replicable finding suggests it is not an anomaly of the sample.

Overall, the impulsivity results are inconsistent with previous literature. Papachristou et al. (2012) found high trait impulsiveness when coupled with alcohol availability influenced cue reactivity. It was assumed that the cue availability effect could be reflected as cue salience in a R-W equation. Therefore, it was hypothesised that high impulsivity would result in reduced extinction and greater response recovery for alcohol, but not food cues. Our results did not support this, in fact it was found that low impulsivity generated greater response recovery. Papachristou et al. (2012) measured impulsivity with the stop-signal task and the present study used the BIS-11. This may explain the result.

Alternatively, Papachristou et al. (2012) was studying cue reactivity whereas the present study was measuring associative strength. Response recovery might have been a proxy measure of cue reactivity as participants could respond indicating they believe they are about to receive alcohol. Overall, the alcohol consumption and impulsiveness data of the present study do not support the R-W predictions.

There are some limitations with this study. Firstly, due a technical fault the cue order was not properly counterbalanced during the recovery test. This limitation only allowed for analysis of overall context recovery collapsed across cues and overall cue recovery collapsed across context. It does not allow for ordering effects. Another limitation is the duration of the experiment. The results showed participants reached ceiling effects during the acquisition phase and flooring effects during the extinction phase quite quickly. This lead to participant fatigue. This could explain why the recovery effect was so weak, participants got very familiar with the repetitive nature of the experiment and may have been bored and not paid enough attention to the context and assumed the recovery phase was business as usual. If this paradigm is to be used again, it would be beneficial to reduce the number of acquisition trials to approximately 20-30 per cue (two or three sessions) and reduce the extinction trials to approximately 20 trials per cue (two sessions).

Another limitation of the experiment was using a median split to determine light and heavy drinking groups. The supplementary analysis correlations revealed no correlation between TLFB data and task performance indicating either a non-dependent sample's drinking behaviour has no relationship to this specific task or the definition of light and heavy drinkers in this chapter is insufficient to capture anything meaningful within the sample in regards to Pavlovian conditioning. As the present study did not have any form of screening for alcohol use as part of the eligibility criteria, 66% of participants were light drinkers; reporting less than the UK Chief Medical Officers' lower risk guidelines for alcohol consumption per week (< 14 units), and so many were placed in the heavy drinker category. Previous research with social drinkers have used other cut-off

points; the recommendations for sensible drinking (Field and Jones, 2017) or ≥ 20 units and ≤ 10 units per week (Field et al, 2004) for determining light and heavy drinking groups. 58% of the present sample reported fewer than 10 units, 33% reported over 14 units and 25% reported over 20 units in the TLFB. Even though the light and heavy drinking groups mean reported units in the TFLB was significantly different from each other, the variance within groups was so huge the groups greatly overlapped and light drinkers were forced into the heavy drinkers group. This could potentially explain why there was no difference between high and low impulsivity groups as measured by the BIS-11. As the majority of participants can be considered light drinkers, any impulsivity differences related to drinking behaviour will not be detectable in the present sample as they in theory should have homogenous impulsivity measurements. This could also be exacerbated by the fact the sample is made up of social drinkers and not problematic drinkers or alcohol-dependent patients as impulsivity differences may only be detectable in clinical and sub-clinical groups.

In conclusion, the results of the present study suggest, the paradigm used is sufficient to study the learning of ABA recovery. It can also be concluded that among social drinkers, there is no difference in CS-US acquisition, extinction or recovery for either alcohol or food rewards.

Chapter 6

Individual Differences and Reinforcer Type in Pavlovian-Instrumental Transfer in Light and Heavy Social Drinkers

6.1 Abstract

The present study aimed to investigate the interaction of levels of alcohol consumption and reinforcer type on instrumental responding in a Pavlovian-instrumental transfer paradigm. Light and heavy social drinking groups completed Pavlovian conditioning training ($CS_1 – O_1$, $CS_2 – O_2$) for beer and chocolate reinforcers. This was followed by instrumental training for the same reinforcers ($R_1 – O_1$, $R_2 – O_2$). At this point in the experiment participants would go home and return to the lab 24 hours later. At this point participants rated how unpleasant they found health warnings for either alcohol or chocolate in an attempt to devalue the rewards. Finally, the participants completed the transfer test which consisted of the instrumental responding in extinction when CS_1, CS_2 and no cue were intermittently presented. The results show a PIT effect for the alcohol cue, however there while was no significant difference between drinking groups in the PIT effect, the results suggested a pattern of general PIT effect for heavy drinkers and specific PIT effect for light.

6.2 Introduction

The previous experiments presented in this thesis have focused on differences between individual's levels of alcohol consumption (light vs heavy/dependent) and differences between reinforcer types (alcohol vs food) in Pavlovian CS-US acquisition, extinction, and response recovery. While there was no difference between light and heavy social drinkers in their Pavlovian conditioning abilities, there was difference between light drinkers and AD patients in both acquisition and extinction. Chapter 4 showed the AD patients were impaired at extinguishing learned CS-US parings during the extinction phase.

There was however, no difference in CS-US acquisition, extinction or recovery between reinforcer types. As discussed in Chapter 1, reinforcer type is an important factor in the development of habitual behaviours. Participants have been shown to be more likely to be insensitive to the devaluation of an alcohol reinforcer compared to non-drug reinforcers (Dickinson et al., 2002). The development of habitual behaviours is believed to be the expression of the strengthening of stimulus-response learning (see Chapter 1 for more details). PIT experiments have shown that drug-related cues exert motivational influence over participants responding despite cue extinction and reward devaluation (Hogarth et al., 2014), however it has been shown that treatment seeking drug users in PIT paradigms do not demonstrate impaired goal-directed behaviour (Hogarth et al., 2018). Therefore, it may be possible that habit does not have an influential role in the development and maintenance of addictive behaviour and may have little impact in explaining ACETP. High trait impulsivity has been shown to be associated with a propensity for habit learning and a reliance on habitual behaviours (Hogarth, Chase, & Baess, 2012; Torregrossa, Quinn, & Taylor, 2002). Therefore, the aim of the present study is to see how levels of alcohol consumption, impulsivity, and reinforcer type affect the expression of goal-directed or habitual behaviour in PIT paradigm.

The present study used the PIT paradigm used in Hogarth & Chase (2011) with some minor adjustments for pragmatic reasons. Firstly, as an alcohol US was used and alcohol administration prior to learning training has been shown to bias in favour of habitual learning (Corbit et al., 2012), the experiment took place over two consecutive days to separate the training and test phases. Also, because alcohol was administered to the participants, the study used an analogous sample of light and heavy social drinkers. Secondly, as there was a day separating training and test phases, there was no extinction session for the concurrent choice task to measure the devaluation effect. This was to minimise the amount of degradation that can occur for the associations learned as part of

the experiment. Instead the devaluation effect was measured by comparing the instrumental phase performance to the no-cue block of the test phase. Finally, the study controlled the nature of Pavlovian conditioning. In Hogarth and colleagues PIT experiments the CSs used were pictures of the USs. However, as experimenters cannot control for the nature and extent of conditioning when they rely on extra-experimental Pavlovian conditioning, this study had participants learn CS-US pairings between neutral stimuli and alcohol and food rewards. The same Pavlovian acquisition paradigm that was used in the previous chapter was used in this study. These Pavlovian cues were presented in the transfer test.

The following hypotheses were tested:

1) There will be no difference between light and heavy drinkers in their rate of acquiring Pavlovian associations for either alcohol or food reinforcers.
2) There will be no difference between light and heavy drinkers in their overall percentage choice of instrumental responses in the training phase.
3) The heavy drinkers will be more insensitive compared to the light drinkers in outcome devaluation for both alcohol and food.
4) The heavy drinking group will have a general PIT effect in the presence of Pavlovian cues in favour of alcohol.
5) The light drinking group will have an outcome-specific PIT in the presence of the Pavlovian cues.

6.3 Methods

6.3.1 Participants

41 participants took part in the experiment, but one participant had to be excluded due to experimental error voiding their data. Therefore, 40 participants (15 male, 25 female) with a mean age of 20.9 years (SD = 2.1, range = 18 – 27) completed the experiment. All but two participants were students at the University of Southampton the

others were in full-time employment. 40% of participants were psychology students, the remainder in a variety of other disciplines. Upon completion of the experiment participants received monetary (£10) or course credit (20) payment.

6.3.2 Materials

The three questionnaires used (AUDIT-C, TLFB, and BIS-11) and the apparatus that ran the computer task were the same as those described in Chapter 2.

6.3.2.1 Drinks

The alcoholic beverage participants consumed was 15ml of 4.8% ABV Stella Artois beer. Participants consumed exactly 15 drinks in the Pavlovian phase (therefore had 1 unit) and on average had approximately 15 drinks in the concurrent choice phase (therefore had approximately 2 units throughout the experiment).

6.3.2.2 Food

The food participants consumed was half of ASDA Milk Chocolate Button. Participants consumed 15 in the Pavlovian phase and on average 15 in the concurrent choice phase.

6.3.2.3 Health Warnings

Participants read health warnings for alcohol and chocolate consumption in the devaluation phase. The alcohol health warnings are taken from the NHS (https://www.nhs.uk/Livewell/alcohol/Pages/Effectsofalcohol.aspx) and drink aware (https://www.drinkaware.co.uk/alcohol-facts/health-effects-of-alcohol/) websites on 29/1/18 and http://digital.nhs.uk/catalogue/PUB23940 on 12/3/18. The food health warnings are taken from Hogarth and Chase (2011). See Appendix 4 for specific alcohol and chocolate health warnings.

6.3.2.4 Computer Task

The computer task consisted of four phases. Participants had to learn Pavlovian and instrumental associations with beer and chocolate USs. After one US was devalued, participants had to complete the transfer test, in which participants had to complete the instrumental task for a second time in extinction. During the transfer test the background displayed on the computer monitor changed between presenting the image of cue A, cue B, and no cue. This was to study the influence the cues exerted over the participants choices of instrumental responses. The experiment took place over two consecutive days. On day one participants completed the Pavlovian and instrumental training phases. On day two participants returned to the lab and completed the devaluation and transfer test phases. A summary of the structure of each of these phases is presented in Table 6.1. The computer program was written in Microsoft Visual Studio 2013 C# language.

Pavlovian phase

There were two sessions for the Pavlovian phase. One session presented the cue with the alcohol US and the other session presented the cue with the chocolate US. The order of sessions was counterbalanced. The Pavlovian phase in this study was identical to the Pavlovian conditioning acquisition phase of the conditioning experiment (see Chapter 5). Participants had to learn which cue was associated with which reinforcer. The cues were neutral coloured shapes randomly assigned to be cue A, cue B or cue C. Cue A predicted a beer outcome, cue B predicted a chocolate outcome and cue C predicted no outcome (wait). The Pavlovian phase of this study differed from the acquisition phase of the previous experiment in several minor ways. Firstly, all cues were presented on a plain light grey background at all times. Secondly, the number of cues used were reduced down from six to three. Finally, there were less trials per cue. There were 15 cue A trials, 15 cue B trials and 30 cue C trials (15 per session). At the end of session two participants had to answer questions to demonstrate if they had conscious awareness of the CS-US

relationships. Participants saw the cue in the middle of the computer monitor with text underneath which read: "What outcome is this cue associated with? 1 = Drink, 2 = Eat, 3 = Wait, 4 = Don't know. Each training session took five minutes. As there was a one hour break between sessions, the Pavlovian phase took one hour and 10 minutes in total.

Instrumental phase

All phases from this point on are based on the methods of Hogarth and Chase (2011). First, participants had to learn which instrumental response (key press) was associated with beer or chocolate reinforcers. The instrumental training utilised a concurrent choice (CC) task. In the CC task participants had to choose to press the D key or H key to win rewards of drink or food. Each trials began with the text: "Select a key" which remained there until either D or H has been pressed. A response by key press replaced this text with either: "You win 15ml of beer" or "You win 1/2 of chocolate button" or "You win nothing" depending on what was pressed. It was counterbalanced between D and H of which alcohol and chocolate were assigned to the keys. Only one outcome was scheduled to be available in each trial. If participants successfully pressed the key that yielded the outcome for that trial, they saw the text: "You win X" otherwise they saw: "You win nothing". Participants then consumed the reward only if they were correct. Participants did not begin the next trial until they had finished their reward and pressed the space bar. There was a single session of 60 trials (30 for D and 30 for H) presented in a randomised order. At the end of the block participants were given questions on their knowledge of contingencies between keys and outcome similar to the Pavlovian cues. In total the CC task took five minutes.

Devaluation phase

The devaluation phase started with five questions, these were identical to the ones asked at the end of the Pavlovian and instrumental phase the previous day to see if the

overnight break affected conscious retention of the contingencies. After this, participants completed the devaluation procedure in which they read the 16 health warnings. Participants were randomly assigned to either alcohol or chocolate health warnings and the order of the statements presentation was also randomised. Presented on the computer monitor were the instructions: *"In this part of the task, we would like to assess how unpleasant you find statements concerning the adverse consequences drinking alcohol [or eating chocolate]. Please read each statement carefully. Then report how unpleasant you find each statement by pressing a number key between 1 and 9, where: 1 _ Not at all unpleasant, 5 _ mildly unpleasant and 9 _ extremely unpleasant. Press the space bar to begin."* Responding with a key press launched a 2000ms ITI before the next statement. The devaluation phase took five minutes to complete.

Transfer test

Participants then completed the transfer test immediately after devaluation. The transfer test is identical to the CC phase with two exceptions. 1) The CC took place in extinction and participants were not given any feedback at all after their key press. Participants were told in the instructions beforehand they are doing the CC task again, but this time collecting points to win alcohol and food rewards and they will not be informed of their success during the task. 2) On 1/3 of the trials the "choose a key" text was presented with cue A tiling the background, on 1/3 there was a tiling of cue B and on 1/3 there was no cue; just a plain white background. In total there were 72 trial (24 with cue A, 24 with cue B and 24 with no cue). The transfer test took in total five minutes.

Table 6.1 Summary of the Pavlovian, concurrent choice, devaluation, and PIT test phases

Pavlovian Phase		Instrumental and Devaluation Phase		Test Phase
Acquisition Cue A	Acquisition Cue B	Concurrent Choice	Devaluation	Transfer Test
A->Alcohol (x15)	B->Food (x15)	D key->Alcohol (x30)	16 trials	**A:** D->Φ or H->Φ (x24)
C->Φ (x15)	C->Φ (x15)	H key->Food (x30)		**B:** D->Φ or H->Φ (x24)
				D->Φ or H->Φ (x24)

Note. A → Alcohol (x15) indicates cue A, outcome present on 15 trials. Φ = wait. **A:** D->Φ or H->Φ (x24) indicates cue A from acquisition sessions are present and either D or H is pressed with no outcome. Trial orders are randomised within blocks.

6.3.3 Design

A mixed design with two between subjects independent variables both with two levels; 1) light vs heavy social drinkers and 2) alcohol vs food reinforcement. The within subjects independent variable has three levels: which CS is present during the transfer test (Alcohol CS, Food CS or no CS). Different dependent variables are measured at different stages of the computer task: 1) Pavlovian conditioning acquisiton (end of phase predictive responding), 2) concurrent choice training/ instrumental training (percentage choice of alcohol vs food key presses), and the primary dependent variable, 3) transfer (percentage of key press choice of alcohol vs food when alcohol CS or food CS or no CS is present).

6.3.4 Procedure

Participants came to the lab for two consecutive days. On day one participants completed the questionnaires after giving informed consent. Participants then started the Pavlovian conditioning phase of the experiment. There was a one-hour break between the two Pavlovian sessions to enable blood alcohol levels to reduce to 0. During this period participants had to remain in the lab except to visit the toilet. The experimenter offered cups of water to participants. Participants occupied their time by using their mobile phones, watching TV on the internet, or studying. After the second Pavlovian session there was a short break to allow for the experimenter to set up the room for the instrumental conditioning phase. Participants completed the instrumental conditioning phase, signed a disclaimer sheet stating they knew they have consumed a small dose of alcohol and knew

to stay safe and not drive for up to three hours after the experiment (see Appendix 1 for disclaimer) and went home. The next day participants came to the lab as close as possible to the same time they arrived on day one. They started the devaluation procedure which was immediately followed by the transfer test. Before the transfer test participants were instructed they would do the CC task again, but this time would be earning points to win beer and chocolate to take home after the experiment. However, they were not informed of their success until the end of the experiment. After the transfer test participants were told of this deceit, debriefed and paid.

6.4 Results

6.4.1 Questionnaires

6.4.1.1 Drinking Data

The participants were categorised into light and heavy drinking groups based on a median split of the TLFB data. Participants reported a median of 20.5 units (SD = 30.5, range = 0 – 114.3) consumed in the week prior to the experiment commencement in the TLFB questionnaire. The light drinking group had a mean of 6 units reported in the TLFB (SD = 6.7, range = 0 – 20) while the heavy drinking group reported a mean of 51.3 (SD = 27.9, range = 20.9 – 114.3). There was a significant difference between the two groups in number of units reported on the TLFB t (21.2) = -7.1, $p < .001$. For the AUDIT-C, the light drinking group reported a mean of 5.3 (SD = 2.8, range = 0 – 10), whereas the heavy drinking group reported a mean of 9.3 (SD = 1.3, range = 5 – 12). These groups were statistically different $U = 43$, $p < .001$.

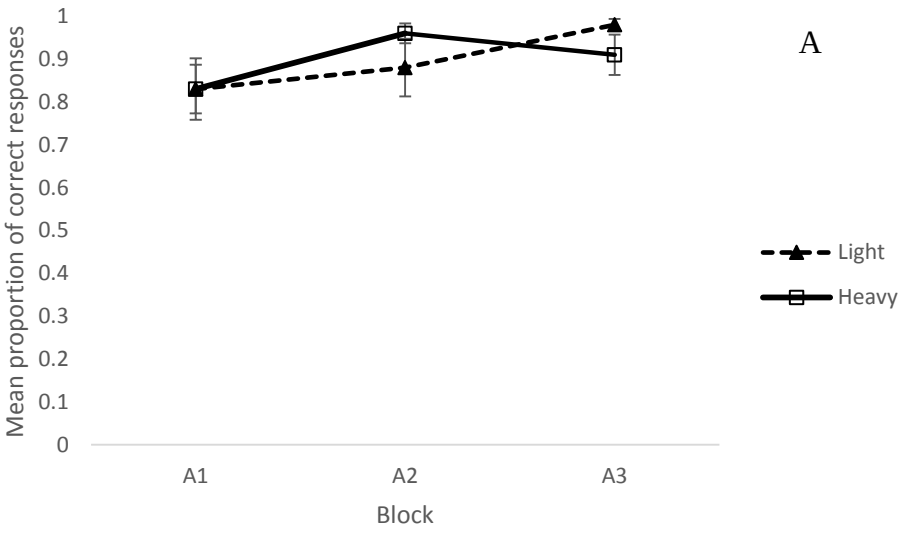
6.4.1.2 Impulsivity

The overall median BIS-11 score was 63.5 (SD = 11.5, range = 44 – 97). The mean BIS-11 score of the light drinking group was 64.4 (SD = 9.3, range 44 – 63) and the heavy drinking group was 66.1 (SD = 13.5, range = 64 – 97). These two groups were not

statistically different $U = 193$, $p = .85$. Due to the lack of difference in impulsivity between the two drinking groups of this sample, the lack of difference between the light and heavy drinking groups on the behavioural data of this experiment (reported in the next sections), and the lack of statistical significant outcomes of the impulsiveness groups in other chapters of this thesis, BIS-11 has been excluded from all further analysis.

6.4.2 Pavlovian conditioning

Figure 6.1a shows the mean proportion of correct responses for cue A and Figure 6.1b shows the same for cue B. The trials were aggregated into three blocks of five for each cue. Inspection of both panels of the figure suggests participants learned the associations near asymptote, within the first block (first 5 trials), which slightly increased to asymptote by the final block. In addition to this, it suggests both light and heavy drinking groups learned the CS-US association for both cues at equivalent rates. A 3 (block) x 2 (light vs heavy drinkers) repeated measures ANOVA was conducted on cue A and an identical ANOVA was conducted on cue B. Both results showed a significant main effect of block, but not a main effect of group or block*group interaction. Both ANOVAs are presented in Table *6.2*. The results support both groups learned the CS-US association at equal rates.



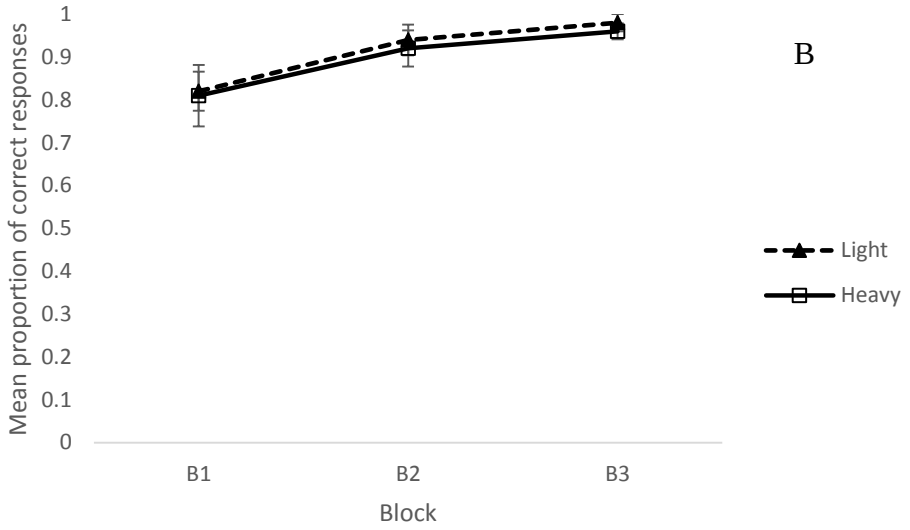


Figure 6.1. Panel A depicts a line graphs displaying the mean proportion of correct responses for cue A between light and heavy drinking groups and panel two displays the same for cue B. Error bars represent standard error.

Table 6.2 Repeated Measures Analysis of Variance for Cue A and Cue B

Cue	Source	*SS*	*df*	*MS*	*F*	*P*	η^2
Cue A	Between-Subjects						
	Drinking	0	1	0	.003	.953	0
	Error	1.21	38	.032			
	Within-Subjects						
	Block	.293	1.59	.184	4.7	.019*	.11
	Block x Drinking	.113	1.59	.071	1.81	.179	.045
	Error	2.37	60.3	.039			
Cue B	Between-Subjects						
	Drinking	.003	1	.003	.147	.703	.004
	Error	.716	38	.019			
	Within-Subjects						
	Block	.518	1.39	.373	9.64	.001**	.202
	Block x Drinking	.001	1.39	0	.012	.960	0
	Error	2.04	52.83	.309			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
**p = .001, *p < .05

6.4.3 Instrumental conditioning

Alcohol key refers to the key that produced an alcohol reward regardless of whether they key was D or H. likewise the same applies to *chocolate key*. Figure 6.2 displays the mean percentage of times the alcohol key was pressed. Inspection of Figure 6.2 shows participants pressed the alcohol key, on average, a little less than 50% of the time and there were no difference between groups in key presses. An independent sample t-tests was performed on mean percentage alcohol key presses to see if there was a difference between

light and heavy drinkers. There were no difference between light and heavy drinkers *t* (38) = -1.34, *p* = .19, *d* = .42.

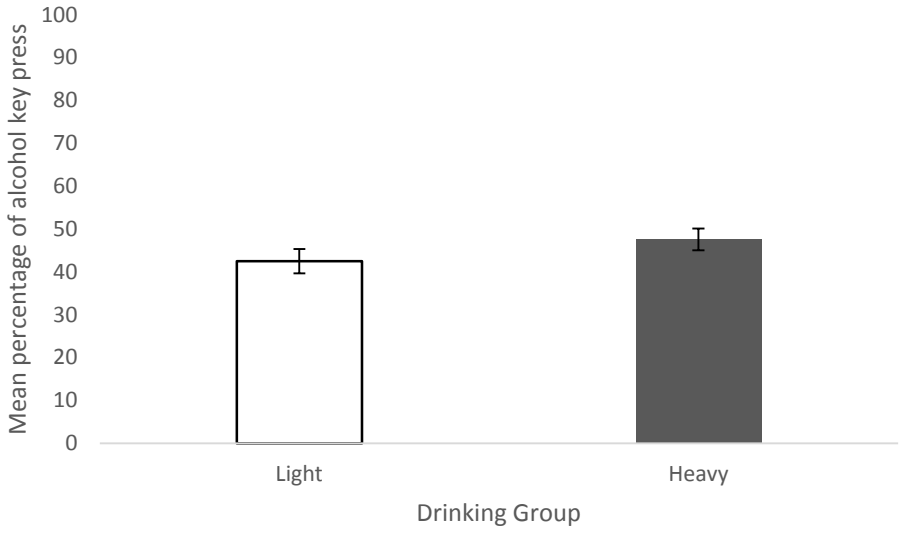


Figure 6.2. A bar graph showing the mean percentage of alcohol key presses between light and heavy drinkers. Error bars represent standard error.

6.4.4 Belief Questions

Participants answered question to determine if they were consciously aware of the cues/ key press reward contingencies at the end of each training session and at the start of the second day. Results presented here are all taken from day two. Table *6.3* summarises the mean percentage of participants who answered correctly for contingency by light and heavy drinkers.

Table 6.3 Summary of the mean percentage of correct answers to the contingency questions by light and heavy drinkers

	Cue A M (SD)	Cue B M (SD)	Alcohol Key M (SD)	Chocolate Key M (SD)
Light	80 (.41)	85 (.37)	65 (.49)	65 (.49)
Heavy	85 (.37)	85 (.37)	75 (.44)	70 (.47)

Four, chi square tests were performed to see if there was a difference between light and heavy drinking groups in their beliefs of each contingency. All test are summarised in Table 6.4. There were no difference between light and heavy drinkers on any of the dependent measures. Therefore, the results showed the majority of participants were aware

of the contingencies and there was no difference between groups in the amount of correct answers.

Table 6.4 Chi square tests for conscious awareness of contingencies for cue A, cue B, alcohol key and chocolate key

Dependent Variable	χ^2	*df*	*p*
Cue A	.173	1	.677
Cue B	0	1	1
Alcohol Key	.476	1	.49
Chocolate Key	.114	1	.736

Note. χ^2 = chi square, *df* = degrees of freedom.

6.4.5 Devaluation

During the devaluation phase participants rated health warning statements on how unpleasant they found them on a likert scale of 1 (not unpleasant) to 9 (extremely unpleasant). Comparing each individual statement to each other was irrelevant, therefore overall unpleasantness ratings were reported. As there were 16 statements, each on a 9 point likert scale, the potential maximum of the total sum of all statement ratings was 144. The median of the sum of all alcohol statement ratings was 90.5 (SD = 18, range = 46 - 116). The median of the sum of all chocolate statement ratings was 68.5 (SD = 16.2, range = 27 – 96). A 2 x2 (alcohol vs chocolate devaluation; light vs heavy drinkers group) between subjects ANOVA was conducted to see if there was a difference between these independent variables on the total unpleasantness rating. ANOVA results are summarised in Table 6.5. The results showed there was a main effect of devaluation type. Overall, the alcohol health warning statements were regarded more unpleasant than the chocolate health warning statements. There was not however, a main effect of drinking group; light and heavy drinking groups rated the statements as equally unpleasant. There was also not a significant drinking*devaluation interaction, meaning the rating difference between devaluation type was independent of drinking group.

Table 6.5 Between subjects ANOVA for devaluations ratings

Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Between-Subjects						
Drinking	56.5	1	56.5	.185	.67	.005
Devaluation	2731.7	1	2731.7	8.94	.005*	.199
Drinking*Devaluation	57.5	1	57.5	.188	.667	.005
Error	11003.6	36	305.7			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
*$p < .01$

To explore the devaluation effect, the mean percentage of alcohol key presses during the instrumental training phase were compared to the mean percentage of alcohol key presses during the transfer test when no cue was present. Figure 6.3 compares the instrumental alcohol key presses to the no cue alcohol key presses for the alcohol devaluation group and the chocolate devaluation group separately. If a devaluation effect were to occur, for the alcohol devaluation group, there would be fewer alcohol key presses in the no cue compared to instrumental time points. This is because participants would be pressing the chocolate key more after devaluation. In contrast, for the chocolate devaluation group, a devaluation effect would be expressed with greater alcohol key presses during the no cue compared to the instrumental time point as participants would have reduced their chocolate key presses.

Figure 6.3 shows the opposite of this; there are small absolute differences in which the alcohol devaluation group have increased their alcohol key presses and the chocolate devaluation group have decreased their alcohol key presses. The magnitude of the absolute differences appear negligible as participants were pressing the alcohol key equivalently during both time periods. This is supported by a 2 x 2 x 2 (time: instrumental vs no cue; devaluation: alcohol vs chocolate; drinking: light vs heavy) ANOVA which generated no significant main effect outcomes and only one significant interaction. The significant interaction was devaluation*drink. This interaction appears to have been primarily caused by high levels of key pressing in the heavy drinking sub-group which had alcohol

devalued. When alcohol key presses were collapsed across time, the heavy drinking sub-group which had alcohol devalued pressed the alcohol key more (M = 52.7, SD = 3.7) compared to the heavy drinking chocolate devaluation sub-group (M = 41, SD = 3.3). In contrast the light drinking sub-group which had alcohol devalued pressed the alcohol key less (M = 42.1, SD = 3.3) compared to the light drinking chocolate devaluation sub-group (M = 45.8, SD = 3.7). However, as there is no significant main effect of time, these differences disappear when instrumental and no cue are separated. All devaluation ANOVAs are summarised in table 6.6. In summary no devaluation effect was observed.

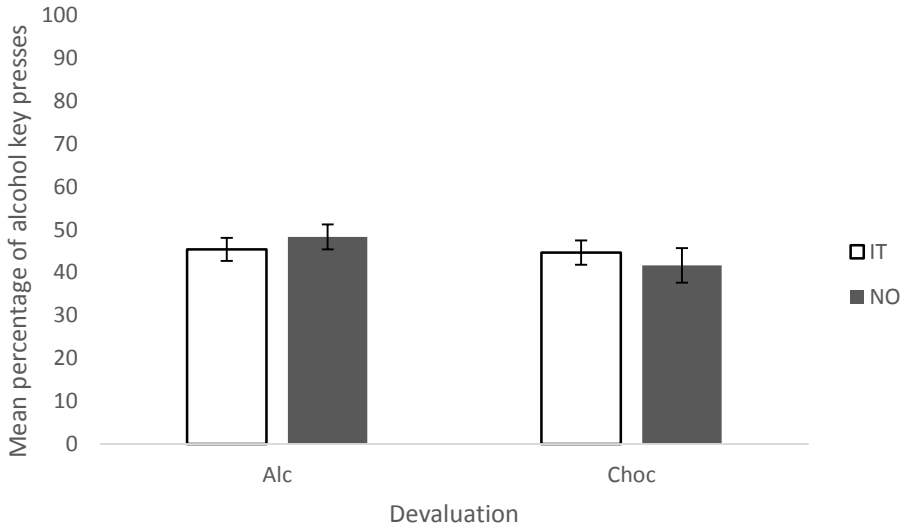


Figure 6.3. A bar graph displaying the mean percentage of alcohol key presses during the instrumental training phase (IT) and the no cue trials of the transfer test (NO) between alcohol devaluation and chocolate devaluation groups.

Table 6.6 Within Subjects ANOVA for devaluation key presses

Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Between-Subjects						
Devaluation	158.7	1	158.7	1.32	.258	.035
Drinking	85.7	1	85.7	.712	.404	.019
Devaluation*Drinking	588	1	588	4.89	.034*	.119
Error	4332.3	36	120.3			
Within-Subjects						
Time	.003	1	.003	0	.996	0
Time*Devaluation	147.7	1	147.7	1.04	.314	.028
Time*Drinking	101.9	1	101.9	.72	.402	.02
Time*Devaluation*Drinking	5.84	1	5.84	.041	.84	.001
Error	5097.9	36	141.6			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
*$p < .05$

6.4.6 Transfer test

For the transfer test participants pressed the alcohol and chocolate keys in extinction while the background displayed on the computer monitor intermittently presented the cues separately in a tiling formation. Figure 6.4 shows the mean percentage of alcohol key presses in cue A context, cue B context and no cue context. Figure 6.4 shows overall participants pressed the alcohol key most frequently in the cue A context. When collapsed across drinking groups, the alcohol key was pressed 56.5% of the time (SD= 26.5, range 0-100) in context A, 41.2% of the time (SD = 25.9, range = 0-100) in context B and 45% of the time (SD = 15.9, range = 0-67) in the no cue context.

Figure 6.4 also shows an absolute difference between light and heavy drinkers in their percentage of alcohol key presses in context A and context B. Table 6.7 shows the results of a 3 (cue A context vs cue B context vs no cue context) x 2 (light vs heavy drinkers) ANOVA with alcohol key presses as the dependent variable.

The results showed there was a main effect of cue, the proportion of alcohol key presses varied according to cue. Pairwise contrasts revealed that the proportion of alcohol key presses was greater in the cue A context compared to no cue context ($p < .05$) but no other pairwise differences were present (cue A CTX vs cue B CTX, $p = .084$; cue B CTX vs no cue CTX, $p = .992$).

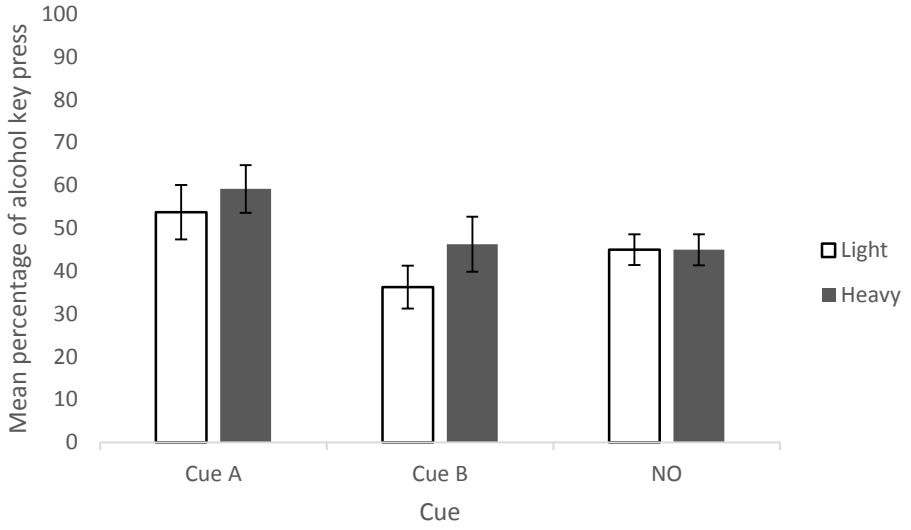


Figure 6.4. A bar graph showing the mean percentage of alcohol key presses in cue A context (alcohol cue), cue B context (chocolate cue) and no cue context. Error bars represent standard error.

Table 6.7 Repeated measures ANOVA for PIT effect

Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Between-Subjects						
Drinking	1055.9	1	1055.9	1.32	.259	.033
Error	30513.2	38	803			
Within-Subjects						
Cue	20088.7	1.33	15165	4.84	.01*	.113
Cue*Drinking	2003.8	1.33	1512.7	.483	.542	.013
Error	157580.1	50.4	3130.5			

Note. *SS* = sum of squares, *MS* = mean square, *df* = degrees of freedom, η^2 = partial eta squared.
*p = .01

6.4.7 Supplementary Analysis

As no difference was found between drinking groups in the PIT analysis, Spearman's Rho correlations were conducted between the TLFB data and the PIT data. The results presented in Table *6.8* revealed there was non-existent correlations (all p-values > .2) between drinking data and the PIT effect indicating the PIT effect has no relationship with alcohol consumption behaviour.

Table 6.8 A table displaying correlations between TLFB data and the PIT effect

	Cue A PIT	Cue B PIT	No Cue PIT
TLFB	.098	.181	-.039

6.5 Discussion

The results showed participants successfully learned the Pavlovian contingencies. This is consistent with the conditioning experiment in Chapter 5 which also showed equivalent learning rates between groups during the acquisition phase. In addition to this, during the concurrent choice task, participants pressed the alcohol and chocolate keys an equivalent amount of times. Approximately 70% of participants displayed conscious awareness of the contingencies between key presses and rewards during the concurrent choice task. Conscious awareness of R-O pairings is a proxy measure of unconscious R-O associative strength. It is unclear how many participants formed the unconscious R-O associations, but the PIT effect (discussed later) suggested participants had formed Pavlovian and instrumental associations adequately. The results also showed there was no difference between light and heavy drinking groups in their formation of these associations; the hypotheses there would be no difference was supported.

The results showed there was no devaluation effect despite the fact that the health warning statements for both alcohol and chocolate were rated as moderately unpleasant. There was no difference between light and heavy drinking groups in their ratings, but the alcohol health warnings were rated significantly more unpleasant than the chocolate warnings. This does not support the hypothesis that there would be a devaluation effect and the heavy drinking group would be more insensitive to devaluation compared to light drinkers. This was predicted because a greater levels of alcohol consumption biases towards impairment in reward revaluation. Past research has shown that early in the instrumental training stage (two weeks) for an ethanol reward, rats are goal-directed as they are sensitive to devaluation, however by eight weeks, instrumental responding has become habitual (Corbit et al., 2012). It is unclear why there was no devaluation effect at all amongst participants. The present study used the same chocolate health warnings as (Hogarth & Chase, 2011) and generated our own alcohol health warnings to match the

chocolate ones. Hogarth & Chase (2011) observed a devaluation effect within their sample. It is possible a devaluation effect was not observed in the present study because instrumental behaviour was compared to the no cue section of the transfer test data. Whereas, Hogarth & Chase (2011) had an extra phase where participants performed the instrumental behaviour in extinction and compared to instrumental to extinction data. The present study did not use an extinction phase in an attempt to limit the amount of R-O degradation that may have happened between days one and two. The present study had a 24 hour gap between training and devaluation/ testing because past research has shown the mere consumption of alcohol biases in favour of habitual learning (Hogarth, Attwood, Bate, & Munafò, 2012). That is why health warnings were selected over satiety to achieve devaluation. Therefore, future research could replicate this study and have participants stay in the lab until BAL have reduced to 0 and then the experiment can continue with the devaluation and test phase.

It was predicted that for the heavy drinking group, the Pavlovian cues would produce a general PIT effect in favour of the alcohol reward and a specific PIT in the light drinkers. This was because the heavy drinkers were predicted to be insensitive to outcome devaluation as they do not take reward features into consideration and instead elicit general appetitive arousal. They were predicted to favour the alcohol reward over the food reward as their greater levels of alcohol consumption would lead to greater incentive for it. The hypothesis was partially supported. Instead the results showed a PIT effect for the alcohol cue, but not a statistically significant PIT effect for the chocolate cue. As can be seen in Figure 6.4 in the no cue condition the alcohol key presses are around 50%, which is to be expected as there is no Pavlovian signal influencing decision making and choice is therefore random. For there to be a PIT effect, the cue A and cue B conditions must be significantly different from no cue. The cue A (alcohol cue) context condition was significant. The participants increased their alcohol key presses over no cue (i.e. over 50%)

therefore demonstrating the alcohol cues PIT effect in influencing motivation towards selecting an alcohol reward.

Figure 6.4 also shows the number of alcohol key presses declined when the cue B context (chocolate context) was presented. What should be noted that while there was no statistically significant difference between light and heavy drinking group in the PIT effect (or any metric of this experiment) the data does show a trend towards the light drinking groups pressing the chocolate key more when the chocolate cue was present, but the heavy drinkers averaging around 50%. This explains why no PIT effect was observed for the chocolate cue. The data suggests some of the heavy drinking group sustained their alcohol key presses during the chocolate cue condition dragging the average alcohol key press up. This suggests, that while not significant, the heavy drinking group had a weak general PIT effect as they pressed their alcohol key regardless of which appetitive cue was present, whereas the light drinkers pressed the key which was congruent to the cue, suggesting a specific-PIT effect.

Suggestions for future research include increasing the sample size to increase power which might change the statistical outcomes, however prior to the experiment a sample size calculation using G*Power was conducted indicating a sample of 40 was adequate. Alternatively, future research could replicate this study, but recruit participants based on better group allocation than a median split e.g. scoring below and above a certain score on an alcohol use questionnaire or drinking fewer or greater a certain number of units weekly. The supplementary analysis showed no correlation between drinking data and the PIT effect. This suggests that the definition of light and heavy drinkers in this chapter is not sufficient and a way to improve this experiment is to have a more robust definition of groups (e.g. recruiting participants that consume within a range of predetermined units per week). A more definitive division of light and heavy drinkers could increase those who display general PIT and specific PIT behaviour. A final change for future research is the

cues used. These results could be due to the use of Pavlovian cues. Hogarth & Chase (2011) used images of the USs as cues. The present study used lab created CSs to control the exact nature and extent of Pavlovian learning of the cues because experimenters are not in control of this factor when they rely on extra-experimental conditioning. Past research has shown that discriminative stimuli that set the occasion exert greater motivational influence than Pavlovian CSs (Troisi II, 2006). Therefore, a replication of this experiment using discriminative stimuli may demonstrate stronger statistically significant PIT effect for both cues.

In conclusion, the results suggest that alcohol-related Pavlovian cues exert motivational influence over instrumental responding for alcohol rewards. It is possible that heavy social drinkers develop a general PIT effect which biases motivation towards alcohol in the presence of non-drug appetitive cues, whereas light drinkers develop a specific PIT effect where cues increase motivation for specific rewards, but this had not been effectively demonstrated.

Chapter 7

General Discussion

7.1 Introduction

The empirical work presented in this doctoral thesis investigated associative learning primarily amongst individuals with differing levels of alcohol consumption in non-clinical samples. In addition to this, the effect of reinforcer type and its interaction with levels of alcohol consumption was also investigated. A secondary interest was how trait impulsivity influenced learning and interacted with the other variables. As discussed in Chapter 1, CET as a treatment for AD has not been shown to be as effective as CET is for treating other psychiatric disorders (we referred to this as ACETP). This led us to hypothesise there may be individual differences between AD patients and non-dependent individuals in Pavlovian conditioning. In addition to this, the extent to which levels of alcohol consumption affects Pavlovian conditioning may be on a continuum where observable differences may be limited to the extremes (i.e. light drinkers vs AD). Moreover, learning with alcohol reinforcers have been shown to impair individual's capacity to revaluate rewards and bias in favour of habitual learning. The hypotheses tested in this thesis were generated through literature based a reasoning frame worked around the R-W.

The work presented in Chapter 3 used the R-W to make predictions based on theoretical cue salience during Pavlovian learning that would theoretically naturally occur in light and heavy social drinkers. In Chapter 4, Chapter 3 was replicated with AD patients and non-dependent controls. Chapter 5 used an ABA and ABC design to measure Pavlovian conditioning between light and heavy drinkers for alcohol and food rewards. In Chapter 6, the influence of Pavlovian cues over instrumental responding was measured in a PIT design. A summary of the findings and implications of the empirical work presented in

this thesis will be discussed in the following sections along with conclusions and directions for future research.

7.2 Summary of Experimental Findings

A consistent finding across all experiments was there was no difference between light and heavy social drinkers in all aspects of associative learning that were empirically examined in the experiments of this thesis. The R-W was applied as a framework to model the hypotheses. In Chapter 3 it was exploring whether differing levels of alcohol consumption affected Pavlovian learning. This was because the ACETP suggests a fundamental difference between AD and non-dependent groups in Pavlovian learning. One mechanism to which this may be was modelled around the R-W framework. As heavy drinkers and AD patients have a heightened bias towards alcohol-related cues when they predict alcohol is available, it was assumed AD patients give greater attention to cues during Pavlovian acquisition (e.g. when alcohol is available and being consumed) and less attention to the cues when unavailable (e.g. in clinical setting). The R-W model predicts when salience to a target cue is reduced (e.g. from reduced attentional bias) this would lead to slower learning. Therefore, if a cue that has been trained to asymptote has reduced salience during extinction training, this would lead to REX and P-F-E which would yield greater response recovery. Chapter 3 used an analogous sample of light and heavy social drinkers to test the assumption that the impact of drinking history is on a spectrum (social drinkers – problematic drinkers – AD). It may be that the samples were not sufficiently different to observe a difference as individuals were clustered close on the continuum. This experiment also used a Pavlovian task of generic CS-US pairings to see if the effects of alcohol consumption generalises to general conditioning or is restricted to alcohol-related stimuli. The results showed there was no difference between drinking groups in Pavlovian acquisition, extinction or recovery. These results also showed the extinction context

became inhibitory which suggests response recovery can be explained by the P-F-E phenomenon.

The results of Chapter 3 led to the experiments in Chapter 4 and Chapter 5. Chapter 4 was a replication of Chapter 3, but with AD patients compared to age and sex matched health controls with very little alcohol consumption. This experiment found that AD patients when compared to the controls had impaired performance Pavlovian extinction. Was this impairment present before the development of addiction or was it caused by addiction-related adaptations. If it is a consequence of addiction (as is likely), then pre-addiction, the individual would have normal alcohol-CS-US acquisition, but impaired cue extinction in treatment. This would result in REX and P-F-E (from the clinical context) and could explain the ACETP.

Chapter 5 extended Chapter 3 by including reinforcer type as a variable. It was unclear from Chapter 3 whether the null result was because the participants consisted of a social drinkers sample or generic CS-US pairings. Chapter 4 kept CS-US pairing constant, but varied the sample. Chapter 5 kept the sample constant, but varied the reinforcers by including biologically relevant USs (alcohol and food). The results showed that when comparing light and heavy social drinkers, there was no difference between the groups in Pavlovian acquisition, extinction and response recovery. The results of Chapter 3, Chapter 4, and Chapter 5, when interpreted together, allow us to conclude with some confidence that differences in alcohol consumption on Pavlovian conditioning performance are not observable amongst social drinkers, but become evident when comparing the extremes of the spectrum. The effect reinforcer type has on AD patients remains unclear. Would we observe a different pattern of Pavlovian conditioning performance if between generic CS-US learning and biologically relevant USs or incentive rewards?

It was also discussed in Chapter 1 that individual differences related to alcohol consumption between AD and non-dependent individuals could be expressed not just in Pavlovian conditioning, but also instrumental learning and the interaction between the two

forms of learning. Therefore, Chapter 6 investigated the effects of differing levels of alcohol consumption within social drinkers and reinforcer type (alcohol vs food) on a PIT paradigm. The results showed a PIT effect for alcohol cues. There was no difference between light and heavy drinking groups in the PIT effect. However, the results suggest a pattern trending towards heavy drinkers displaying a general PIT (i.e. appetitive cues, alcohol related and food-related, increasing motivation for alcohol rewards) and light drinkers displaying specific PIT (i.e. alcohol cues increase alcohol seeking motivation and food cues increase food seeking). However, in addition to there being a non-statistically significant difference between drinking groups, there was also no correlation between TLFB and the PIT effect. Therefore, it must be concluded from that differences in PIT in regards to reward type were not observed. This is consistent with previous research that has shown no correlation between drug dependence and devaluation sensitivity and the PIT effect (Hogarth et al., 2018; Hogarth & Chase, 2011). This result adds to the growing body of evidence that doubts habits importance in addictive behaviour. Taken together with Chapter 3 and Chapter 5, it appears levels of alcohol consumption within a social drinking sample have no measureable effect on any type of associative learning or how they interact.

Two very important limitations to consider for Chapters 3, 5, and 6 is the sample used and the median split used to define groups. Using a median split is not a robust method for creating groups. This flaw is worsened by the fact that the median of the TLFB data varies widely between chapters and therefore the definition of what constitutes a light or heavy drinker also varies widely. The medians are displayed in Table *7.1*. This lack of consistency compromises the ability to compare and draw parallels between the chapters. Using a median split has made it ambiguous as to whether there is no difference between light and heavy social drinkers in this thesis' measurements or whether the group allocation criteria made the groups so arbitrary that they are actually one homogenous sample in regards to alcohol consumption that has been meaninglessly split into two.

The experiments in these chapters would have benefitted from a more robust definition of light and heavy drinkers to align them closer to Chapter 4. A definition such as light drinkers consuming < 14 units per week and heavy drinkers consuming > 20 units per week as one possible example. It should be noted however, that the TLFB data failed to correlate with any measurement in the supplementary analyses of Chapters 3, 5, and 6. This showed associative learning and PIT performance was completely independent of the participants drinking behaviour. This indicates the current samples alcohol consumption history had no effect on associative learning.

Regardless of whether them median split was an adequate method for group allocation, a student sample may not be the most optimal way to measure alcohol-related differences. As the variety of medians from Chapters 3, 5, and 6 showed there was huge variability of drinking behaviour within a student sample. Not only is there huge variability between students, but also within students as students are more likely to consume less alcohol when they face a lot of deadlines and consume more alcohol in periods of celebration (or commiseration) post-deadline. It must also be considered that while some of the heavier student drinkers would meet problematic drinking criteria measured on screening questions (e.g. AUDIT), this problematic or abusive consumption of alcohol will only be present for a limited time in their lives. Most students reduce or cease their heavy drink behaviour after university or by late twenties. It is possible they were not subjected to any maladaptations related to heavy or chronic alcohol use at the time of the experiment. Therefore, it is doubtful that students are a valid analogous sample. As the average age of the AD sample in Chapter 4 was 41.5 years a better analogous sample for the experiments in the other chapters would have been adults of a comparable age. Heavy drinking middle-aged participants might better capture problems associated with problem drinking and would therefore increase comparability with Chapter 4.

Table 7.1. A table displaying the medians and standard deviations of the TLFB data for the main experiments in Chapters 3, 5, and 6

Chapter 3 Med (SD)	Chapter 5 Med (SD)	Chapter 6 Med (SD)
10.95 (23.8)	7.15 (21.4)	20.5 (30.5)

The impulsivity data largely mirrors the social drinking group's data. There was no difference between low and high impulsiveness groups in Pavlovian acquisition and extinction for generic and biologically relevant reinforcers. However, it was repeatedly found that the low impulsiveness group had greater response recovery than the high impulsiveness group. In Chapter 3 and within the spontaneous recovery block of the conditioning experiment of Chapter 5, the low impulsiveness group accounted for the response recovery to a greater extent than the high impulsiveness group. Moreover, within the actual response recovery phase of Chapter 5, this difference was eliminated. This is suggests that when extinction training reaches asymptote, response suppression is strong and equivalent across all individuals. However, when this is not the case, the less impulsive individuals are more sensitive to response recovery. This result is peculiar, but indirectly supported by Papachristou et al. (2014). Papachristou and colleagues found high cravings and low trait impulsivity predicted relapse. If relapse in a product of response recovery to alcohol-related cues, then the experiments in this thesis that show low impulsiveness individuals have greater response recovery align with Papachristou's predictor of relapse. Papachristou claims their results may be different in a larger and younger sample. Every experiment in this thesis has a larger and on average, younger sample. A flaw of the experiments of this thesis and Papachristou et al. (2014) is only one self-report impulsivity measurement was taken (BIS-11). However, impulsivity was a secondary interest of this thesis which explains the use of one impulsivity questionnaire. Therefore, a lot of future research is needed to fully explore the impact of impulsivity (using behavioural measures) in relation to associative learning in AD and reinforcer type and to see if the results of this thesis and Papachristou et al. (2014) are related.

7.3 Conclusions and Directions for Future Research

This thesis answered some important questions in regards to associative learning and drinking status. It can be firmly concluded that light alcohol consumption does not have observable effects on human associative learning in regards for generic CS-US learning and biologically relevant USs. This thesis went part way to support that AD develop REX which could explain the CET. However, more research is needed. The result of impaired extinction in Chapter 4 warrants a new randomised control trial that compares CET to both 1) an ineffective treatment (e.g. relaxation) or waiting list and 2) CBT. For future research like this however, the CET procedure needs to be modified to accommodate the impaired extinction learning by increasing the number of treatment sessions and potentially including extinction reminders via smartphone.

The most supportive evidence for the ACETP would be research demonstrating a difference of associative learning between AD and other psychiatric disorders. Therefore, another future direction would be to expand comparison groups beyond AD and non-dependent. Future research can do similar experiments presented in this thesis, but include anxiety disorder patients and binge eating disorder patients. It could also include a fear US and aversion/ avoidance learning into the reinforcer type variable. If AD performance on a Pavlovian conditioning task displayed a REX and all other comparison groups did not, it would be incontrovertible that alcohol consumption is related REX explains and could explain ACETP.

If individual difference in Pavlovian conditioning do explain the ACETP then another direction for future research would be to determine cause and effect. One method of doing this would be a cross sectional experiment with a sample consisting of between subjects method of differing groups along the alcohol consumption spectrum. Future experiments could compare social drinkers to problematic or prodromal drinkers to AD on a Pavlovian conditioning task (with the relevant number of trials). In addition to this there

the option to delineate AD patients into recently abstinent and long-term abstinent. If social drinkers and long-term abstinent groups had equivalent performance on the Pavlovian task, but significantly better performance than problematic and recently abstinent groups, that would be a very strong indicator that REX plays a central role in explaining ACETP. A second way to do this research is, to do a large scale long term study similar to the IMAGEN consortium. Adolescents from multiple sites can be followed and periodically collect drinking/ drug use data, associative learning data and a battery of cognitive and questionnaire measurements that are relevant to allow us to measure changes overtime.

A final way to test the cause and effect hypothesis is to compare participants on two independent variables: 1) with risk factors for addiction or without, 2) those who drink heavy compared to light drinkers. If the results show those with risk factors regardless of drinking status have impaired associative learning similar to the results of Chapter 4, then it suggest impairment is an antecedent to addiction. If heavy drinkers, but not light drinkers have impairment regardless of risk factors, then it suggests impairment is a result of heavy alcohol use.

Finally, more research is needed into the roles of alcohol consumption and reinforcer type on instrumental learning and Pavlovian-instrumental interaction in humans. Firstly, research needs to be done using a discriminative stimulus instead of a Pavlovian CS. In addition to this, PIT experiments need to be conducted with AD participants. As it is unethical to give alcohol to AD patients, the experiment could compare food with monetary rewards.

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Image of Dog Food (Figure 1.1), Webstockreview.net, accessed 24/01/2019, https://webstockreview.net/explore/pets-clipart-feed-pet/#gal_post_2025_clipart-dog-

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Image of Neutral Face (Figure 1.3), Emojipedia.org, accessed 24/01/2019, https://emojipedia.org/apple/ios-12.1/expressionless-face/
Image of Open Sign (Figure 1.3), Webstockreview.net, accessed 24/01/2019, https://webstockreview.net/explore/open-clipart/#gal_post_1922_open-clipart-1.png
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Image of Red Wine (Figure 1.3), Webstockreview.net, accessed 24/01/2019, https://webstockreview.net/explore/italy-clipart-wine/#gal_post_1524_clipart-food-party-17.png
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Appendix 1 – Information Sheets, Consent Forms, and Debriefing

Chapter 3

Participant Information Sheet

Participant Information Sheet (version number: T2/2016, 07/ 01/ 2016)

Study Title: Associative learning in light and heavy drinkers

Researcher: Carl Buckfield and Steven Glautier
ERGO Study ID number: 18770

Thank you for responding to our appeal for research participants. Please read this information carefully before deciding to take part in this research. If you are happy to participate you will be asked to sign a consent form.

What is the research about?
This is a computer-based experiment designed to study how people learn about predictive and causal relationships in their environment. It is part of an ongoing series of studies carried out at the University of Southampton, all geared towards developing our understanding of human learning.

What will happen to me if I take part?
This is a single 40 minute session comprised of questionnaires and a computer-based experimental task. Your participation involves filling out questionnaires which will take approximately 10 minutes in total and an experimental task that lasts about 30 minutes. We use a variety of different experimental methods, but all experiments have a similar general format. Each experiment will be described in more detail just before you do it. For example, in one experiment you might get a series of trials and on each trial you would be shown images of viruses that had infected a hospital patient. You would then find out whether the patient becomes ill or not. Your task would be to learn which viruses were the most potent causes of illness. Although differing in detail all the experiments are designed to study how people learn to predict events that happen in their environment and each involves simple computer tasks similar to the virus task outlined above.

Are there any risk and benefits in my taking part?
We are not aware of any special risks involved in these experiments, beyond those involved with the operation of a computer. Your participation will help develop scientific approaches to understanding human behaviour and some of these studies we carry out aimed at helping and treat serious problems such as addiction and phobias. Upon completion you will also receive 6 course credits (for Psychology UG only) OR be entered into a prize draw for a chance to win a £50 Amazon voucher. You'll also be able to take a piece of confectionary from a lucky dip bag.

Will my participation be confidential?
All information collected will only be used for the purpose of this study, will only be present anonymously, treated confidentially, and stored on a password protected computer.

What happens if I change my mind?

You may ask any questions that you wish to ask before starting and you are free to withdraw at any time without prejudice.

What happens if something goes wrong?

In the case of any concern or complaint please contact Dr. Steven Glautier in the School of Psychology at University of Southampton (spg@soton.ac.uk or (+44)023-8059-2589). Alternatively you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk
or Dr. Martina Prude, Head of Research Governance (+44)023-8059-5058.

Where can I get more information?

If you would like any additional information please contact Carl Buckfield on cb2g15@soton.ac.uk.

Appendix
Consent Form

CONSENT FORM (version number: T2/2016, 07/ 01/ 2016**)**

Study title: Associative learning in light and heavy drinkers

Researcher name: Carl Buckfield and Steven Glautier
ERGO Study ID number:18770

Please initial the box(es) if you agree with the statement(s):

I have read and understood the information sheet (T22016, 07/ 01/ 2016) and have had the opportunity to ask questions about the study ☐

I agree to take part in this research project and agree for my data to be used for the purpose of this study ☐

I understand my participation is voluntary and I may withdraw at any time without my legal rights being affected ☐

Data Protection
I understand that information collected about me during my participation in this study will be stored on a password protected computer and that this information will only be used for the purpose of this study. All files containing any personal data will be made anonymous.

Name of participant (print name)……

Signature of participant……..

Date……

Debriefing Statement

Debriefing Statement (version number: T2/2016, 07/ 01/ 2016) ERGO ID: 18770
Study Title: Associative learning in light and heavy drinkers
Researchers: Carl Buckfield and Steven Glautier

Thank you for taking part in this experiment. As explained at the start, this is part of a programme of studies running at the University of Southampton's Psychology Department. These studies address questions about the conditions under which people are able to learn about which things are most likely to be causes of significant events.

One of the things this study is looking at is the role of context in learning. Learning is highly context dependent. For example, the meaning of a stimulus can change from one setting to another. If I shouted "fire!" in a restaurant, you'd have a much different reaction to if I shouted "fire!" in a rifle range – the same stimulus, but different response. You may have noticed that the screen background changed during the experiment. This is how we try to study context in our experiments. People learn to predict the different flashes in one context and then we change the context (by changing the screen background) and we can see how well what they learn in one setting transfers to another.

Mechanisms of learning play an important role in drug addiction. People make associations between environmental cues and the positive effects of the drug "high". When they are exposed to these cues it evokes a memory of the "high" and elicits craving which motivates drug seeking behaviour. The aim of this study is to see if people who drink more are better or worse at extinguishing learned associations. Unpublished research in this lab shows preliminary results that those who drink more can more quickly learn to inhibit responses to objects that used to predict a flash outcome when that object no longer predicts said outcome. However, some research suggests that those who drink more become less able to inhibit behaviours and would therefore be slower at learning to inhibit responses when they are no longer appropriate. We're trying to find out which is correct.

Do you have any questions? Once again thank you for taking part, but before you go let's sort out your course credits payment or entry into the prize draw.

If you want to learn more about similar studies and this topic you might like to read:

- Bouton, M., E., (2000). A learning theory perspective on lapse, relapse, and their maintenance of behaviour change. *Health Psychology*, 19, 57-63.
- Glautier, S., Elgueta, T. & Nelson, J,B. (2013). Extinction produces context inhibition and multiple context extinction reduces response recovery in human predictive learning. *Learning and Behaviour*, 41 (4), 341 – 352.

If you have any queries on the background, aim or purpose of this experiment or want to know the results, you may contact Carl Buckfield: email: cb2g15@soton.ac.uk.

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk

If you are experiencing problematic drinking and would like support, I would encourage you to visit your GP. There are also confidential listening services available, including student run listening service Nightline 8am – 8pm everyday on (02380) 59236 OR Drinkline on 03001231110.

Appendix

Drinking Safely

- **Men** should drink no more than 21 units of alcohol per week, no more than four units in any one day, and have at least two alcohol-free days a week.
- **Women** should drink no more than 14 units of alcohol per week, no more than three units in any one day, and have at least two alcohol-free days a week.
- **Pregnant women** or women trying to conceive should not drink alcohol at all.

1 unit

- Half pint of 3.5% beer/ larger/ ale.
- Half a pint of 4% cider.
- 25 ml (one shot) of 40% spirits.
- Half a 175 ml glass (87.5 ml) of 12% wine.

Please go to the app store and add: 'know your numbers (Wessex Academic Health Science Network)' to monitor unit intake to help drink responsibly.

Chapter 4

Participant Information Sheet (for Alcohol-Dependent Participants)

Participant Information Sheet (version number: 2, 24/ 01/ 2017)

Study Title: The effects of alcohol dependence on human associative learning

Researchers: Carl Buckfield, Julia Sinclair and Steven Glautier
ERGO Study ID number: 21201.A2
IRAS Project ID number: 210273

Thank you for responding to our appeal for research participants. Please read this information carefully before deciding to take part in this research. Once you have read the participant information sheet please feel free to ask any questions you feel necessary. Participation is entirely voluntary, if you are happy to participate you will be asked to sign a consent form.

Why have I been asked to take part?
This is a psychology experiment investigating the differences in learning between people with alcohol dependence and occasional drinkers or non-drinkers. To test this properly we need people who fit into each condition.

Who is eligible to take part?
To be eligible you must have been recently dependent on alcohol, but now abstinent and post withdrawal and detox. All participants must also be 18 years or over, not taking benzodiazepine medication, not have consumed alcohol on the day of testing, not had a head injury resulting in an overnight hospital stay in the last year, not have a moderate to severe learning difficulty, not have a physical impairment that impairs you from using a keyboard (e.g. arthritis) and speak English well enough to comprehend the experiment to give full informed consent and comprehend the task to complete it properly.

What is the research about?
This is a computer-based experiment designed to study how people learn about predictive and causal relationships in their environment. It is part of an ongoing series of studies carried out at the University of Southampton, for developing our understanding of human learning. This current experiment is investigating if people with alcohol dependence learn differently to those without. The results of this study will help us understand some of the learning processes in people with alcohol dependence which may have clinical applications for recovery. No images of alcohol are used in this study.

What will happen to me if I take part?
This experiment is a single session lasting up to a maximum of 1 hour. The experiment is comprised of 2 parts. Your participation for the first part involves filling out questionnaires which will take approximately 30 minutes in total. These questionnaires will collect information on things such as your drinking and drug use history, your emotions and personality and how you think and behave in certain situations. Don't worry, all data collected will be confidential among the research team and data will be anonymised. The second part involves the computer task. This task is a computerised game in which you must learn to complete the task. On the computer monitor you will see different objects falling and when they pass a sensor located at the bottom of the screen you must indicate if you think the sensor will flash red, flash green or won't flash by pressing a keyboard key

that represents your response. The computer task lasts about 30 minutes. Approximately 6 weeks after the session, with your permission, we will also contact you with a telephone call (which will last approximately 10 minutes) to follow up if there have been any changes in your level of alcohol consumption.

Are there any risk and benefits in my taking part?
We are not aware of any special risks involved in these experiments, beyond those involved with the operation of a computer. Your participation will help develop scientific understanding of human learning and may help develop more effective treatments for alcohol addiction. Upon completion of the experiment you will receive £10. If you are a psychology student at the University of Southampton you may choose between £10 or 8 course credits for completing the experiment. In addition to this any travel costs will be reimbursed.

Will my participation be confidential?
All information which is collected about you during the course of the research will be kept strictly confidential and will conform to the Data Protection Act of 1998 with respect to data collection, storage and destruction. Unless there is information which puts you or others at serious risk of harm, information collected in the study will not be shared without your consent. A code number will be used to identify data about you, and we will keep the list that links codes to people's identity locked separately room the study data. Your name will not be used in any reports or publications. Records of the study will be held for 10 years.

What happens if I change my mind?
You may ask any questions that you wish before starting and you are free to withdraw at any time without prejudice.

What happens if something goes wrong?
In the case of any concern or complaint please contact either Dr. Julia Sinclair in the Faculty of Medicine at University of Southampton (Julia.Sinclair@soton.ac.uk or (023) 8071 8520) or Dr. Steven Glautier in the School of Psychology at University of Southampton (spg@soton.ac.uk or (+44)023-8059-2589).

Alternatively you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk.

Where can I get more information?
If you would like any additional information please contact Carl Buckfield (PhD student and principle investigator) on cb2g15@soton.ac.uk or 07375 997312.

Participant Information Sheet (for Control Participants)

Participant Information Sheet (version number: 3, 24/ 01/ 2017)

Study Title: The effects of alcohol dependence on human associative learning

Researchers: Carl Buckfield, Julia Sinclair and Steven Glautier
ERGO Study ID number: 21201.A2
IRAS Project ID number: 210273

Thank you for responding to our appeal for research participants. Please read this information carefully before deciding to take part in this research. Once you have read the participant information sheet please feel free to ask any questions you feel necessary. Participation is entirely voluntary, if you are happy to participate you will be asked to sign a consent form.

Why have I been asked to take part?
This is a psychology experiment investigating the differences in learning between people with alcohol dependence and occasional drinkers or non-drinkers. To test this properly we need people who fit into each condition.

Who is eligible to take part?
To be eligible you must have a history of drinking very little alcohol or none at all. All participants must also be 18 years or over, not taking benzodiazepine medication, not have consumed alcohol on the day of testing, not had a head injury resulting in an overnight hospital stay in the last year, not have a moderate to severe learning difficulty, not have a physical impairment that impairs you from using a keyboard (e.g. arthritis) and speak English well enough to comprehend the experiment to give full informed consent and comprehend the task to complete it properly.

What is the research about?
This is a computer-based experiment designed to study how people learn about predictive and causal relationships in their environment. It is part of an ongoing series of studies carried out at the University of Southampton, for developing our understanding of human learning. This current experiment is investigating if people with alcohol dependence learn differently to those without. The results of this study will help us understand some of the learning processes in people with alcohol dependence which may have clinical applications for recovery. No images of alcohol are used in this study.

What will happen to me if I take part?
This experiment is a single session lasting up to a maximum of 1 hour. The experiment is comprised of 2 parts. Your participation for the first part involves filling out questionnaires which will take approximately 30 minutes in total. These questionnaires will collect information on things such as your drinking and drug use history, your emotions and personality and how you think and behave in certain situations. Don't worry, all data collected will be confidential among the research team and data will be anonymised. The second part involves the computer task. This task is a computerised game in which you must learn to complete the task. On the computer monitor you will see different objects falling and when they pass a sensor located at the bottom of the screen you must indicate if you think the sensor will flash red, flash green or won't flash by pressing a keyboard key that represents your response. The computer task lasts about 30 minutes.

Appendix

Are there any risk and benefits in my taking part?

We are not aware of any special risks involved in these experiments, beyond those involved with the operation of a computer. Your participation will help develop scientific understanding of human learning and may help develop more effective treatments for alcohol addiction. Upon completion of the experiment you will receive £10. If you are a psychology student at the University of Southampton you may choose between £10 or 8 course credits for completing the experiment. In addition to this any travel costs will be reimbursed.

Will my participation be confidential?

All information which is collected about you during the course of the research will be kept strictly confidential and will conform to the Data Protection Act of 1998 with respect to data collection, storage and destruction. Unless there is information which puts you or others at serious risk of harm, information collected in the study will not be shared without your consent. A code number will be used to identify data about you, and we will keep the list that links codes to people's identity locked separately rom the study data. Your name will not be used in any reports or publications. Records of the study will be held for 10 years.

What happens if I change my mind?

You may ask any questions that you wish before starting and you are free to withdraw at any time without prejudice.

What happens if something goes wrong?

In the case of any concern or complaint please contact either Dr. Julia Sinclair in the Faculty of Medicine at University of Southampton (Julia.Sinclair@soton.ac.uk or (023) 8071 8520) or Dr. Steven Glautier in the School of Psychology at University of Southampton (spg@soton.ac.uk or (+44)023-8059-2589).

Alternatively you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk.

Where can I get more information?

If you would like any additional information please contact Carl Buckfield (PhD student and Principle Investigator) on cb2g15@soton.ac.uk or 07375 997312.

Consent Form (for Alcohol-Dependent Participants)

CONSENT FORM (version number: 2, 24/ 01/ 2017**)**

Study title: The effects of alcohol dependence on associative learning

Researchers: Carl Buckfield, Julia Sinclair and Steven Glautier
ERGO Study ID number: 21201.A2
IRAS Project ID number: 210273

Please initial the box(es) if you agree with the statement(s):

I have read and understood the information sheet (2, 24/ 01/ 2017) and have had the opportunity to ask questions about the study	☐
I agree to take part in this research project and agree for my data to be used for the purpose of this study	☐
I agree to give my contact details to be contacted in a post experiment follow-up.	☐
I agree for my data to be shared confidentially within the research team.	☐
I understand that relevant sections of my data collected during the study, may be looked at by individuals from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this data.	☐
I understand my participation is voluntary and I may withdraw at any time without my legal rights being affected	☐

Data Protection
I understand that information collected about me during my participation in this study will be stored on a password protected computer and that this information will only be used for the purpose of this study. All files containing any personal data will be made anonymous.

Name of participant (print name)……

Signature of participant……..

Date……

Name of researcher……CARL BUCKFIELD…….

Appendix

Signature of Researcher…………………………………………………………..

Date…………………………………………………………………………………

Consent Form (for Control Participants)

CONSENT FORM (version number: 3, 24/ 01/ 2017**)**

Study title: The effects of alcohol dependence on associative learning

Researchers: Carl Buckfield, Julia Sinclair and Steven Glautier
ERGO Study ID number: 21201.A2
IRAS Project ID number: 210273

Please initial the box(es) if you agree with the statement(s):

I have read and understood the information sheet (3, 24/ 01/ 2017) and have had the opportunity to ask questions about the study	☐
I agree to take part in this research project and agree for my data to be used for the purpose of this study	☐
I agree for my data to be shared confidentially within the research team.	☐
I understand that relevant sections of my data collected during the study, may be looked at by individuals from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this data.	☐
I understand my participation is voluntary and I may withdraw at any time without my legal rights being affected	☐

Data Protection
I understand that information collected about me during my participation in this study will be stored on a password protected computer and that this information will only be used for the purpose of this study. All files containing any personal data will be made anonymous.

Name of participant (print name)……

Signature of participant……..

Date……

Name of researcher……CARL BUCKFIELD…….

Signature of Researcher……………………………………………………………..

Date………………………………………………………………………………

Debriefing Statement (for Alcohol-Dependent Participants)

Debriefing Statement (version number: 4, 29/ 03/ 2017) ERGO ID: 21201.A2
IRAS ID: 210273

Study Title: The effects of alcohol dependence on human associative learning
Researchers: Carl Buckfield, Julia Sinclair and Steven Glautier

Thank you for taking part in this experiment, which investigated if people with alcohol dependence have a different way of linking events and objects (called learned associations) which may have an impact on their recovery. Many of our thoughts and actions (both the ones that we are aware of as well as those happening unconsciously) are controlled by learned associations. For instance you may feel hungry at the smell of nice food and run out of a building when you hear a fire alarm. It is believed this is true for addiction as well. The sight and smell of alcohol or the sight of a beer glass or a place where you drink become paired with positive feelings. Therefore exposure to these objects or places can trigger cravings for alcohol and may trigger relapse. This study was looking to see if there are differences between alcohol dependent and non-dependent people in how they acquire and "unlearn" learned associations.

The results of this study (and others like it) could help in the design of future experiments to see if treatments that help dependent people "unlearn" the pairing of the sight of alcohol with positive associations may reduce cravings and help prevent relapse.

This experiment compared two groups. People with alcohol dependence in the early stage of recovery, with people who drink very little or no alcohol.

Do you have any questions? Once again thank you for taking part, but before you go let's sort out your payment.

If you have any queries on the background, aim or purpose of this experiment or want to know the results, you may contact Carl Buckfield: email: cb2g15@soton.ac.uk.

If you have any concerns ***about your*** recovery please contact GP or recovery team.

- For Society of St. James patients please contact Dean Latona (Psychosocial Treatment Manager): 07872 317056

- For Manor Clinic patients please contact Jane Willet (Centre Manager): 02380464721

If you have any immediate concerns, we will assist you in making contact with them.

In the unlikely event they are not available, the researcher will contact Dr Julia Sinclair (honorary consultant in alcohol liaison) who will offer assistance.

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk

Appendix
Debriefing Statement (for Control Participants)

Debriefing Statement (version number: 5, 29/ 03/ 2017) ERGO ID: 21201.A2
IRAS ID: 210273

Study Title: The effects of alcohol dependence on human associative learning
Researchers: Carl Buckfield, Julia Sinclair and Steven Glautier

Thank you for taking part in this experiment, which investigated if people with alcohol dependence have a different way of linking events and objects (called learned associations) which may have an impact on their recovery. Many of our thoughts and actions (both the ones that we are aware of as well as those happening unconsciously) are controlled by learned associations. For instance you may feel hungry at the smell of nice food and run out of a building when you hear a fire alarm. It is believed this is true for addiction as well. The sight and smell of alcohol or the sight of a beer glass or a place where you drink become paired with positive feelings. Therefore exposure to these objects or places can trigger cravings for alcohol and may trigger relapse. This study was looking to see if there are differences between alcohol dependent and non-dependent people in how they acquire and "unlearn" learned associations.

The results of this study (and others like it) could help in the design of future experiments to see if treatments that help dependent people "unlearn" the pairing of the sight of alcohol with positive associations may reduce cravings and help prevent relapse.

This experiment compared two groups. People with alcohol dependence in the early stage of recovery, with people who drink very little or no alcohol.

Do you have any questions? Once again thank you for taking part, but before you go let's sort out your payment or course credits.

If you have any queries on the background, aim or purpose of this experiment or want to know the results, you may contact Carl Buckfield: email: cb2g15@soton.ac.uk.

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk

Drinking Safely

- **Men** should drink no more than 21 units of alcohol per week, no more than four units in any one day, and have at least two alcohol-free days a week.
- **Women** should drink no more than 14 units of alcohol per week, no more than three units in any one day, and have at least two alcohol-free days a week.
- **Pregnant women** or women trying to conceive should not drink alcohol at all.

If you ever experience problematic drinking and would like support, I would encourage you to visit your GP. There are also confidential listening services available, including Drinkline on 03001231110 OR call No Limits on **02380 224224 and arrange to go to their drugs and alcohol advice centre.**

Chapter 5

Pilot study

Participant Information Sheet

Participant Information Sheet (version number: 1, 13/09/16)

Study Title: Alcohol Detection - Pilot
Researcher: Carl Buckfield, Jahn Hartland, Julia Sinclair and Steven Glautier
ERGO Study ID number: 23697

Thank you for responding to our appeal for research participants. Please read this information carefully before deciding to take part in this research. If you are happy to participate you will be asked to sign a consent form.

What is the research about?
This is an experiment designed to study if people can detect whether a drink contains alcohol by sight and taste. This is a pilot study to help us select stimuli used for future alcohol consumption studies. It is part of an ongoing series of studies carried out at the University of Southampton, all geared towards developing our understanding of the role of learning in addiction.

What will happen to me if I take part?
This is a single session, lasting no more than 15 minute comprised of a questionnaire and a perception task. Your participation involves filling out a questionnaire which will take 2 minutes or less and a perception task that lasts about 10 minutes. The perception task consists of two parts. The first part you will have to choose which of two identical rooms contain alcoholic drinks. The second part you will be presented with drink pairs and have to choose which in the pairs contains alcohol from sight and taste.

Are there any risk and benefits in my taking part?
If you are pregnant or trying to conceive or taking ANY medication that adversely interacts with alcohol we advise you do not participate in this experiment. We are not aware of any special risks involved in these experiments. Alcohol consumption will be limited to approximately 1 unit. This is unlikely to result in blood/breath alcohol levels that exceed the legal limit for driving. However, we advise you to take care to be aware of your surroundings and not to operate heavy machinery or drive for up to 3 hours after the experiment. Your participation will help develop scientific approaches to understanding human behaviour and some of these studies we carry out aimed at helping and treat serious problems such as addiction and phobias. Upon completion you will also receive 3 course credits (for Psychology UG only) OR £2.

Will my participation be confidential?
All information collected will only be used for the purpose of studies in this series of studies for Carl Buckfield's PhD thesis and Jahn Hartland's 3rd year project. All information used for these purposes will only be present anonymously, treated confidentially, and stored on a password protected computer.

What happens if I change my mind?
You may ask any questions that you wish to ask before starting and you are free to withdraw at any time without prejudice.

What happens if something goes wrong?
In the case of any concern or complaint please contact Dr. Steven Glautier in the School of Psychology at University of Southampton (spg@soton.ac.uk or (+44)023-8059-2589). Alternatively you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk
or Dr. Martina Prude, Head of Research Governance (+44)023-8059-5058.

Where can I get more information?
If you would like any additional information please contact Carl Buckfield on cb2g15@soton.ac.uk.

Consent Form

CONSENT FORM (version number: 1, 13/09/2016**)**

Study title: Alcohol Detection - Pilot

Researcher name: Carl Buckfield, Jahn Hartland, Julia Sinclair and Steven Glautier
ERGO Study ID number: 23697

Please initial the box(es) if you agree with the statement(s):

I have read and understood the information sheet (1, 13/09/2016) and have had the opportunity to ask questions about the study	☐
I agree to take part in this research project and agree for my data to be used for the purpose of this study	☐
I understand and agree to the consumption of alcohol for the purpose of this study	☐
I declare, to the best of my knowledge, I am not pregnant or trying to conceive	☐
I declare I am not taking ANY medication that adversely interacts with alcohol	☐
I understand my participation is voluntary and I may withdraw at any time without my legal rights being affected	☐

Data Protection
I understand that information collected about me during my participation in this study will be stored on a password protected computer and that this information will only be used for the purpose of this study. All files containing any personal data will be made anonymous.

Name of participant (print name)……

Signature of participant……..

Date……

Appendix
Debriefing Statement

Debriefing Statement (version number: 1, 13/09/2016) ERGO ID: 23697
Study Title: Alcohol Detection - Pilot
Researchers: Carl Buckfield, Jahn Hartland, Julia Sinclair and Steven Glautier

Thank you for taking part in this experiment. As explained at the start, this is part of a programme of studies running at the University of Southampton's Psychology Department. This study was a pilot study to help us select the most suitable stimuli to use for future experiments. The series of studies running at this University of which these stimuli may be used, addresses questions about the conditions under which people are able to learn.

One of the things this study is looking at is whether people can detect the difference between alcoholic and dealcoholised beverages. Placebo drinks are an important component of alcohol related research. In some cases it is important to know whether participants can distinguish between alcoholic and placebo drinks on the basis of sight, smell and taste. The quality of dealcoholised drinks have vastly improved recently and this study was concerned with the degree to which they are similar to their alcoholic counter-part.

One improvement of dealcoholised drinks is the complete removal of ethanol. Historically non-alcoholic beverages contained 0.5% ABV whereas now they are 0%. This has important clinical applications for alcohol dependent patients who are trying to remain abstinent, but want to drink non-alcoholic beverages. There is research to suggest heavy drinkers are better at detecting the difference between alcoholic and non-alcoholic drinks. The results of this study will help us select the most suitable stimuli to use for experiments looking at cue reactivity and learning in alcohol dependent populations.

Do you have any questions? Once again thank you for taking part, but before you go let's sort out your course credits or monetary payment.

If you want to learn more about similar studies and this topic you might like to read:

- Glautier, S., Taylor, C. & Remington, B. (1992). A method for producing alcohol placebos. *British Journal of Addiction*, 87, 303-308.

If you have any queries on the background, aim or purpose of this experiment or want to know the results, you may contact Carl Buckfield: email: cb2g15@soton.ac.uk.

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk

If you are experiencing problematic drinking and would like support, I would encourage you to visit your GP. There are also confidential listening services available, including student run listening service Nightline 8am – 8pm everyday on (02380) 59236 OR Drinkline on 03001231110.

Drinking Safely

- **Men** should drink no more than 21 units of alcohol per week, no more than four units in any one day, and have at least two alcohol-free days a week.
- **Women** should drink no more than 14 units of alcohol per week, no more than three units in any one day, and have at least two alcohol-free days a week.
- **Pregnant women** or women trying to conceive should not drink alcohol at all.

1 unit

- Half pint of 3.5% beer/ larger/ ale.
- Half a pint of 4% cider.
- 25 ml (one shot) of 40% spirits.
- Half a 175 ml glass (87.5 ml) of 12% wine.

Please go to the app store and add: ‘know your numbers (Wessex Academic Health Science Network)’ to monitor unit intake to help drink responsibly.

Appendix
Disclaimer

Disclaimer (version number: 1, 26/09/2016) ERGO ID: 23697

Study Title: Alcohol Detection - Pilot
Researchers: Carl Buckfield, Jahn Hartland, Julia Sinclair and Steven Glautier

I understand that my participation in this experiment involved consumption of a small dose of alcohol (maximum of 1.14 standard units). I have been advised by the experimenter that although my breath alcohol level may be below the legal limit for driving that I should not, for 3 hours after the termination of the experiment, drive, operate machinery, or undertake any activity that may be dangerous after alcohol consumption. I have been advised that I may, if I so wish, remain in the laboratory for a period of time until my breath alcohol level falls to zero. I however, I'm choosing to leave the laboratory before my breath alcohol level is 0.

Participant's Name (Print)……

Participant's Signature…….

Date……..

Conditioning Experiment

Participant Information Sheet

Participant Information Sheet (version number: 3, 27/ 04/ 2017)

Study Title: Associative learning with an Alcohol Unconditioned Stimulus in Light and Heavy Drinkers.

Researcher: Carl Buckfield, Julia Sinclair and Steven Glautier
ERGO Study ID number: 28666

Thank you for responding to our appeal for research participants. Please read this information carefully before deciding to take part in this research. If you are happy to participate you will be asked to sign a consent form.

What is the research about?
This is a computer-based experiment designed to study how people learn the environment predicts food and drink. It is part of an ongoing series of studies carried out at the University of Southampton, all geared towards developing our understanding of human learning.

What will happen to me if I take part?
This experiment is comprised of 15 sessions; 3 session per day for 5 days. Each session (except the final) takes 35 minutes (the final takes 2 minutes). There is also a 60 minute break in between each session. Therefore, each day of testing takes 3 hours and 45 minutes and the entire experiment takes 18 hours and 45 minutes of your time. In addition to this after each day of testing you may have a Blood Alcohol Concentration (BAC) level greater than 0. On these days we advise you to stay in the lab until BAC reaches 0. Staying would increase the overall experiment time to 22 hours. This is optional and you'd have to sign a disclaimer to leave. If you do stay you will receive payment for this time. You are asked to not eat anything for 2 hours prior to every day you come to the lab. In the first session your participation involves filling in 3 questionnaires and doing a computer task. The task is a computerised game in which you must learn which coloured shapes win a reward of either drink or food. Sometimes the drink reward can be alcoholic. For every session after the first session you will only do the computer task. The maximum number of alcohol units per session will be 2.4; alcohol could appear in any session, but you will not be told which ones in advance. There can sometimes be a maximum of 4.8 units per day (you will not be told which days in advance). Due to the amount of hours alcohol consumption is spread across, BAC levels will never reach 4.8 units at any given time.

Are there any risk and benefits in my taking part?
If you are pregnant or trying to conceive or taking ANY medication* that adversely interacts with alcohol we advise you do not participate in this experiment. We are not aware of any special risks involved in these experiments, beyond those involved with the operation of a computer. You will have consumed alcohol that is likely to produce detectable subjective effects so we recommend you stay in the lab until your BAC=0. You may however sign a disclaimer and leave before this time. If you do leave early we advise you stay safe and do not drive or operate heavy machinery for up to 3 hours after the session.

Appendix

Your participation will help develop scientific approaches to understanding human behaviour and some of these studies we carry out aimed at helping and treat serious problems such as addiction and phobias. Upon completion of the experiment you will receive a minimum of 225 course credits (for psychology students) or £112.5 if you sign the disclaimer and leave or a maximum of 264 course credits (for psychology students) or £132 if you do stay.

*the most common, **but not complete list** of medication are: any anti-depressants, Valium, Xanax, Aspirin, Ibuprofen, Paracetamol, Codeine, Metformin, Olanzapine, Quetiapine, Metronidazole, Tinidaozle, Cycloserine, Ketoconazole.

Will my participation be confidential?

All information collected will only be used for the purpose of this study, will only be present anonymously, treated confidentially within the research team, and stored on a password protected computer.

What happens if I change my mind?

You may ask any questions that you wish to ask before starting and you are free to withdraw at any time without prejudice.

What happens if something goes wrong?

In the case of any concern or complaint please contact Dr. Steven Glautier in the School of Psychology at University of Southampton (spg@soton.ac.uk or (+44)023-8059-2589). Alternatively you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk.

Where can I get more information?

If you would like any additional information please contact Carl Buckfield on cb2g15@soton.ac.uk.

Consent Form

CONSENT FORM (version number: 2, 27/ 04/ 2017**)**

Study title: Associative learning with an Alcohol Unconditioned Stimulus in Light and Heavy Drinkers.

Researcher name: Carl Buckfield, Julia Sinclair and Steven Glautier
ERGO Study ID number: 28666

Please initial the box(es) if you agree with the statement(s):

I have read and understood the information sheet (3, 27/ 04/ 2017) and have had the opportunity to ask questions about the study ☐

I agree to take part in this research project and agree for my data to be used for the purpose of this study ☐

I understand and agree to the consumption of alcohol for the purpose of this study ☐

I declare, to the best of my knowledge, I am not pregnant or trying to conceive ☐

I declare I am not taking ANY medication* that adversely interacts with alcohol ☐

*the most common, **but not complete list** of medication are: any anti-depressants, Valium, Xanax, Aspirin, Ibuprofen, Paracetamol, Codeine, Metformin, Olanzapine, Quetiapine, Metronidazole, Tinidaozle, Cycloserine, Ketoconazole.

I have not been advised, for medical or other reasons, to avoid alcohol ☐

I understand my participation is voluntary and I may withdraw at any time without my legal rights being affected ☐

Data Protection
I understand that information collected about me during my participation in this study will be stored on a password protected computer and that this information will only be used for the purpose of this study. All files containing any personal data will be made anonymous.

Name of participant (print name)……

Signature of participant……………………………………………………………..

Date………………………………………………………………………………

Debriefing Statement

Debriefing Statement (version number: 2, 27/ 04/ 2017) ERGO ID: 28666

Study Title: Associative learning with an Alcohol Unconditioned Stimulus in Light and Heavy Drinkers.

Researchers: Carl Buckfield, Julia Sinclair and Steven Glautier.

Thank you for taking part in this experiment. As explained at the start, this is part of a programme of studies running at the University of Southampton's Psychology Department. These studies address questions about the conditions under which people are able to learn when the environment predicts drink or food.

Learning about the availability of alcohol plays an important role in addiction. People make associations between environmental stimuli and the subjective feeling of being inebriated. When they are exposed to these stimuli it can trigger cravings and relapse in people with alcohol dependence. Cue-exposure therapy (CET) is a behavioural treatment for addiction in which conditioned stimuli that are associated with alcohol are exposed to patients when alcohol drinking is withheld (i.e. in extinction) to attempt to weaken the association and therefore weaken cravings by extension. Research shows CET does not reliably treat addiction, but it is very successful for other disorders which are learned through similar mechanisms (e.g. phobias, OCD, binge eating to name a few). Therefore this study is attempting to see if there are differences between light and heavy drinkers in learning about alcohol and another biologically significant reward (i.e. food) to help understand why CET doesn't always treat addiction.

Another aspect of this study is looking at is the role of context in learning. Learning is highly context dependent. For example, the meaning of a stimulus can change from one setting to another. If I shouted "fire!" in a restaurant, you'd have a much different reaction to if I shouted "fire!" in a rifle range – the same stimulus, but different response. You may have noticed that the screen background changed during the experiment. This is how we try to study context in our experiments. People learn the associations in one context and then we change the context (by changing the screen background) and we can see how well what they learn in one setting transfers to another.

Do you have any questions? Once again thank you for taking part, but before you go let's sort out your payment or course credits.

If you want to learn more about similar studies and this topic you might like to read:

- Conklin, C., A. & Tiffany, S., T. (2002). Applying extinction research and theory to cue-exposure addiction treatments. *Addiction*, 97 (2), 155-167.

- Everitt, B., J. & Robbins, T., W. (2016). Drug Addiction: Updating actions to habits to compulsion 10 years on. *Annual Review of Psychology*, 67, 23-50.

- Glautier, S., Elgueta, T. & Nelson, J,B. (2013). Extinction produces context inhibition and multiple context extinction reduces response recovery in human predictive learning. *Learning and Behaviour*, 41 (4), 341 – 352.

- Minkea, S. & Oehlberg, K. (2008). The relevance of recent developments in classical conditioning to understand the etiology and maintenance of anxiety disorders. *Acta Psychologica*, 127 (3), 567-580.

If you have any queries on the background, aim or purpose of this experiment or want to

know the results, you may contact Carl Buckfield: email: cb2g15@soton.ac.uk.

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk

If you are experiencing problematic drinking and would like support, I would encourage you to visit your GP. There are also confidential listening services available, including student run listening service Nightline 8am – 8pm everyday on (02380) 59236 OR Drinkline on 03001231110.

Drinking Safely

- **Men** should drink no more than 21 units of alcohol per week, no more than four units in any one day, and have at least two alcohol-free days a week.
- **Women** should drink no more than 14 units of alcohol per week, no more than three units in any one day, and have at least two alcohol-free days a week.
- **Pregnant women** or women trying to conceive should not drink alcohol at all.

1 unit

- Half pint of 3.5% beer/ larger/ ale.
- Half a pint of 4% cider.
- 25 ml (one shot) of 40% spirits.
- Half a 175 ml glass (87.5 ml) of 12% wine.

Please go to the app store and add: 'know your numbers (Wessex Academic Health Science Network)' to monitor unit intake to help drink responsibly.

Disclaimer

Disclaimer (version number: 2, 27/04/17) ERGO ID: 28666

Study Title: Associative learning with an Alcohol Unconditioned Stimulus in Light and Heavy Drinkers.
Researchers: Carl Buckfield, Julia Sinclair and Steven Glautier

I understand that my participation in this experiment involved consumption of a small dose of alcohol (maximum of 2.4 standard units). I have been advised by the experimenter that I should not, for 3 hours after the termination of the experiment, drive, operate machinery, or undertake any activity that may be dangerous after alcohol consumption. I have been advised that I may, if I so wish, remain in the laboratory for a period of time until my breath alcohol level falls to zero. I however, I'm choosing to leave the laboratory before my breath alcohol level is 0.

Participant's Name (Print)……

Participant's Signature……

Date……..

Appendix
Chapter 6

Participant Information Sheet

Participant Information Sheet (version number: 1; date: 25/1/18)

Study Title: Pavlovian and instrumental learning with an alcoholic unconditioned stimulus in light and heavy social drinkers

Researchers: Carl Buckfield, Dr. Steven Glautier, Dr. Julia Sinclair.
Research assistant; Harry Barnard and Elenie Biscombe.
ERGO number: 31723

Please read this information carefully before deciding to take part in this research. It is up to you to decide whether or not to take part. If you are happy to participate you will be asked to sign a consent form.

What is the research about?
This is experiment is for Carl Buckfield's PhD. This is a computer-based experiment designed to study how people learn when the environment predicts food and drink. It is part of an ongoing series of studies carried out at the University of Southampton, all geared towards developing our understanding of human learning.

What will happen to me if I take part?
This experiment is comprised of two visits to the lab across two days. We ask for you to fast for two hours prior to arriving at the lab both days. The first visit to the lab will last 1 hour and 40 minutes. If you consent to take part you will start off by completing three questionnaires. These will be followed by completing a nine minute computer task. The task is a computerised game in which you must learn which coloured shapes predict a reward of either beer or chocolate. You will do this task a second time after a one hour break. The maximum amount of alcohol consumed during these two tasks will be one unit. After this you will start a new task. During this task you must choose between pressing one of two keyboard keys. If you press correctly you could win beer or chocolate. If you guess incorrectly, you win nothing. The maximum number of alcohol that can potentially be consumed during this task 2.16 units. This task will take five minutes. At this point you first day at the lab will come to an end. As you will have a blood alcohol level (BAL) above 0 you will be asked to sign a disclaimer before you leave stating you are aware you have consumed alcohol and know not to drive or operate heavy machinery up to three hours after leaving the lab. Day two will start on the day immediately after the first. You will come to the lab and read statements on beer or chocolate and answer questions about the statements. This will only take three minutes. After this, you will redo the key choice task, however this time you will not receive immediate rewards and will not receive feedback on their performance until after the task. This will take five minutes. You will then be debriefed and paid. Therefore, the entire experiment will take no longer than 1 hour and 50 minutes.

Are there any benefits in my taking part?
Your participation will help develop scientific approaches to understanding human behaviour and some of these studies we carry out aimed at helping and treat serious problems such as addiction and phobias. Upon completion of the experiment you will receive 20 course credits (for psychology students) or £10 (or a mixture of both). You will also get to drink free beer and eat free chocolate as part of the experiment.

Are there any risks involved?
If you are pregnant or trying to conceive or taking ANY medication* that adversely interacts with alcohol we advise you do not participate in this experiment. We also advise you not to drive for up to three hours after the experiment on both days. We are not aware of any special risks involved in these experiments, beyond those involved with the operation of a computer. You will have consumed alcohol (a maximum of two units) that could produce detectable subjective effects. We advise you stay safe and do not drive or operate heavy machinery for up to 3 hours after the session.

Will my participation be confidential?
Data sharing, preservation and access will comply with all aspects of the Data Protection Act 1998. All information collected will only be used for the purpose of this and related studies, will be kept strictly confidential within the research team, made anonymous, and stored on a password protected computer. Data will only be present anonymously. Anonyminity will be ensured by participants being given a unique ID, which will be the only identifier on questionnaires and names will only appear on consent forms. A single sheet of paper will link the ID to the participant's name. This paper will be kept in a locked filing cabinet in a locked room which only the research team have access to. The paper will be destroyed after the anonymised data has been checked and input into a password protected computer. All hard copies of consent forms and questionnaires will be kept in locked cabinets in locked rooms within the University's Psychology Department at Highfield Campus and then archived as per department policy.

What should I do if I want to take part?
If you wish to take part please tell the experimenter and they'll answer any questions and start the informed written consent process with you.

What happens if I change my mind?
You may ask any questions that you wish to ask before starting and you are free to withdraw at any time without prejudice.

What will happen to the results of the research?
The research forms a substantive part of Carl Buckfield's PhD work and for future related projects. Results will be presented as part of his final thesis and abstracts will be submitted at regional and national meetings throughout his candidature (e.g. The Society for the Study of Addictions conferences and symposiums). Results will also be written up for publication in peer reviewed scientific journals. The results of the study will be anonymised and will not identify individuals taking part in any way.

If you would like a copy of the results please let the researcher know at any time throughout your duration of the experiment or by contacting the researcher via the contact details in this document which can also be found in the debriefing statement (given to you upon completion of this experiment).

Where can I get more information?
If you would like any additional information please contact Carl Buckfield on cb2g15@soton.ac.uk.

What happens if something goes wrong?
In the case of any concern or complaint please contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059

Appendix
3856, email fshs-rso@soton.ac.uk.

Thank you for taking the time to read the information sheet and considering taking part in this experiment.

Consent Form

CONSENT FORM (version number: 1; date: 25/1/18)

Study title: Pavlovian and instrumental learning with an alcoholic unconditioned stimulus in light and heavy social drinkers

Researcher names: Carl Buckfield, Dr. Julia Sinclair, Dr Steven Glautier.
Research assistants: Harry Barnard and Elenie Biscome.
ERGO number: **ERGO number:** 31723

Please initial the box(es) if you agree with the statement(s):

I have read and understood the information sheet (**version number: 1; date: 25/1/18**) and have had the opportunity to ask questions about the study.	
I agree to take part in this research project and agree for my data to be used for the purpose of this study and for future related projects.	
I understand and agree to the consumption of alcohol for the purpose of this study.	
I declare, to the best of my knowledge, I am not pregnant or trying to conceive	
I declare I am not taking ANY medication* that adversely interacts with alcohol. *the most common, **but not complete list** of medication are: any anti-depressants, Valium, Xanax, Aspirin, Ibuprofen, Paracetamol, Codeine, Metformin, Olanzapine, Quetiapine, Metronidazole, Tinidaozle, Cycloserine, Ketoconazole.	
I have not been advised, for medical or other reasons, to avoid alcohol.	
I understand my responses will be anonymised in reports of the research.	
I understand my participation is voluntary and I may withdraw (at any time) for any reason without my rights being affected.	

Data Protection
I understand that information collected about me during my participation in this study will be stored on a password protected computer and that this information will only be used for the purpose of ethically approved research studies.

Name of participant (print name)……

Signature of participant………………………………………………………………………

Date…………………………………………………………………………………………..

Debriefing Statement

Debriefing Statement (version 1; date 25/1/18)
Study title: Pavlovian and instrumental learning with an alcoholic unconditioned stimulus in light and heavy social drinkers

ERGO ID: 31723
Researchers: Carl Buckfield, Dr. Julia Sinclair and Dr. Steven Glautier.
Research assistants: Harry Barnard and Elenie Biscombe.

Thank you for taking part in this experiment. As explained at the start, this is part of a programme of studies running at the University of Southampton's Psychology Department. These studies address questions about the conditions under which people are able to learn when the environment predicts drink or food.

Pavlovian conditioning (learning about the contingency of environmental stimuli and outcomes) and instrumental conditioning (learning about the contingency of ones actions and outcomes) both play important and interacting roles in developing and maintaining addictions. These influences can become so strong that alcohol dependent people seek and drink alcohol even when they know it will have adverse effects. Cue-exposure therapy (CET) is a behavioural treatment for addiction in which Pavlovian conditioned stimuli that are associated with alcohol are exposed to patients when alcohol drinking is withheld (i.e. in extinction) to attempt to weaken the association and therefore weaken cravings by extension. Research shows CET does not reliably treat addiction. CET only attempts to degrade Pavlovian learning, but instrumental learning left untouched. Therefore this study is attempting to see if there are differences between light and heavy drinkers in their ability to learn Pavlovian and instrumental associations and a difference between these two groups in how Pavlovian cues exert control over instrumental behaviour. Hence the final task in which the Pavlovian cues wit intermittently present after we attempted to devalue the reward by highlighting the health concerns surrounding them.

Do you have any questions? Once again thank you for taking part, but before you go let's sort out your payment or course credits.

If you want to learn more about similar studies and this topic you might like to read:

- Conklin, C., A. & Tiffany, S., T. (2002). Applying extinction research and theory to cue-exposure addiction treatments. *Addiction*, 97 (2), 155-167.

- Everitt, B., J. & Robbins, T., W. (2016). Drug Addiction: Updating actions to habits to compulsion 10 years on. *Annual Review of Psychology*, 67, 23-50.

- Hogarth, L. & Chase, H., W. (2011). Parallel goal-directed and habitual control of human drug-seeking: Implications for dependence vulnerability. *Journal of Experimental Psychology*, 37 (3), 261-276.

If you have any queries on the background, aim or purpose of this experiment or want to know the results, you may contact Carl Buckfield: email: cb2g15@soton.ac.uk.

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: +44 (0)23 8059 3856, email fshs-rso@soton.ac.uk

Appendix

If you are experiencing problematic drinking and would like support, I would encourage you to visit your GP. There are also confidential listening services available, including student run listening service Nightline 8am – 8pm everyday on (02380) 59236 OR Drinkline on 03001231110.

Drinking Safely

- **Men** should drink no more than 21 units of alcohol per week, no more than four units in any one day, and have at least two alcohol-free days a week.
- **Women** should drink no more than 14 units of alcohol per week, no more than three units in any one day, and have at least two alcohol-free days a week.
- **Pregnant women** or women trying to conceive should not drink alcohol at all.

1 unit

- Half pint of 3.5% beer/ larger/ ale.
- Half a pint of 4% cider.
- 25 ml (one shot) of 40% spirits.
- Half a 175 ml glass (87.5 ml) of 12% wine.

Please go to the app store and add: 'know your numbers (Wessex Academic Health Science Network)' to monitor unit intake to help drink responsibly.

Thank you for your participation in this research.

Signature _____ Date _____

Name

Disclaimer

Disclaimer (version number: 1, 25/01/18) ERGO ID: 31723

Study Title: Pavlovian and instrumental learning with an alcoholic unconditioned stimulus in light and heavy social drinkers
Researchers: Carl Buckfield, Julia Sinclair and Steven Glautier.
Research Assistants: Harry Barnard and Elenie Biscombe

I understand that my participation in this experiment involved consumption of a small dose of alcohol (approximately 2 standard units). I have been advised by the experimenter that I should not, for 3 hours after the termination of the experiment, drive, operate machinery, or undertake any activity that may be dangerous after alcohol consumption. I have vouch that I will take precautions to be careful for the next 3 hours including remaining extra-vigilant and staying in locations I am familiar with.

Participant's Name (Print)……

Participant's Signature……

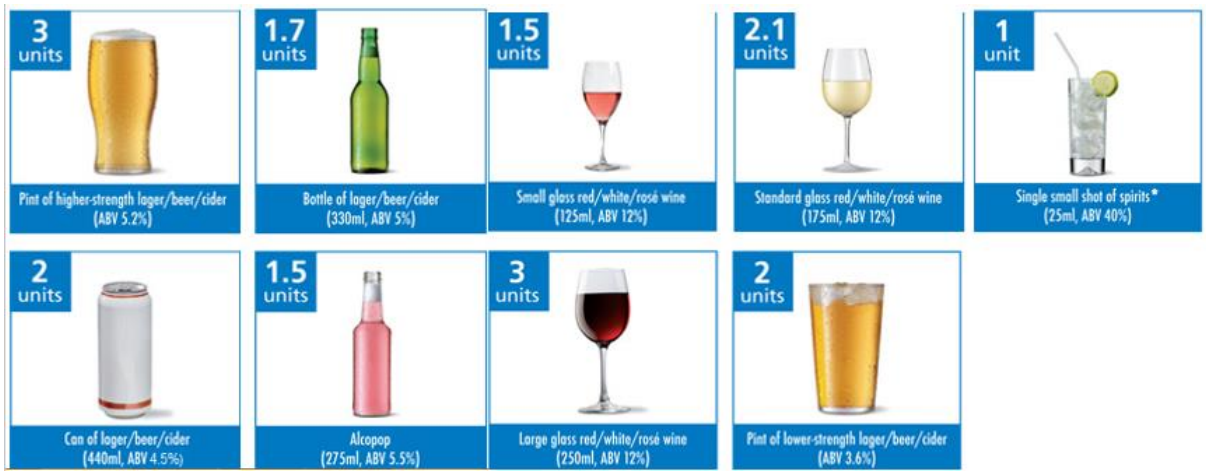
Date……..

Appendix 2 – Questionnaires

Six questionnaires in total were used within this thesis. Three of the questionnaires were used in every chapter (AUDIT, TLFB, BIS-11) while the remaining three were used in Chapter 4 only (HADS, 44-BFI, drug use history checklist). The drug use history checklist was created by the author. All questionnaires with their instructions are printed below.

Alcohol Use Disorders Identification Test (AUDIT)

1 unit of Alcohol is 10 ml (8 g) of pure ethanol. Because alcoholic drinks come in different shapes and sizes this translates into:



<u>1 unit</u>

- Half pint of 3.5% beer/ larger/ ale.
- Half a pint of 4% cider.
- 25 ml (one shot) of 40% spirits.
- Half a 175 ml glass (87.5 ml) of 12% wine.
- 300 ml of 4% alcopops.

Please circle the answer that is correct for you from over the last 6 months

Questions	0	1	2	3	4	Your Score
How often do you have a drink containing alcohol?	Never	Monthly or less	2 - 4 times per month	2 – 3 times per week	4+ times per week	
How many drinks containing alcohol do you have on a typical day when you are drinking?	1 - 2	3 - 4	5 - 6	7 - 9	10+	
How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last 6 months have you failed to do what was normally expected from you because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last 6 months have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last 6 months have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last 6 months have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
Have you or somebody else been injured as a result of your drinking?	No		Yes, but not in the 6 months		Yes, during the 6 months	
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?	No		Yes, but not in the 6 months		Yes, during the 6 months	
					Total:	

Appendix

TimeLine FollowBack

This questionnaire will be filled out by the experimenter based on your verbal responses. Starting with when you woke up today and going back seven days I would like you to recall how much alcoholic drinks you consumed on each day. It is important that you recall as much information as possible. If you can remember, it is vital for you to recall the volume of the drink(s) consumed and the alcohol percentage or alcohol brand of your drink(s) so units can be calculated later.

Day	Drink(s)	Unit(s)
Today		
-1		
-2		
-3		
-4		
-5		

-6		

Total units:

Appendix

Barratt Impulsiveness Scale 11th Ed

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

	① Rarely/Never	② Occasionally	③ Often	④ Almost Always/Always
1	I plan tasks carefully.			① ② ③ ④
2	I do things without thinking.			① ② ③ ④
3	I make-up my mind quickly.			① ② ③ ④
4	I am happy-go-lucky.			① ② ③ ④
5	I don't "pay attention."			① ② ③ ④
6	I have "racing" thoughts.			① ② ③ ④
7	I plan trips well ahead of time.			① ② ③ ④
8	I am self controlled.			① ② ③ ④
9	I concentrate easily.			① ② ③ ④
10	I save regularly.			① ② ③ ④
11	I "squirm" at plays or lectures.			① ② ③ ④
12	I am a careful thinker.			① ② ③ ④
13	I plan for job security.			① ② ③ ④
14	I say things without thinking.			① ② ③ ④
15	I like to think about complex problems.			① ② ③ ④
16	I change jobs.			① ② ③ ④
17	I act "on impulse."			① ② ③ ④
18	I get easily bored when solving thought problems.			① ② ③ ④
19	I act on the spur of the moment.			① ② ③ ④
20	I am a steady thinker.			① ② ③ ④
21	I change residences.			① ② ③ ④
22	I buy things on impulse.			① ② ③ ④
23	I can only think about one thing at a time.			① ② ③ ④
24	I change hobbies.			① ② ③ ④
25	I spend or charge more than I earn.			① ② ③ ④
26	I often have extraneous thoughts when thinking.			① ② ③ ④
27	I am more interested in the present than the future.			① ② ③ ④
28	I am restless at the theater or lectures.			① ② ③ ④
29	I like puzzles.			① ② ③ ④
30	I am future oriented.			① ② ③ ④

Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

I feel cheerful:	**D**
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	**A**
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	**A**
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	**D**
Often	0
Sometimes	1
Not often	2
Very seldom	3

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'Scoring: Total score: Depression (D) _____ Anxiety (A) _____ 0-7 = Normal 8-10 = Borderline abnormal (borderline case) 11-21 = Abnormal (case)

Appendix

The Big Five Inventory (BFI)

Here are a number of characteristics that may or may not apply to you. For example, do you agree that you are someone who likes to spend time with others? Please write a number next to each statement to indicate the extent to which you agree or disagree with that statement.

Disagree Strongly	Disagree A Little	Neither Agree Nor Disagree	Agree A Little	Agree Strongly
1	2	3	4	5

Do you see Yourself as Someone Who…

___1.___ Is talkative	___23.___ Tends to be lazy
___2.___ Tends to find fault with others	___24.___ Is emotionally stable, not easily upset
___3.___ Does a thorough job	___25.___ Is inventive
___4.___ Is depressed, blue	___26.___ Has an assertive personality
___5.___ Is original, comes up with new ideas	___27.___ Can be cold and aloof
___6.___ Is reserved	___28.___ Perseveres until the task is finished
___7.___ Is helpful and unselfish with others	___29.___ Can be moody
___8.___ Can be somewhat careless	___30.___ Values artistic, aesthetic experiences
___9.___ Is relaxed, handles stress well	___31.___ Is sometimes shy, inhibited
___10.___ Is curious about many different things	___32.___ Is considerate and kind to almost everyone
___11.___ Is full of energy	___33.___ Does things efficiently
___12.___ Starts quarrels with others	___34.___ Remains calm in tense situations
___13.___ Is a reliable worker	___35.___ Prefers work that is routine
___14.___ Can be tense	___36.___ Is outgoing, sociable
___15.___ Is ingenious, a deep thinker	___37.___ Is sometimes rude to others
___16.___ Generates a lot of enthusiasm	___38.___ Makes plans and follows through with them
___17.___ Has a forgiving nature	___39.___ Gets nervous easily

___18. Tends to be disorganized	___40. Likes to reflect, play with ideas
___19. Worries a lot	___41. Has few artistic interests
___20. Has an active imagination	___42. Likes to cooperate with others
___21. Tends to be quiet	___43. Is easily distracted
___22. Is generally trusting	___44. Is sophisticated in art, music, or literature

Appendix

Drug Use History Checklist

Have you ever taken these drugs in the last 6 months?

	0 Never	1 Infrequently	2 Regularly
Tobacco			
Cannabis			
Stimulants (cocaine, amphetamines, ecstasy etc)			
Opioids (heroin, codeine tramadol etc)			
Hallucinogens (LSD, mushrooms etc)			
Benzodiazepines			
Ketamine			
Other (please specify)			

Have you ever taken these drugs in the last week?

	0 Never	1 Infrequently	2 Regularly
Tobacco			
Cannabis			
Stimulants (cocaine, amphetamines, ecstasy etc)			
Opioids (heroin, codeine, tramadol etc)			
Hallucinogens (LSD, mushrooms etc)			
Benzodiazepines			
Ketamine			
Other (please specify)			

Appendix 3 – Experimental Instructions and Stimuli

The computer tasks used within this thesis came with verbal and on-screen instruction. The verbal instructions were abridged versions of the text read on the computer monitor. Every computer tasks instructions are listed here. Chapter 3 and Chapter 4 used the same task (and therefore instructions) Chapter 5 had instructions at the start of each session which were identical across all sessions. Chapter 6 had separate instructions at the start of each phase of the experiment all of which are listed here. The stimuli used in Chapter 5 were six different coloured shapes on three types of background. Not all possible shape and background combos are presented here. Only enough figures are presented to displays all shapes once. The stimuli used in Chapter 6 were three of the shapes (red diamond, blue circle, and green triangle) from Chapter 5 on light grey backgrounds and are not presented here. The countdown stimuli was the same used in Chapter 5 and Chapter 6.

Instructions

Chapter 3 & Chapter 4

In this experiment you will watch tests of various objects passing a special sensor.

Your job is to learn how the sensor responds to the different test objects.
The sensor may show red or green and you have to try to predict the sensor response while the objects are passing through a prediction window.

Make your predictions by pressing the key R or the key G while the objects are in the prediction window.Key presses made while the objects are outside the window will not count.

You should aim to make as many correct predictions as possible, and minimise incorrect predictions.

Tests may be carried out in one of four test containers, each of which might hold a different gas.

Before the experiment starts for real, we will have some practise trials.
In the practise trials you have to predict which objects turn the sensor blue.
Make your predictions by pressing the key B while the practise objects are in the prediction window.

Review these instructions on the screen.

When you are sure that you understand what is required, press the key C to continue.

You will be told when the practise trials have finished and when the experiment begins running for real.

Remember, during the practise trials you have to predict when the sensor will turn blue.

When the experiment begins running for real you have to predict red or green.

Ask the experimenter if you have any questions or press the key C to begin.

Appendix
Chapter 5

In this experiment you will see different coloured shapes in different environments.

You must assume the role of a person participating in a scavenger hunt looking for prizes of drink and food. In each environment the different coloured shapes predict if you have located either a drink, some food or found nothing at all.

On the computer screen you will see a background of a natural environment. Imposed on this background will be the coloured shape you have found during the scavenger hunt.

If you believe one coloured shape predicts you've found either drink, food or no prize you must press a keyboard key while the coloured shape is still on the screen. You will then be told what you really found by one of the words: "drink", "food1", "food2", or "wait" flashing on the screen. Once you have been told the correct prize you will have 45 seconds to either drink a sample, eat a sample or simply do nothing and wait for the next trial depending on what the correct prize is.

If you believe the coloured shape you've found predicts a drink press the "A" key. If you believe the coloured shape predicts food press the "G" key. If you believe the coloured shape predicts nothing press the "L" key. Remember you must press you key while the coloured shape is on the screen.

Please do not consume the drink and food samples until you have been instructed. At first you will have to guess which coloured shape predicts which prize, but as the experiment progresses please try to maximise correct predictions and minimise incorrect predictions.

If you have any questions please ask the experimenter.

When you are ready press the start button to begin.

Chapter 6

Pavlovian Phase

In this experiment you will see different coloured shapes on the monitor. Your job is to learn which shapes predict the onset of a reward.

The shapes could predict the onset of a drink reward of beer or a food reward of chocolate or no reward at all.

The shapes will appear on the screen for a maximum of 4 seconds. During this time you must press a keyboard key indicating your prediction. If you think the shape predicts a drink reward press the "A" key. If you predict a food reward press the "G" key. If you predict no reward press the "L" key. Failure to press a key within the 4 second window will result in a missed trial.

Once a key press has been made you will be told the correct answer. Regardless if your prediction was right or wrong or missed, you will then have 10 seconds to consume the correct reward before you start the next trial.

At first you are completely guessing, but as the experiment progresses you must try to maximise your correct predictions and minimise your incorrect predictions.

Please ask the experimenter any questions.

When you are ready click the button below to begin.

Instrumental Phase

In this experiment you will select keyboard key "D" or "H". Only one key will be active at any given trial. Each trial you have to guess which key is activated. If you select the correct key you win a prize. The prizes you can win are beer and chocolate. If you select the wrong key you win nothing. Once you select a key you are told what you win. Please consume a reward only if you win one. Please do not select a key until you have finished consuming your reward from the previous trial.

After the task is over you will be asked two questions about the task.

If you have any questions please ask the experimenter.

When you are ready click the button below to begin.

Devaluation Phase

In this part of the task, we would like to assess how unpleasant you find statements concerning the adverse consequences of [drinking alcohol/ eating chocolate]. Please read each statement carefully. Then report how unpleasant you find each statement by pressing a number key between 1 and 9, where: 1 _ Not at all unpleasant, 5 _ mildly unpleasant and 9 _ extremely unpleasant. When you are ready click the button below to begin.

Appendix
Transfer Phase

In this phase of the experiment you will now select "D" or "H" again. This time however, you will do the task without immediate rewards and while receiving no feedback. You will collect points to earn beer and chocolate, but be given no idea of your success until the end. At the end of the experiment you will be able to receive your rewards earned during the task.

If you have any questions please ask.

When you are ready click the button below to begin.

Stimuli

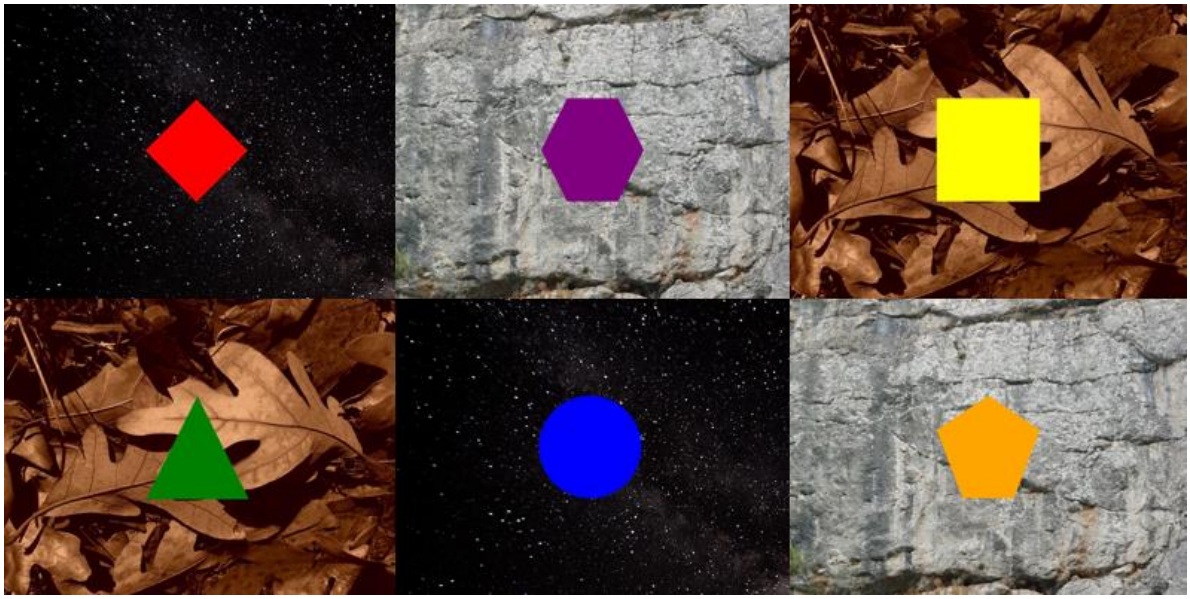


Figure A3.1. Image of the stimuli presented in the computer task of the main experiment of Chapter 5. Example of the three backgrounds (night sky, brown leaves, and grey stone) and the six cues (red diamond, purple hexagon, yellow square, green triangle, blue circle, and orange pentagon).

Figure A3.2. Image of the countdown screen in the computer task of the main experiment of Chapter 5.

Appendix 4 – Health Warnings

Alcohol

1. Alcohol is a poison and can sometimes have lethal consequences.
2. Around 1.1 million people were admitted to hospital for alcohol related reasons in England in 2015/16.
3. There were 6, 813 alcohol related deaths in England in 2015.
4. There is no minimum amount of alcohol that could cause alcohol poisoning. It is true that binge drinking is often the cause of alcohol poisoning, but this is not always the case.
5. Men and women are advised not to drink more than 14 units a week on a regular basis.
6. If you drink less than 14 units a week, this is considered low-risk drinking. It's called "low risk" rather than "safe" because there is no safe drinking level.
7. Regular drinking has been linked to cancers of the mouth, throat, bowel and breast.
8. Regular drinking has been linked to pancreatitis.
9. Regular drinking has been linked to strokes.
10. Regular drinking has been linked to heart disease.
11. Regular drinking has been linked to liver disease.
12. Regular drinking has been linked to brain damage and damage to the nervous system.
13. Alcohol intoxication can lead to unconsciousness.
14. Alcohol intoxication can impair you gag reflex resulting in choking on or inhaling your own vomit.
15. Alcohol intoxication can make you misjudge risky situations.
16. Alcohol intoxication can lead to unprotected sex.

Chocolate

1. Approximately half of the UK adult population is overweight, and 20% are clinically obese
2. Eating too many calories is the main cause of obesity
3. The percentage of adults who are clinically obese has roughly doubled since the mid-1980s
4. Increased consumption of calorie-dense foods, such as chocolate, is the main cause of obesity
5. One treat-size Cadburys chocolate bar contains 13.9% of your guideline daily amount of saturated fat
6. Dairy products, such as chocolate, contain a high proportion of saturated fat
7. Diets high in saturated fat are associated with atherosclerosis, stroke, coronary heart disease, cholesterol, and obesity
8. A Mediterranean diet (which is low in saturated fat) has been shown to significantly decrease the likelihood of suffering a second heart attack, cardiac death, heart failure, and stroke
9. The center for disease control has recommended that we reduce saturated fat intake to less than 7% of total calories
10. Chocolate contains theobromine, caffeine, phenylethylamine and anandamide, which affect neurotransmission in the brain
11. The World Health Organization recommends avoiding saturated fats to reduce the risk of a cardiovascular disease
12. Chocolate is 30–45 percent fat, of which about half is saturated fat

13. Chocolate is not a “health food,” despite some manufacturer’s claims
14. People who eat more calories need to burn more calories, otherwise the surplus is stored as fat
15. Guideline Daily Amounts are the most effective way to help people control their consumption of unhealthy food choices
16. By 2050, 60% of men, 50% of women, and 25% of children in the UK are likely to be clinically obese