Running head: Learning in alcohol dependence (<= 50 CHARACTERS)

Slow associative learning in alcohol dependence and the

Alcohol Cue Exposure Treatment Paradox

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Abstract

Cue exposure treatment for alcohol dependence is based on extinction of conditioned responses to alcohol related cues but despite a sound rationale and clear evidence of effectiveness in other conditions, cue exposure has had only limited effectiveness for alcohol dependence. Here we examined two explanations for this observation, namely, that alcohol dependent individuals have either slower extinction or greater contextual specificity of extinction than non-dependent individuals. Two experiments were carried out. Seventy-four (54 female, age $M=20.4$ years) participants took part in Experiment 1 and 102 (40 female, age $M=41.3$ years) participants took part in Experiment 2. In both experiments participants completed the Alcohol Use Disorders Identification Test, answered one-week time-line follow-back alcohol consumption questions, filled in the Barratt Impulsiveness Scale (11th Ed), and participated in a computerised learning task. In Experiment 2 participants additionally completed the 44-item Big Five Inventory, a drug use history checklist, and the Hospital Anxiety and Depression Scale. In Experiment 1 we found no difference in learning task performance on any of Pavlovian acquisition, extinction, response recovery, and context inhibition between light and heavy drinkers. However, in Experiment 2, there was slower extinction in abstinent alcohol dependent participants compared to light drinkers and some evidence that participants with alcohol dependence acquired knowledge of the CS-US pairings more slowly than light drinkers. An exploratory follow-up analysis showed that the observed relationship between learning and dependence was not mediated by group differences on personality nor due to group differences on drug use other than alcohol. We conclude that slow associative learning, especially in extinction, may be a characteristic of alcohol dependence and this finding may provide an explanation for the relatively poor outcomes that have been obtained for alcohol cue-exposure treatment.

Keywords: alcohol dependence, associative learning, extinction, cue exposure

Slow associative learning in alcohol dependence and the Alcohol Cue Exposure Treatment Paradox

Contemporary theories place Pavlovian and instrumental learning as an integral part of the aetiology of alcohol dependence (AD, Everitt & Robbins, 2016). The Pavlovian account of AD proposes that discrete environmental stimuli and contexts (e.g. sight and smell of alcohol or a bar-room setting) are conditioned stimuli (CSs) that have become associated with the effects of alcohol, an unconditioned stimulus (US), through repeated pairings during alcohol consumption as illustrated in Figure 1. The consequence of this learning is that exposure to alcohol CSs can produce conditioned responses (CRs) which may be experienced as craving and increase the probability of drinking (Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Corbit & Janak, 2007; Wittman et al., 2015). Thus, alcohol-related cues can be crucial antecedents to relapse and a threat to abstinence.

However, Pavlovian conditioning involves more than acquisition of responses. Extinction is a phenomenon of Pavlovian conditioning wherein the CS is repeatedly presented in the absence of the US and the CRs weaken and may ultimately disappear. Alcohol cues that have undergone extinction have been shown to produce weaker craving than they did pre-extinction in social (Collins & Brandon, 2002), heavy (MacKillop & Lisman, 2008), and dependent drinkers (Staiger & White, 1991; Stasiewicz, Brandon, & Bradizza, 2007). Staiger and White demonstrated that cue-induced cravings were virtually extinguished after 20 extinction trials. Therefore an extinction based treatment is a theoretically grounded and potential intervention for treating alcohol-dependence.

Cue-Exposure Therapy (CET) for AD involves exposing AD individuals to alcohol cues in extinction (i.e. without consumption of alcohol) to weaken CS-US associations and therefore reduce the capacity of the CSs to produce CRs and impact alcohol seeking behaviour. However, despite strong theoretical support and support from some clinical trials (Drummond & Glautier, 1994; Sitharthan, Sitharthan, Hough, & Kavanagh, 1997), meta-analyses demonstrate that CET has not proved effective in treating alcohol dependence (Conklin & Tiffany, 2002; Martin, Larowe, & Malcolm, 2010; Mellentin et al., 2017). This is in stark contrast to the efficacy of CET for other disorders, such as phobia and obsessive-compulsive disorder (OCD), where learning plays a role parallel to that in AD.

Here we coin the term “Alcohol Cue Exposure Treatment Paradox” (ACETP) to refer to the relatively poor CET outcomes in AD and we explore two potential explanations. Candidate explanations for the ACETP may be identified by looking for features of AD that are relevant to Pavlovian conditioning and which differentiate it from other disorders. For example, there is research which suggests that alcohol reinforcement may be qualitatively different from other reinforcement including studies which show that instrumental responding for alcohol is less sensitive to reinforcer devaluation than is responding for sucrose (Dickinson, Wood, & Smith, 2002). This work and similar results using other drug reinforcers (e.g. nicotine reinforcement is also relatively insensitive to devaluation, Clemens, Castino, Cornish, Goodchild, & Holmes, 2014) has led to the view that addiction involves dominance of habitual over goal-directed behaviour and in part this is a function of drug reinforcement (Everitt & Robbins, 2016). Since instrumental drug reinforcement differs from non-drug instrumental reinforcement it would be reasonable to examine whether or not drug-based Pavlovian reinforcement differed from non-

drug Pavlovian reinforcement in a way which might account for the ACETP e.g. CRs to alcohol CSs may be relatively resistant to extinction.

However, in the current work, we looked at an alternative candidate explanation for the ACETP. Specifically we hypothesised that the AD population differs from the non-dependent population. For example, perhaps people with AD do not extinguish CRs as quickly as non-dependent individuals. This could be due to the effects of a history of alcohol consumption or due to some other factor that may pre-date alcohol consumption. We are not aware of any existing research that clearly demonstrates impaired Pavlovian extinction in AD but two lines of work suggest that this is an avenue worthy of study. First, there is some direct experimental evidence from studies of learning and second there is some indirect evidence on inhibitory control, a process that is relevant to extinction. Turning first to studies of learning Gass et al. showed, in rats, that exposure to alcohol during adolescence led to impaired extinction of instrumental lever pressing for ethanol (Gass et al., 2014). There is also work with humans and rats which suggests deficits in Pavlovian learning due to alcohol exposure and due to individual difference factors that pre-date alcohol exposure. A number of studies have shown that early life exposure to alcohol produced deficits in acquisition of conditioned eyeblinks in rats (e.g. Green, Rogers, Goodlett, & Steinmetz, 2000), whereas Broadwater & Spear and Pajser Breen, Fisher, & Pickens looked at conditioned fear conditioning (Broadwater & Spear, 2013; Pajser, Breen, Fisher, & Pickens, 2018). The results from Broadwater et al. (2013) and Pajser et al. (2018) were complex but suggested deficits in learning due to alcohol exposure under some circumstances. Some of the results in Pajser et al. (2018) indicated that learning deficits due to group differences which may have pre-dated alcohol exposure but note some studies which have shown ‘enhanced learning’ -- stronger conditioned fear conditioning in high-alcohol-drinking rats (e.g. Rorick,

Finn, & Steinmetz, 2003). With human participants and an eyeblink conditioning procedure Fortier, Lafleche, Venne, & McGlinchey (2008) found that a group of alcohol dependent participants showed deficits in reversal learning compared to normal controls but detailed analyses showed that the main difference between the groups was on the acquisition of responding to the reinforced CS rather than on extinction of responding to the non-reinforced CS (Fortier et al., 2009).

The second line of work which encourages investigation of the possibility that there may be differences in extinction between AD and non-dependent individual concerns response inhibition. Response inhibition refers to the capacity to prevent the initiation of a response or to terminate a response that has already been initiated and is often measured in go/no-go or stop signal-reaction-time tasks. Response inhibition is weaker in AD (e.g. Smith, Mattick, Jamadar, & Iredale, 2014) and therefore suggests extinction deficits because extinction is fundamentally about the capacity to inhibit a response to a cue which has previously signalled the arrival of a US. Although there are clear conceptual links between response inhibition as measured in the go/no-go and stop signal-reaction-time tasks and conditioned inhibition there is surprisingly little linkage of these two areas in the literature (Sosa & Santos, 2019). Therefore it is a matter of general interest to determine whether or not a group which is known to be weak on response inhibition would also be weak on the inhibitory process underlying extinction as well as being of specific interest in relation to the ACETP.

In summary there is existing work 1) which demonstrates learning differences related to AD, some of which implicate extinction, and 2) which suggests that the AD population has deficits on inhibition which may be relevant to extinction. In the following investigation we therefore undertook to examine whether or not there was any evidence for differences between

light, heavy, and dependent drinkers that might support the hypothesis that slower Pavlovian extinction learning could be a contributing factor to account for the ACETP. We also examined an alternative way in which learning in the AD population may differ from learning in the non-dependent population that could also be relevant to understanding the ACETP. One leading explanation for relapse after extinction-based treatment is based on the fact that extinction does not tend to generalise well across contexts -- recovery of CRs after extinction is frequently observed if there is a contextual change (Bouton, 2004; Nelson, 2002). Although response-recovery after extinction has been put forward as a possible explanation for poor CET outcomes in AD (Collins & Brandon, 2002; Conklin & Tiffany, 2002) context dependent response-recovery cannot on its own explain why CET works for some disorders and not for others. Therefore, in the studies to be described below, our second aim was to determine whether or not there was any evidence of differences between light, heavy, and dependent drinkers that might support the hypothesis that greater response-recovery after extinction could be a contributing factor to account for the ACETP.

Experiment 1

Approval was obtained from the University of Southampton Ethics Committee. The experiment involved a computer-based associative learning task which included acquisition, extinction, and response-recovery test phases in an ABC design. An ABC design involves training a CS as a signal for a US in context A, extinguishing by CS alone trials in context B, and then presenting the CS for a recovery test in a novel third context, context C. We examined the performance of light and heavy drinker performance in this learning task. The primary aim of the experiment was to test the two candidate explanations outlined above for the relatively poor CET

outcomes for AD, namely slower extinction and/or greater response-recovery in dependent drinkers. However, extinction and response-recovery may be mediated by the extinction context becoming inhibitory (Glautier, Elgueta, & Byron Nelson, 2013; Polack, Laborda, & Miller, 2012) so we also looked for any signs of group differences on the development of inhibitory control by the extinction context.

Our comparison of light and heavy drinkers was based on the assumption that there exists a continuum between light drinking and dependent drinking (American Psychiatric Association, 2013). Therefore, if we were to observe differences between light and heavy drinkers, this would imply, using the continuity assumption, that differences between light and dependent drinkers would be at least as great and so this ‘analogue’ design could provide evidence relevant to the questions about poor CET outcomes for AD.

Participants

Seventy-four participants were recruited via electronic and poster advertisements and by word of mouth from the University of Southampton’s Highfield campus. Participants elected to receive course credit or be entered into a prize draw for a chance to win a £50 Amazon voucher upon completion of the experiment. Demographic characteristics of the participants are given in Table 1.

Materials and apparatus

Participants completed the AUDIT-C (Saunders, Aasland, Babor, Delafuente, & Grant, 1993), a one week timeline follow-back questionnaire (TLFB, Sobell & Sobell, 1992) to establish weekly UK units of alcohol consumption (1 unit = 8g ethanol), the Barratt

Impulsiveness Scale 11th ed. (BIS-11, Patton, Stanford, & Barratt, 1995), and carried out a computer-based learning task. The AUDIT-C was in relation to six months prior the start of the experiment. Three personal computers were used for the learning task. The screens measured 41 cm x 26 cm (W x H) and the display was controlled by a computer program written by SG in the Microsoft Visual Studio 2008 C# language. XNA Game Studio Version 3.1 was used for 3-D rendering of the experimental scenario. Auditory information (a musical background and a voice-over reading of the experimental instructions) was presented via speakers located to the left and right of the screens.

The computer task was designed to study the learning of Pavlovian associations between visually distinctive onscreen cues (CSs) and outcomes (USs) consisting of red or green flashes of a “sensor” shown on the computer screen. The computer screen background could be rendered in different 3-D environments for the purposes of manipulating context. The task consisted of a series of trials with each trial lasting approximately 4.8s during which a distinctive object would “fall” from the top to the bottom of the computer screen. During its transit the object passed behind a translucent band forming a prediction window. Whilst the object was in the prediction window participants could press a key to indicate their expectation of the trial outcome (e.g. red or green flash) or indicate no outcome expected by not responding. The scheduled trial outcome occurred as the object passed a pyramid shaped “sensor” located at the bottom of the computer screen. The experiment instructions explained that the sensor may be triggered to flash by some of the objects and that the task was to learn to how the sensor responded to the different objects. An illustrative video of the task can be found at <https://tinyurl.com/y6v5unpj>.

Design

A mixed design was used with a single between-subjects independent variable, drinking status, with two levels: light and heavy drinkers. Participants were categorised as light or heavy drinkers on the basis of a median split on weekly UK units of alcohol consumption using their responses to the TLFB questionnaire. Light drinkers were those who reported consuming less than 10.95 units per week and heavy drinkers reported consuming 10.95 units per week or more. Each participant took part in the learning task the overall design of which is given in

Table 2. All trials of the learning task were carried out within subjects. There were four distinct stages in the learning task. During Stage 1, acquisition, participants learned, in context A, associations between different cues (A, B, C, and G) and outcomes (X, Y, and Z). During Stage 2, extinction, which took place in context B, participants continued to experience cues B and C with outcomes Y and Z respectively but cue A was now paired with outcome Z (no outcome) extinguishing the Stage 1 learning which had involved cue A being paired with outcome X. In Stage 2a a summation test for inhibition took place in context B. Cue G, which was paired with outcome X in Stage 1, was presented for the first time in extinction context B. If, during extinction, context B had become inhibitory for outcome X responses to cue G should be suppressed during this summation test, a standard approach to testing for inhibition (Rescorla, 1969). Finally, in Stage 3, the recovery test was carried out. This involved presenting cue A in a novel context, context C.

The four objects assigned to cue functions A, B, C and G were randomly selected without replacement for each participant from a set of 16 objects that were generated from combinations of four binary-valued features. The objects varied 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]. The outcomes serving the roles X and Y were randomly set to be either a red or a green flash for each participant. The onscreen 3D environments forming contexts A, B, and C were randomly selected without replacement for each participant from a set of four. Trial order was randomised with stages for each participant subject to the constraint that no more than four trials of a single type could occur in sequence.

Procedure

Testing was carried out in the learning laboratory in the Department of Psychology at Southampton University. Participants attended individually and, on arrival, were given a brief verbal description of the experiment, read an information sheet, and signed a consent form. Participants then completed their questionnaires before being seated in an experimental cubicle containing a chair, desk, and computer where they had an additional brief verbal description of the task. The experiment then began with detailed instructions, available in full in the illustrative video at the URL given above, which were presented with a voice-over and onscreen text. After these instructions participants were given the opportunity to ask questions after which the experimental task began. There was a short practice phase of eight trials during which participants learned about cues O and P and a blue outcome before the main experiment, as detailed above and in

Table 2, began. The experiment took about 30 minutes in total and on completion of the computer task, participants were thanked and debriefed.

Analysis

Participant responses on each trial involving the critical cues A and G were coded 1 if outcome X was predicted and 0 otherwise. Trials were then averaged into two trial blocks for the analyses presented below. SPSS Analysis of Variance procedure was used and in cases of sphericity violation, based on Mauchley's test, Greenhouse-Geisser adjusted degrees of freedom were applied (Greenhouse & Geisser, 1959; Mauchley, 1940). Results are reported as significant below with $\alpha=0.05$. The data and SPSS code are available at <https://osf.io/r273p/>.

Results

Cue A

Figure 2 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 (block 11) for light and heavy drinkers. As can be seen in Figure 2 participants increased their X responses during the acquisition phase and X responses decreased in the extinction phase, with most extinction complete in the first two blocks of extinction. Finally, X responses increased again 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 response-recovery effect. The results in Figure 2 suggest no clear difference between the two drinking groups in their performance at any stage of the task. Although the extinction data showed numerically less extinction and more response-recovery in the heavy as compared to the

light drinkers the statistical analysis reported below shows that these differences were not significant.

A series of three similar mixed ANOVAs were conducted, one for each stage of the learning task. Each had a 2-level between-subjects factor of drinking status (light vs heavy). The acquisition and extinction ANOVAs each had a 5-level repeated measures factor for block (blocks 1-5 for the acquisition analysis and blocks 5-9 for the extinction analysis). The recovery test had a 2-level repeated measures factor for block (blocks 9 and 11). These ANOVAs produced significant main effects of block for acquisition [$F(3.13, 225.6) = 26.5, p < .001, \eta^2 = .269$], extinction [$F(2.65, 190.7) = 120.8, p < .001, \eta^2 = .627$], and for the recovery test [$F(1, 72) = 31.1, p < .001, \eta^2 = .302$]. However, there were no main effects of group nor block by group interactions for acquisition [$F(1, 72) = .341, p = .561, \eta^2 = .005$ and $F(3.13, 225.6) = .746, p = .531, \eta^2 = .01$ for group and block by group respectively], extinction [$F(1, 72) = .017, p = .896, \eta^2 = 0$ and $F(2.65, 190.7) = .355, p = .761, \eta^2 = .005$ for group and block by group respectively], and for the recovery test [$F(1, 72) = 1.28, p = .262, \eta^2 = .017$ and $F(1, 72) = .43, p = .514, \eta^2 = .006$ for group and block by group respectively].

Cue G

Figure 3 displays the mean proportion of X responses to cue G across the acquisition phase (blocks 1 - 5) and the summation test phase (block 10) for light and heavy drinkers.

Figure 3 shows that X responses to cue G increased during the acquisition phase and decreased during the summation test. This indicates that appropriate responses to cue G were learned in the acquisition phase and the response suppression during summation was suggestive of context inhibition. There is no clear indication of group differences.

Two similar mixed ANOVAs were conducted on these data, one for the acquisition phase and one for the summation test. Both had a 2-level between-subjects factor of drinking status (light vs heavy) and both had a repeated measures factor for block (blocks 1-5 for the acquisition analysis and blocks 5 and 10 for the summation analysis). The ANOVAs showed a significant main effect of block for the acquisition [$F(3.26, 234.5) = 21.69, p < .001, \eta^2 = .232$] and summation test data [$F(1, 72) = 78.16, p < .001, \eta^2 = .52$]. However, there were no main effects of group nor block by group interactions for acquisition [$F(1, 72) = .167, p = .684, \eta^2 = .002$ and $F(3.26, 234.5) = 1.67, p = .171, \eta^2 = .023$ for group and block by group respectively] and summation tests [$F(1, 72) = 1.89$ and $p = .173, \eta^2 = .026$; $F(1, 72) = .14, p = .71, \eta^2 = .002$ for group and block by group respectively].

Discussion

In this experiment participants successfully learned the CS-US associations for both cues A and G. They also showed extinction of responding to cue A when cue A was presented alone during the extinction trials. The extinction trials were carried out in context B and responding to cue A recovered when cue A was presented in novel context C. Light and heavy drinkers did not differ on either extinction or on response-recovery. Thus we have no evidence in support of the hypothesis that relatively poor CET outcomes in AD could be due to differences on extinction or on response-recovery between the AD populations and other populations where CET has been

used with success. Perhaps unsurprisingly, because the groups did not differ on extinction or on response-recovery, we did not observe any group differences in the summation test which provided a measure of extinction context inhibition. However, these conclusions are not definitive. As noted in the introduction to Experiment 1 the logic of the continuity hypothesis puts a lower bound on the differences that might be expected between light and dependent drinkers – these differences should be at least as great as the difference between light and heavy drinkers. The continuity hypothesis does not, in contrast, put an upper bound on differences between light and dependent drinkers. In fact if AD is linked to learning, either via a history of alcohol consumption or some other factor which may pre-date that history, then it seems reasonable to assert that differences between light and dependent drinkers should be greater than differences between light and heavy drinkers.

Experiment 2

In Experiment 2 we revisited the same questions addressed in Experiment 1 but this time we compared light drinkers with age and gender-matched dependent drinkers. Approval was obtained from the University of Southampton Ethics Committee and Research Governance Office and the National Health Service Research Ethics Committee and Health Research Authority (16/SW/0343 17/EM/0111 East Midlands-Nottingham1). Differences from Experiment 1 are given below.

Participants

One hundred and two participants took part. Fifty-one participants in the AD group were recruited from two Southampton treatment services, the Manor Clinic and the Society of St.

James. Fifty-one participants in the light drinking group, age and sex matched to the AD group, 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. Additional specific inclusion criteria for the alcohol-dependent group were: 7) a diagnosis of alcohol dependence, 8) abstinent for more than 15 days but less than 365 days. A specific inclusion criterion for the light drinker group was: 9) scoring ≤ 5 on the AUDIT-C. Participants received £10 upon completion of the experiment. Demographic characteristics of the participants are given in Table 1.

Materials and apparatus

The AD participants completed the full AUDIT which recorded alcohol consumption in the six months prior to the participants' abstinence. The control participants completed the consumption questions (AUDIT-C) only in regards to their alcohol consumption six months prior to the experiment and one week TLFB. In addition to this, all participants completed the BIS-11, Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983), and the 44-item Big Five Inventory (44-BFI, John, Donahue, & Kentle, 1991) questionnaires. Participants also reported their prescribed and non-prescribed drug use in an author-made checklist which covered tobacco, cannabis, stimulant, opiate, hallucinogen, benzodiazepine, and ketamine categories. The

computer task used was identical to Experiment 1 run on a laptop computer with a screen measuring 30.5 cm x 19.2 cm (W x H) running at 60 Hz.

Procedure

Testing for AD participants took place in a quiet private room within their treatment facility and, for the questionnaires, the experimenter read the questions out loud and participants responded by giving the Likert scale number representing their answer.

Analysis

Regression and mediation analysis was used in exploratory analyses to examine whether or not the differences in extinction that we found between the light drinker and AD groups could be explained in terms of differences that we observed on personality traits and on drug taking rather than differences in alcohol dependence *per se*. An SPSS macro ‘PROCESS’ (Hayes, 2013) was used to run the mediation analysis.

Results

Cue A

Figure 4 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 (block 11) for light and heavy drinkers. As can be seen in Figure 4 the overall pattern for the light drinkers closely resembled that seen in Experiment 1 -- X responses increased during the acquisition phase and decreased in the extinction phase, with most extinction complete in the first two blocks of extinction; X responses increased again during the recovery test. This indicates that the light drinkers successfully learned the CS-US association, learned to extinguish said association during extinction training, and demonstrated an ABC response-recovery effect. However, Figure 4 also shows that the AD group was slower to acquire the CS-US pairing than the light drinkers, but learned it to a comparable level by block 5. The Figure also shows that the AD group was slower to extinguish, showed less extinction overall, and showed less response-recovery than the light drinkers.

ANOVAs applied to these data showed a significant main effect of block for acquisition [$F(3.47, 347) = 16.7, p < .001, \eta^2 = .143$], extinction [$F(3.09, 309.1) = 80.6, p < .001, \eta^2 =$

.446], and for the recovery test [$F(1, 100) = 4.49, p < .05, \eta^2 = .043$] but there was no main effect of group for acquisition [$F(1, 100) = 3.23, p = .075, \eta^2 = .031$], extinction [$F(1, 100) = 1.03, p = .312, \eta^2 = .01$]. The recovery test, in contrast, did produce a main effect of group [$F(1, 100) = 4.68, p = .05, \eta^2 = .045$]. However, whilst there was no significant block by group interaction for acquisition and for the recovery test [$F(3.47, 347) = 1.86, p = .126, \eta^2 = .018$] and $F(1, 100) = 3.37, p = .069, \eta^2 = .033$ for acquisition and recovery test respectively] there was a significant block by group interaction for extinction [$F(3.09, 309.1) = 3.17, p < .05, \eta^2 = .031$]. Independent t-tests for the effect of group at each block (5-9) during extinction showed a group difference in block 9 [$t(100) = 2.74, p < .01$].

Cue G

Figure 5 displays the mean proportion of X responses to cue G across the acquisition phase (blocks 1 - 5) and the summation test phase (block 10) for light and heavy drinkers. As was observed for cue A Figure 5 shows that the light drinkers in Experiment 2 behaved comparably with the light drinkers from Experiment 1 -- X responses to cue G increased during the acquisition phase and decreased during the summation test. However, Figure 5 also shows that the AD group was slower to acquire the CS-US pairing than the light drinkers, but learned it to a comparable level by block 5.

ANOVAs showed, for the acquisition data, a significant main effect of block [$F(3.55, 355.2) = 26.9, p < .001, \eta^2 = .212$] and main effect of group [$F(1, 100) = 7.44, p < .01, \eta^2 = .069$], but the block by group interaction fell short of significance [$F(3.55, 355.2) = 2.46, p = .052, \eta^2 = .024$]. For the summation test there was a main effect of block [$F(1, 100) = 106.2, p$

$< .001$, $\eta^2 = .515$], but no main effect of group [$F(1, 100) = .089$, $p = .766$, $\eta^2 = .001$] nor a block by group interaction [$F(1, 72) = .3.02$, $p = .086$, $\eta^2 = .029$].

Exploratory Analyses

Two dependent measures were used alongside two analyses. The first dependent measure, EA, summarised performance over the extinction phase for cue A and was obtained from a regression of $P(xrsp)$ for cue A 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. The second dependent measure, AG, summarised performance during the acquisition phase for cue G and was obtained by averaging $P(xrsp)$ for cue G across blocks 1-5 for each participant.

In the first analysis we assessed whether or not the differences in drug use which were observed between light and dependent drinkers (c.f. Table 1) could better account for the observed group differences on extinction and acquisition. Regressions of EA and AG on group (light or AD) and drug taking (report no or report some drug taking in last six months) produced a significant overall regression effects in all cases ($ps < .05$). For EA the group effect was not significant when tobacco use was taken into account ($p = .08$) but when excluding tobacco use the group effect was significant ($p < .05$). For AG the group effect was significant whether or not tobacco use was taken into account ($ps < .05$). In no case was the effect of drug taking significant ($ps > .08$).

In the second analysis we assessed whether or not the differences on personality variables which were observed between light and dependent drinkers (c.f. Table 1) could better account for the observed group differences on extinction and acquisition. The SPSS package PROCESS allows a mediation analysis in which indirect effects of continuous independent variables can be

assessed as well as the direct effects obtained from standard regression (Hayes, 2013). All variables where there was a significant difference between light and dependent drinkers (BIS11, HADS-D, HADS-A, 44BFI-N, 44BFI-A, and 44BFI-C) were standardised and entered as parallel mediators (Model 4 PROCESS version 3.1) with group entered as a direct effect variable for analysis of dependent variables EA and AG.

The results of this analysis indicated a direct effect of group on EA (effect = 0.08, $t = 2.67$, $p < 0.01$) and there were no indirect effects of group on EA mediated via personality variables (largest effect = -0.014, $p > 0.285$ for HADS-A) confirming that the observed effect of dependence on extinction learning was not mediated by group differences on personality traits. There was also a direct effect of group on AG (effect = 0.146, $t = 2.29$, $p < .05$) and direct effects of 44BFI-A and 44BFI-C on AG (effect = -0.065, $t = 2.25$, $p < .05$ and effect = -0.078, $t = 2.19$, $p < .05$ respectively) but no indirect effect of group on AG mediated by personality variables (largest effect = -0.054, $p > 0.065$ for 44BFI-C) confirming that the observed effect of dependence on acquisition learning was not mediated by group differences on personality traits.

Discussion

The key results presented above showed that light drinkers and AD participants differed on extinction and on acquisition. Specifically 1) extinction proceeded more slowly in the AD participants than in the light drinkers and 2) there was lower responding during acquisition in the AD participants 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 despite matching on age and gender it was reported above that the light and dependent drinking groups differed on a

number of personality traits and on drug taking. There exists, therefore, the possibility that the observed effect of AD on extinction performance could be confounded or mediated through these variables. However, regression and mediation analyses showed that the effect of AD on learning remained after drug taking was included in the regression models and that the effects of AD of learning was mediated by personality variables.

General discussion

In the Introduction we highlighted the fact that cue-exposure treatment for AD has not produced clear-cut positive results despite a clear theoretical base and evidence for the effectiveness of cue-exposure treatment in anxiety disorders where the underlying theoretical reasoning is directly analogous. Here we coin the term Alcohol Cue Exposure Treatment Paradox to refer to this observation and the experiments described above looked at one candidate explanation for the ACETP, namely that the AD population differs from the general population on some features that are relevant to extinction of Pavlovian conditioning. *A priori* we speculated that slow Pavlovian extinction and/or greater response-recovery after extinction and contextual change may differentiate the AD and general population and form a plausible explanation for ACETP. Our initial investigation in Experiment 1 was an analogue study in which we compared light and heavy drinker performance in our learning task. In the event we found no differences between these groups and although a positive result in Experiment 1 could have provided support for the hypothesis the null finding was inconclusive. In Experiment 2, using the same procedures as Experiment 1, but this time substituting heavy drinkers with currently abstinent AD participants we looked once again for group differences in our learning task and we found a clear difference in extinction learning. The AD participants extinguished more slowly than the light

drinkers but there was no difference between light drinkers and AD participants on response-recovery -- the main effect of group in the analysis of the recovery test was due to higher responding in the AD group on the last extinction trial. Furthermore, we also found some evidence that AD participants learned more slowly than the light drinkers during acquisition. During acquisition, for cues A and G, learning in the AD group lagged behind that of the light drinkers. However, whilst in neither case did the group x block interaction reach significance and the performance of the groups was equivalent by the end of the acquisition phase, there was a main effect of group in the acquisition phase for cue G. Follow-up exploratory analyses showed that group differences on acquisition and extinction remained after controlling for differences between the groups on drug taking (other than alcohol) and personality variables leading to the conclusion that the observed differences between light and AD drinkers on learning are linked to AD. We finish with some discussion and consideration of some salient implications of these results for our understanding of the ACETP and suggestions for follow-up work.

First, we address the question of whether or not our principle finding, slow extinction in alcohol dependence, really could provide an explanation for the ACETP. This question is perhaps best answered by a direct comparison of extinction in e.g. specific phobia and AD patients and such a follow-on study is clearly warranted on the basis of the current work. If that study showed relatively slow extinction in AD then this would provide clear support for the idea that the ACETP could be due to population differences on extinction. But what inference does our comparison of AD and normal controls license? There are some examples of general learning deficits which may differentiate participants with anxiety disorders from normal controls e.g. poorer discrimination of faces in panic disorder (Lenaert, Boddez, Vervliet, Schruers, & Hermans, 2015) or reduced excitatory and inhibitory learning with high neuroticism (He,

Cassaday, Bonardi, & Bibby, 2013). However, despite the existence of an enormous literature on learning in anxiety disorders which has clearly established slower extinction of conditioned responding based on aversive USs in anxiety disorders as compared to normal controls (Duits et al., 2015; Lissek et al., 2005) we are not aware of any work which has shown slower extinction in other forms of associative learning (e.g. with appetitive USs or in predictive or causal learning preparations) in anxiety disorders as compared to normal controls. We therefore speculate that normal and anxiety disordered controls would be interchangeable for comparison with AD participants using the current, or similar, tasks.

Second, although our primary finding was slower extinction in AD we also found some indication of slower acquisition and there is an interesting pattern in the learning curves of Figure 4 – there is a crossover between acquisition and extinction with responding in the AD group lower at the end of acquisition and higher at the end of extinction. Using a leading standard model of associative learning, the Rescorla-Wagner model (Rescorla & Wagner, 1972), to help interpret the signature crossover of these curves we can infer that the difference between AD participants and light drinkers is not likely to be due simply to slower learning on non-reinforced trials. Without elaboration here (but see e.g. Anderson, 1999) for an introduction to the Rescorla-Wagner model) learning in the Rescorla-Wagner model is governed by two learning rate parameters α and β . The parameter α is used to model the salience of the CS whereas β is used to model the salience of the US and we carried out simple simulations using the Rescorla-Wagner model and varying α and β to see how the crossover signature can be produced. The simulations, available at <https://osf.io/r273p/>, showed that reducing β for the non-reinforced trials alone to model a “pure” reduced extinction effect did not produce crossed learning curves. However, crossed learning curves could be produced by reducing α alone or in combination with

reducing β for the non-reinforced trials. Thus, the simplest explanation for the observed pattern, in terms of the Rescorla-Wagner model, is that the AD participants have lower α than the light drinking controls. We cannot rule out the possibility that β for non-reinforced trials may also differ for AD and control participants but clearly it would be of value to carry out further studies to try to better characterise the observed group difference in terms of formal model parameters.

Third, these results have implications for CET. Our results showed that AD patients in the early abstinent stages of their recovery extinguish learned CS-US pairings slower than light drinking controls. This suggests the possibility that AD patients undergoing CET would fail to comprehensively extinguish CRs to their alcohol-related cues and therefore would still be prone to relapse after treatment. A straightforward follow-up study would involve a comparison of standard and extended CET to determine whether or not there is any benefit from an increase in the amount of cue exposure to accommodate the impairment in extinction learning. How much cue exposure might be needed? In order to address this question a review of alcohol CET studies was carried out. Studies were identified through prior inclusion in the systematic reviews mentioned previously (Conklin & Tiffany, 2002; Martin et al., 2010; Mellentin et al., 2017) and by search using the terms “cue exposure alcohol dependence” and “cue exposure therapy alcohol randomised control trials” (US spelling variation randomized also used) in online databases PubMed, PsycINFO, ScienceDirect, and the University of Southampton’s library search engine DelphiS. Application of the following criteria led to selection of 12 studies. The selection criteria were a) cue exposure had to have been one of the experimental treatment methods and a primary focus, b) there needed to be a control 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 > 18 years old.

Examination of the selected CET studies revealed that cue exposure time has ranged between 30 and 90 minutes (e.g. Kiefer et al., 2015; Loeber, Croissant, Heinz, Mann, & Flor, 2006) so perhaps a reasonable way to find out whether or not extended cue-exposure would lead to improved outcomes would be to compare a “standard” treatment including 60 minutes of exposure with extended treatment involving 180 or 240 minutes of cue-exposure.

In conclusion we note that, as far as we are aware, this is the first study to report differences between AD participants and controls on a predictive associative learning task. As such the results are preliminary but they are of considerable interest because of the implications they carry for treatment and some suggestions for follow-up work are given above which we think should be prioritised. However, there is another important issue worthy of mention, touched on in the introduction, concerning causality. Assuming that impaired extinction learning in AD is a confirmed finding a crucial question arises about the contribution of alcohol exposure to the effect. It is well established that acute alcohol administration reduces response inhibition and a history of alcohol exposure is linked to reduced inhibition (e.g. Field, Wiers, Christiansen, Fillmore, & Verster, 2010; Spear, 2018) and therefore we might expect that alcohol has a causal role in impaired extinction -- since extinction seems at face value a plausible assay for response inhibition. Alternatively, perhaps impaired extinction learning would be seen prior to alcohol exposure and thereby be in a position to have a causal role in the development of AD. It is currently an open issue as to whether or not response inhibition deficits seen across a range of substance dependencies, including AD, have a causal role in those dependencies. Of course these two causal scenarios are not mutually exclusive (Smith et al., 2014).

Table 1 Participant characteristics for Experiments 1 and 2. Ns and Means (SD). For the HADS subscale D=depression and A=anxiety. For the 44BFI subscales E=extroversion, N=neuroticism, A=agreeableness, C=conscientiousness, and O=openness. \$ Drug taking, number of participants reporting use in last six months, significant difference χ^2 (1 df), $p<0.001$. + Dependent drinkers in Experiment 2 were abstaining at the time of test and had an average of 78.4 abstinent days (SD=69.5). For the AD group the full AUDIT score mean was 30.7 (SD=5.6). NA=not available. Asterisks indicate between group differences using t-tests (100df) * $p<0.05$, ** $p<0.001$.

	Experiment 1		Experiment 2	
	Light drinkers	Heavy drinkers	Light drinkers	Dependent drinkers
N	37	37	51	51
Gender Ns (♀,♂)	24,13	30,7	20,31	20,31
Age	20.7 (3.8)	19.9 (1.7)	41.1 (12.4)	41.5 (11.6)
AUDIT-C	5.2 (2.4)	7.9 (2)**	2.3 (1.7)	10.8 (1.6)**
BIS-11	64.6 (10)	65.8 (8.3)	56.6 (7.5)	74.7 (15.8)**
Weekly units	4.74 (3.79)	31.2 (27.8)**	4.5 (6.1)	0 ⁺
HADS – D	NA	NA	2.7 (2.6)	5.7 (4.0)**
HADS – A	NA	NA	5.4 (3.1)	10.4 (5.0)**
44BFI – E	NA	NA	25.8 (6)	27.9 (7.2)
44BFI – N	NA	NA	19.8 (5.4)	27.6 (6.4)**
44BFI – A	NA	NA	36.6 (4.4)	34.1 (6.4)*
44BFI – C	NA	NA	35.9 (5.1)	30.6 (8.6)**
44BFI – O	NA	NA	36.9 (5.4)	36.6 (6.6)
Drug taking	NA	NA	7	46 ^{\$}
Drug taking exc. tobacco	NA	NA	5	30 ^{\$}

Table 2 Summary of learning task, see text for additional details. A: $A \rightarrow X$ (x10) indicates context A:, cue A, outcome X presented for 10 trials. X and Y red or green flash outcomes, Z is no outcome.

Stage 1 - acquisition	Stage 2 - extinction	Stage 2a – summation test	Stage 3 – recovery test
A: $A \rightarrow X$ (x10)	B: $A \rightarrow Z$ (x8)		C: $A \rightarrow Z$ (x2)
A: $B \rightarrow Y$ (x20)	B: $B \rightarrow Y$ (x8)		
A: $C \rightarrow Z$ (x20)	B: $C \rightarrow Z$ (x8)		
A: $G \rightarrow X$ (x10)		B: $G \rightarrow Z$ (x2)	

Figure 1 A schematic depicting the conditioning of alcohol-related cues. In the preconditioning phase the sight and smell of an alcohol containing drink is neutral and elicits no response. However, alcohol is a pharmacological agent and consumption causes rising blood alcohol levels and a number of psychological and physiological effects. Alcohol therefore acts as a potent US. In the conditioning phase the sight and smell of alcohol is paired repeatedly with rising blood alcohol levels so an association between the two is learned. The post-conditioning phase shows the consequence of this learned association. Now the sight and smell of the drink produces CRs such as memories of alcohol effects, craving for alcohol, and increased probability of alcohol seeking behaviour.

Pre-conditioning

Conditioning

+

Post-conditioning

Figure 2 Probability of an X-outcome prediction in response to cue A during Experiment 1.

Acquisition (blocks 1-5), extinction (blocks 6-9), and recovery test (block 11) for light and heavy drinkers. Means ± 1 standard error.

Figure 3 Probability of an X-outcome prediction in response to cue G during Experiment 1.

Acquisition (blocks 1-5) and summation test (block 10) for light and heavy drinkers. Means ± 1 standard error.

Figure 4 Probability of an X-outcome prediction in response to cue A during Experiment 2. Acquisition (blocks 1-5), extinction (blocks 6-9), and recovery test (block 11) for light and dependent drinkers. Means ± 1 standard error.

Figure 5 Probability of an X-outcome prediction in response to cue G during Experiment 2.

Acquisition (blocks 1-5) and summation test (block 10)) for light and dependent drinkers. Means ± 1 standard error.

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