No-Think, No Drink? Assessing the ability of reconsolidation interference by intentional forgetting to suppress alcohol memories in hazardous drinkers

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Abstract

Memory reconsolidation offers an opportunity to modify previously consolidated memories by first reactivating them. The process is triggered by the presentation of retrieval cues (reminders of the memory to be reactivated). However, reconsolidation is not universally triggered upon retrieval. Here we investigate one boundary condition thought to constrain memory reactivation: retrieval length. We also investigate the effects of a novel post-retrieval manipulation: intentional suppression. We assessed this with the think/no-think (TNT) task, in a clinically relevant sample of hazardous drinkers, using alcohol-related paired associate learning. 73 participants took part in four online sessions. On the first session participants were required to learn 36 image-word pairs. On the second session participants received 0, 4, 18 or 36 retrieval cues followed by the TNT task. The recall of the pairs was assessed 2 and 7 days after the retrieval+TNT procedure. The 4-trial retrieval procedure was the most consistent with triggering memory reconsolidation. This group showed greater practice effects and was the only group in which suppression-induced forgetting was observed at test. However, suppression-induced forgetting of alcohol cues was lower than in normative samples, indicating that intentional forgetting effects may depend upon population, salience of material and time between suppression and retrieval.

Keywords: Reconsolidation, Think/no-think Task, Memory suppression, Alcohol, Memory, Addiction

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1. Introduction

It has been repeatedly demonstrated that the retrieval of consolidated memories, induced by memory-relevant cues, can cause memories to enter a temporary window of lability, after which they must then restabilise (Elsey, Van Ast, & Kindt, 2018; Lee, Nader, & Schiller, 2017). This process of memory 'reconsolidation' may offer an opportunity to modify memories while they are briefly unstable prior to re-storage in long-term memory. Manipulating memories in this way could offer a breakthrough for the development of treatments for disorders where strongly encoded maladaptive memory associations putatively play a key role, such as substance use disorders and threat-related disorders (Paulus, Kamboj, Das, & Saladin, 2019; Walsh, Das, Saladin, & Kamboj, 2018).

Despite the theoretical promise of memory modification via reconsolidation-interference, several replication failures (Chalkia, Van Oudenhove, & Beckers, 2020; Elsey et al., 2018) highlight a key aspect of the memory destabilisation/reconsolidation process: It is not universally triggered upon memory retrieval. Prior failures to observe reconsolidation-interference effects may therefore represent a failure to destabilise memories at retrieval. For the successful development of novel treatments leveraging reconsolidation-interference we must first develop procedures that can consistently and reliably destabilise memories. Animal studies have elicited key 'boundary conditions' that constrain the process of reconsolidation. These include age and strength of a memory (Eisenberg, Kobilo, Berman, & Dudai, 2003; Milekic & Alberini, 2002; Suzuki et al., 2004; Wang, de Oliveira Alvares, & Nader, 2009), the retrieval 'length' (number of retrieval cues) (Pedreira, Pérez-Cuesta, & Maldonado, 2004; Suzuki et al., 2004), and the presence of a 'prediction error' at retrieval (Díaz-Mataix, Ruiz Martinez, Schafe, LeDoux, & Doyère, 2013; Morris et al., 2006; Pedreira et al., 2004).

Repeated, massed presentation of retrieval cues tends to induce new contingency learning, rather than destabilisation/updating of extant memories (Bouton, 2004); however too-brief retrieval procedures may be insufficient to destabilise a retrieved memory (Suzuki et al., 2004). Human research showing transient effects of post-retrieval manipulations when retrieval procedures are very brief (T. T. de Beukelaar, Woolley, Alaerts, Swinnen, & Wenderoth, 2016) suggest the original memory may not have been altered and memory reconsolidation may not have occurred (Elsey et al., 2018). Further, mismatch between memory-predicted (e.g. the presentation of a reinforcer) and actual events (e.g. absence of a reinforcer) at retrieval also appears to be a key determinate of destabilisation. This 'prediction error' (PE) is a cross-modality learning signal, driving 'memory updating' (R. K. Das, Walsh, Hannaford, Lazzarino, & Kamboj, 2018; Exton-McGuinness, Lee, & Reichelt, 2015; Fernandez, Boccia, & Pedreira, 2016; Sevenster, Beckers, & Kindt, 2014), but if it is too great, instead produces new learning. This was elegantly demonstrated by Sevenster, Beckers, & Kindt (2014), where the memory process engaged varied as a function of the number of reminder trials. Two retrieval trials with one prediction error appeared to trigger reconsolidation, whilst four retrieval trials with two prediction errors failed to do so. There are thus optimal degrees of retrieval length and PE for destabilising any given memory, but the exact values of these are dependent upon the learning history that underlies the memory trace. These boundary conditions have

begun to be explored in human studies, but further work is needed (R. K. Das et al., 2018; T. de Beukelaar, Woolley, & Wenderoth, 2014; T. T. de Beukelaar et al., 2016; Elsey et al., 2018; Forcato, Fernandez, & Pedreira, 2014; Schroyens, Beckers, & Kindt, 2017; Suzuki et al., 2004; Sevenster, Beckers, & Kindt, 2014). Indeed, given the seemingly critical reliance of memory destabilisation on the parameters of retrieval, these are often somewhat side-lined in the reconsolidation intervention literature, which tends to focus instead on post-retrieval manipulations. A primary aim of the current study will thus be to determine the impact of varying the number of retrieval cues and PEs on the destabilisation of explicit associative memories.

A key requirement of modifying a target memory is to complete a memory-modifying manipulation within the temporal window of memory lability (the 'reconsolidation window') triggered by destabilisation. Research has tended to focus on extinction learning post-retrieval, but authors have suggested that alternative 'corrective learning' manipulations might show promise (Keller, Hennings, & Dunsmoor, 2020; Levy, Mika, Radzyminski, Ben-Zvi, & Tibon, 2018). One such manipulation is intentional suppression of memories following retrieval cues; typically studied via the think/no-think (TNT) paradigm. The paradigm consists of three stages: training (where participants learn cue-target pairs), intentional suppression (the TNT task itself) and finally testing (Anderson & Green, 2001). During the TNT task, learned cues are presented and participants are instructed to 'Think' (of the target) or 'No Think' (intentionally prevent the associated target word from coming into awareness). Many studies have demonstrated suppression-induced forgetting (SIF) of associations in the 'No-think' condition using this technique (Anderson & Hanslmayr, 2014; Anderson & Huddleston, 2012; Benoit, Hulbert, Huddleston, & Anderson, 2015; Depue, Burgess, Willcutt, Ruzic, & Banich, 2010) and ability to suppress in this paradigm is predictive of PTSD symptomatology. However, it is yet to be investigated as a means of inducing *lasting* suppression of memory retrievability by targeting destabilised memories. We hypothesise that completing the TNT task during the reconsolidation window will enhance the difference in recall between think (recalled) and no-think (suppressed) items and prolong the effect. However, the ability to intentionally suppress may depend on the priors for 'associability' of cue-target pairs (e.g. table-chair may be harder to suppress than table-river). With an eye on future clinical implementation of these effects, we assess this possibility in a clinically relevant sample of hazardous drinkers, using alcohol-related cue-target learning.

It is known that incentive salience towards alcohol-related stimuli is heightened with frequent alcohol use (Robinson & Berridge, 2001). We predict the increased salience of alcohol cues in hazardous drinkers (Field & Cox, 2008) will make it particularly difficult for hazardous-drinking individuals to suppress targets associated with alcohol. Only one study has investigated suppression-induced forgetting of alcohol associates using the TNT task (López-Caneda, Crego, Campos, González-Villar, & Sampaio, 2019). The study successfully demonstrated the think/no-think effect on alcohol-related cues in a *healthy* population. However, the ability to achieve this in a population of hazardous drinkers is of particular interest as the learned salience of these cues (Robinson & Berridge, 2001) may prevent SIF, precluding clinical translation of a SIF-based intervention in heavy drinkers. Equally, if reconsolidation mechanisms can enhance and prolong the effect of SIF of alcohol cue triggered responses in a drinking population, this would be of great

clinical interest for the development of procedures that allow the forgetting of the maladaptive associative memories that putatively underpin alcohol abuse.

The aims of the current study are threefold. Firstly, we will establish the impact of alcohol-related cues on the TNT effect in hazardous drinkers. Secondly, we aim to determine the effect of the number of retrieval cues/PEs used to destabilise an experimentally-induced memory. Finally, we establish if the TNT effect can be enhanced and prolonged by first destabilising the cue-target pair memory. We predict alcohol-related associations will be harder to suppress and update than non-alcohol related associations in a sample of hazardous drinkers. The demonstration of the ability of reconsolidation enhanced TNT to update alcohol related associative memories could lead to the generation of novel and effective therapies for problematic alcohol use.

2. Methods

2.1 Participants

Participants were 73 'hazardous drinking' healthy volunteers aged 18-35. Inclusion criteria were: Alcohol use identification test score >8 (AUDIT, Saunders et al., 1993), drinking alcohol >3 days in 7, regularly drinking beer, normal colour vision and fluent English. Exclusion criteria were: No current or previous diagnosis of drug or alcohol use disorders or any current diagnosis of any psychiatric disorder, and not currently suffering from insomnia defined as score >14 on the insomnia severity index (Morin, 1993), as disrupted sleep is known to impact memory consolidation (Cellini, 2017). Eligibility was assessed using an online screening survey and telephone screen. All participants gave informed consent and all procedures for the study were approved by the UCL Research Ethics Committee. All participants were paid for their participation in the study.

2.2 Design and Procedure

Eligible participants were contacted by telephone to verbally verify intention to participate. Due to Covid-19 restriction, all four study sessions were completed online (see figure 1). Sessions were conducted at the same time of day within participants. The study had two within-subjects factors of 'think/no-think category' (word recalled (think), suppressed (no-think) or unpresented (baseline) on *session 2* and image-word *pair type* (beer-beer/beer-neutral/neutral-beer/neutral-neutral), as well as a double-blind randomised between-subjects factor of *retrieval* length (36/18/4/0 retrieval cues on *session 2*).

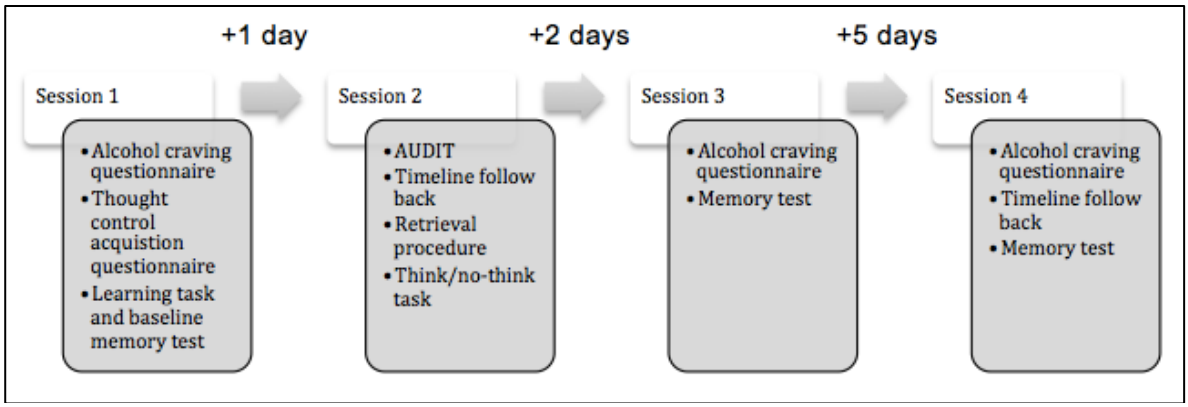

Figure 1: *Study timeline*

2.3 Questionnaire measures

Alcohol use identification test (AUDIT; Saunders et al., 1993) – is a 10-item questionnaire measure used to assess alcohol consumption, drinking behaviour and problematic drinking. A score of 8 or more is associated with harmful or hazardous drinking.

A calendar-based *Timeline Follow Back* (TLFB; Sobell & Sobell, 1992) was used to assess alcohol use over the previous 2 weeks on session 2, and the previous week on the final session.

Alcohol Craving Questionnaire – Short Form (ACQ-SF; Singleton, 2000) is a 12-item self-report questionnaire designed to measure state craving for alcohol. It has 4 subscales: compulsivity (loss of control over drinking), expectancy (desire for the benefits of drinking), purposefulness (intent/plan to drink to satisfy desires) and emotionality (urge to drink to relieve withdrawal/negative affect).

Thought Control Ability Questionnaire (TCAQ;(Luciano, Algarabel, Tomás, & Martinez Soria, 2005) is a 25-item self-report questionnaire designed to measure the perceived ability to control unwanted thoughts. Past research has shown that a high score on this measure was associated with being better able to voluntarily forget in a think/no-think task (Kupper et al., 2014).

2.4 Stimuli

Images: 18 images of beer and 18 images of water were taken from the Galician beverage picture set (GBPS;(Eduardo López-Caneda & Carbia, 2018) to be used as visual 'cues'.

Words: 18 'target' words, found to be recalled when given the word 'beer', were taken from the 'small world of words' word association study (De Deyne, Navarro, Perfors, Brysbaert, & Storms, 2019). The affective norms for English words (ANEW; Bradley & Lang, 1999) database was used to find neutral 'target' words that matched the beer words on word length, had neutral valence ratings (between 4.5 and 5.5) and arousal ratings (between 4 and 6).

Image-word pairs were created such that there were: 9 beer-image – beer-word pairs (beer-beer), 9 beer-image – neutral-word pairs (beer-neutral), 9 water-image – beer-word pairs (neutral-beer) and 9 water-image – neutral-word pairs (neutral-neutral). This pairing allowed us to investigate the impact of alcohol-relevant cues and targets on learning and forgetting processes.

2.5 Cue-Target Learning (Session 1)

Participants were instructed they must try to learn 36 image-word pair associates. The learning procedure was based on previous TNT learning tasks (Anderson and Green, 2001; López-Caneda, 2018). However, it was modified with monetary incentive (15p per correct answer in the final test on each session) to encourage participant engagement when completing the task online and to better engage motivated mnemonic processing.

Learning blocks (see figure 2) consisted of all image-word pairs being displayed in a random order for four seconds. The image-word pairs were split in to three blocks of 12 image-word pairs. After every four pairs recall was tested on the four image *cues* just presented. Participants were given the correct answer if an incorrect answer was given. After all the 36 image-word pairs had been presented the participants completed a full practice recall test. The learning blocks were presented once more followed by the 'final'

test. Participants were required to enter correct targets on at least 60% of trials. Participants that failed to do so were asked to complete the learning block again, followed by another 'final' test, until >60% accuracy was reached. For further details of the cue-target learning task see supplementary materials.

The number of correct responses/errors on the final 'test' of 36 images was used as the Session 1 assessment of learning.

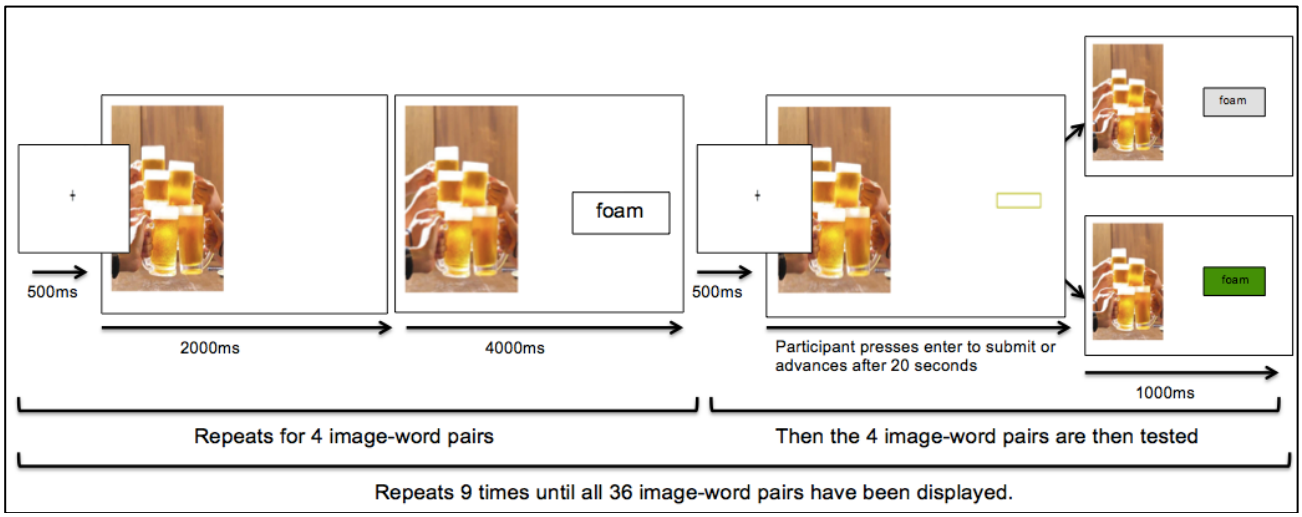

Figure 2: *Schematic of the learning task on session 1*

Participants were randomly assigned using a 'randomiser' in the Qualtrics software to one of four experimental 'retrieval' groups. The groups differed in the number of retrieval cues (images) shown. Either 0 (no retrieval), 4, 18 or 36 retrieval cues were shown. In the 4 and 18 retrieval cue groups the cues were selected randomly from the correct pairs recalled on session 1. The numbers we chose to investigate were based on the number of retrieval cues shown to induce memory destabilisation in previous studies in hazardous drinkers (Das et al., 2019; Das, Lawn, & Kamboj, 2015; Das et al., 2018) and in the paired associates task from which the current task was adapted (Forcato, Rodríguez, Pedreira, & Maldonado, 2010), as well a median point (18) and a no-retrieval control group (0 cues).

The retrieval and prediction error procedure were adapted from Forcato et al. (2007) to destabilise explicit memory associates. As in the training on session 1, images (retrieval cues) appeared on the left-hand side of the screen with a text box on the right. To create a 'prediction error', once the participant entered two letters of their answer a notice was displayed stating 'interruption', and not allowing participants to complete the answer. As the session was completed remotely, we were unable to reassure participants that they should continue with the task following this 'error'. To ensure participants continued we included a button in the top of right of the screen to click if participants thought the task was not working correctly. On clicking the button participants were informed they should continue with the task.

As per Das et al. (2015, 2018, 2019, 2020), participants then completed forwards and backwards digit span tasks, lasting approximately 5 minutes. With this high working- memory distractor task, we aimed to ensure cognitive offset and 'separation' of the retrieval task and the subsequent think/no-think task, but also to ensure participants were not covertly rehearsing the word pairs in the retrieval-extinction break.

2.7 Think/No-Think (Session 2)

We used a thought substitution form of the TNT task. Participants were instructed to 'replace' rather than just 'suppress' the no-think words to provide a metric of task performance and prevent participants from simply disengaging from the task, which was of concern, given the remote nature of testing due to Covid-19. Studies that have previously used explicit instructions to substitute rather than to inhibit have successfully shown the think/no-think effect (Racsmány, Conway, Keresztes, & Krajcsi, 2012).

During the think/no-think task, 24 of the 36 images from the learning task on *session 1* were presented. On *think* trials, (k = 12; 3 per *pair type*) participants were instructed to: "*think of the previously learnt word, enter it into the text box and keep it in mind during the entire presentation."*
For no-think trials (k = 12) participants were instructed to: "not let the previously associated word enter your consciousness. You should instead type the first word that comes to mind (that is not the previously learnt word) into the text box. […] Continue to think of the replacement word for the entire presentation". They were also instructed that the replacement word should not be related to alcohol. Participants were also given examples of a think and a replace trial using an image-word pair that had not been shown previously. They were required to answer three questions about the task instructions correctly before they were allowed to continue to ensure the task was fully understood. The final twelve images were not presented to serve as baseline comparison at subsequent test. See the supplementary materials for the complete instructions given to participants.
The images were pseudo-randomised to think, no-think or baseline conditions, with the restriction that the image-word *pair types* were evenly distributed between the three conditions. Once an answer had been entered the image was displayed with the participant's answers for a further 4 seconds. During the task on-screen text reminded participants of the task instructions: that they should continue to think of the original word (think trials) or not-think of the original word and instead enter the replacement word (no-think trials) (See figure 3). Between each presentation a fixation cross was displayed for 500ms. The colour of the fixation cross indicated the condition. A red fixation cross denotes a 'no-think trial', and a green fixation cross denotes think trials (Curran 2006). After each trial the participants were asked if the original word entered their mind, this gave us a measure of task adherence.

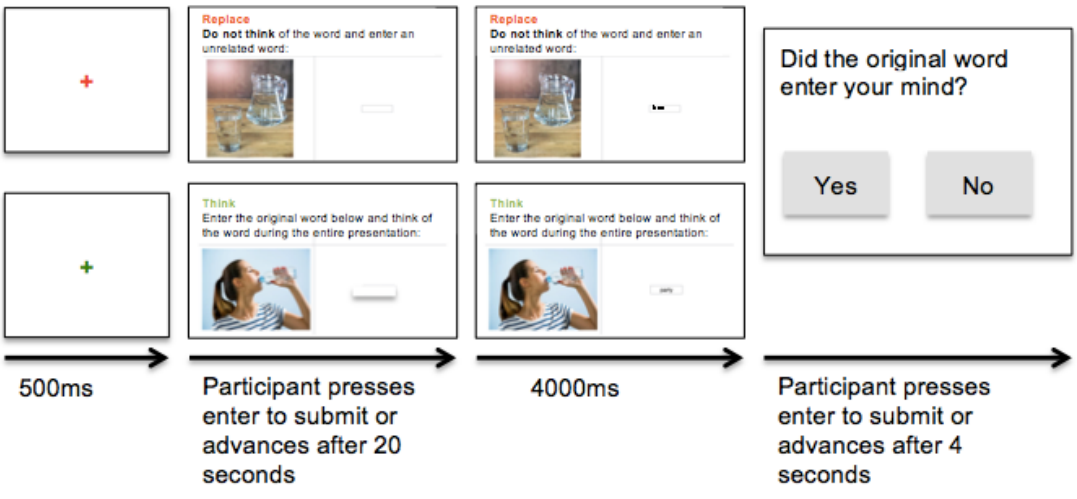

Figure 3: *Schematic of the think/no-think task on session 2*

2.8 Test (Session 3 & 4)

The test on session 3 and 4 (+2 days, + 1 week) was identical to the 'final test' on the first session and correct recall was again rewarded monetarily with 15p per correct answer given.

3. Data and analysis

All analyses were performed in IBM SPSS version 26.

One-way ANOVAs were used to check for differences on continuous measures between groups on session 1 (baseline).

As the recall data were highly skewed count data, with all factors of interest fixed, generalized estimating equations (GEE) with Poisson distribution and log link were used to model performance data, with an unstructured working correlation matrix (Zhang et al., 2012; Hubbard et al., 2010). The analysis of session 1 cue target learning included the subject factors of prospective *think/no-think* condition (3: Think/No-Think/ Baseline) and cue-target type (4: Beer-Beer/Beer-Neutral /Neutral-Beer /Neutral-Neutral), and a between-subjects factor of prospective retrieval group (4: retrieval=0 / retrieval=4 /retrieval=18 /retrieval=36 cues). Retrieval group and TNT were included in this analysis to ensure there were no differences at baseline. All possible interaction terms were also included (full factorial 3 x 4 x 4).

The main analyses of recall at session 3 and 4 included the subject factors of session (Session 1/Session 3 or Session 1/ Session 4 as appropriate) *think/no-think* condition (Think/No-Think/ Baseline) and cue-target type (Beer-Beer/Beer-Neutral /Neutral-Beer /Neutral-Neutral), and a between-subjects factor of retrieval group (retrieval=0 / retrieval=4 /retrieval=18 /retrieval=36 cues). All interaction terms that included the factor session were included. Other interaction terms were not included as they were not hypothesised to have an effect and models with greater parsimony can have greater predictive power (a full factorial analysis is included in the appendix which confirms these terms did not have a significant effect).

4. Results

Gender distribution was equivalent between retrieval groups and participants were well within the 'hazardous drinking' category (see table 1). There were no significant between-group differences at baseline.

Table 1: Descriptive statistics and test of between groups differences

	Retrieval=0 (N=18)	**Retrieval=4** (N=19)	**Retrieval=18** (N=18)	**Retrieval=36** (N=18)	**Statistical test of difference between groups** (ANOVA/Chi square)
Gender	5:12(F:M)	8:11(F:M)	9:10(F:M)	8:10(F:M)	$X^2(3,73)=.62$, $p=.891$
Age	24.82(4.08)	23.79(3.41)	23.37(2.67)	26.22(3.32)	$F(3,69)=2.34$,$p=.081$
AUDIT	12.82(4.22)	12.37(4.26)	13.37(4.76)	11.44(3.88)	$F(3,69)=.62$, $p=.610$
ACQ Total	45.24(15.43)	45.42(15.99)	47.37(13.66)	42.28(9.88)	$F(3,69)=.47$, $p=.703$
ACQ compulsivity	7.18(3.84)	8.37(5.34)	9.95(4.02)	6.83(3.01)	$F(3,69)=1.65$, $p=.186$
ACQ_Expectancy	11.94(4.37)	12.37(4.73)	13.16(4.15)	11.61(3.18)	$F(3,69)=.89$, $p=.448$
ACQ_purposefulness	14.59(3.95)	13.42(3.15)	13.32(3.53)	12.83(2.75)	$F(3,69)=.65$, $p=.584$
ACQ Emotionaility	11.53(5.08)	11.26(5.09)	10.95(4.47)	11(4.41)	$F(3,69)=.04$, $p=.990$
Total pints of beer drank in 2 weeks prior	20.09(7.83)	18.71(11.62)	17.42(13.2)	21.72(19.84)	$F(3,69)=.45$, $p=.722$
Total units consumed in 2 weeks prior	76.97(25.36)	76.61(36.28)	77.89(57.37)	83.88(57.12)	$F(3,69)=.10$, $p=.962$
Number of days drinking in 2 weeks prior	10.41(2.79)	9.58(2.95)	8.68(3.94)	10.33(3.07)	$F(3,69)=1.59$, $p=.199$
TCAQ	69.59(18.85)	72.79(11.76)	75.53(16.15)	76.67(17.64)	$F(3,69)=.57$, $p=.635$

Insomnia Severity Index	6.94(4.29)	5.68(4.18)	6.47(3.99)	5.67(3.69)	F(3,69)=.60, *p*=.620

4.1 Session 1 – Cue-Target Learning

The mean percent learnt on session 1 was 83.30% (range: 61.11%-100%).

Effect of pair type on learning of image-word pairs on session one

GEE analysis was used to investigate differences between pair types in immediate recall on *session 1*. Prospective retrieval group and prospective TNT condition were also included to ensure there were no differences at baseline (table 2; figure 4). This analysis found *pair-type* was a significant predictor of the number of pairs recalled on session one ($\chi^2(3)=20.79$, $p<.001$). Pairwise comparisons revealed this effect was driven by greater recall of *beer-beer* image-word pair types vs. all other image-word pair types ($p<.001$). As expected, on session 1 there was no significant effect of retrieval group ($\chi^2(3)=5.69$, $p=.862$). Unexpectedly, there was a significant effect of (prospective) T/NT condition ($\chi^2(2)=10.93$, $p=.004$. Pairwise comparisons revealed this was because 'baseline' words were better recalled than (what would be) 'think' words subsequently ($p=.002$*).*

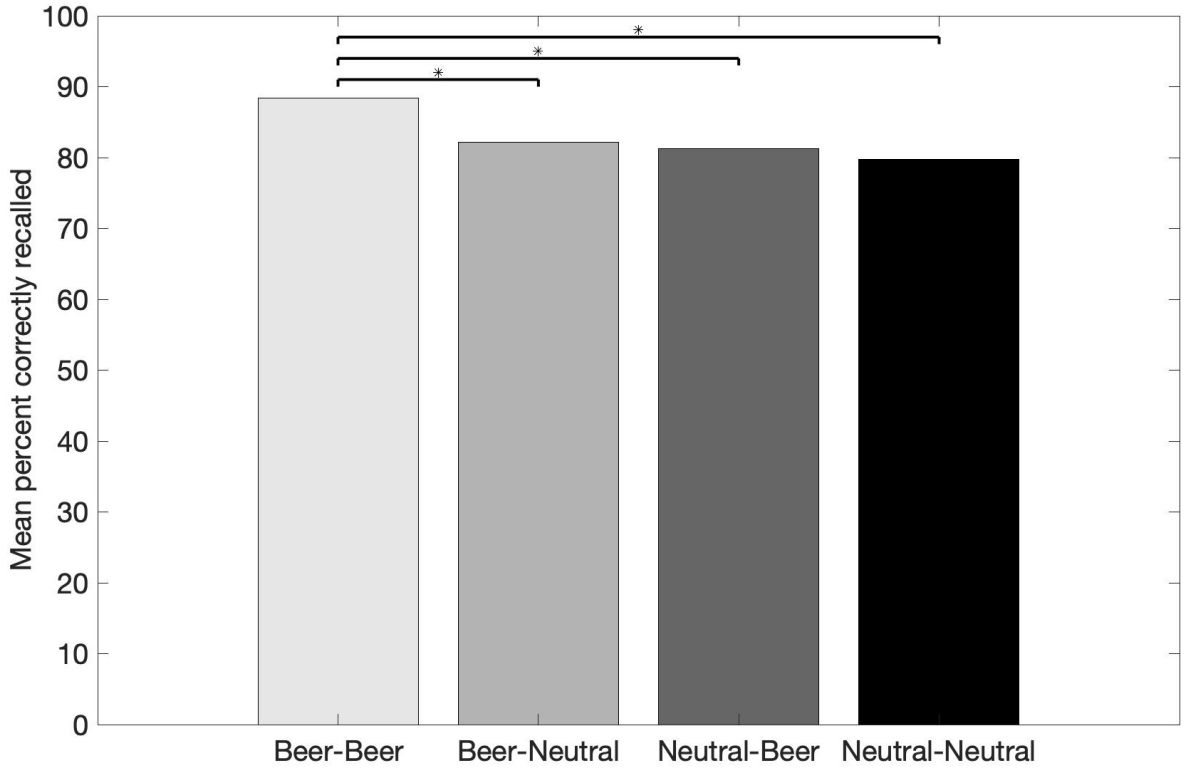

Figure 4: *Bar graph of recall percent on session 1. See supplementary materials for histograms of this data.*

Table 2: Results of GEE analysis used to assess effects on cue-target learning on session 1

Parameter		**Wald Chi Square**	**95% CI**	**df**	**Sig**	**Effect size Cramér's V**
Group		0.64		3	.887	.054
	Retrieval = 0 trials		[.36, .72]			
	Retrieval = 4 trials		[.30, .61]			
	Retrieval = 18 trials		[.36, .71]			
	Retrieval = 36 trials		[.35, .65]			
Pair-Type		18.73		3	**<.001**	.292
	Beer-Beer		[.25, .43]			
	Beer-Neutral		[.41, .65]			
	Neutral-Beer		[.44, .66]			
	Neutral-Neutral		[.45, .71]			
TNT		10.93		2	**.004**	.274
	Think		[.45, .66]			
	No-Think		[.37, .58]			
	Baseline		[.35, .53]			
Group*Pair-Type		5.34		9	.804	.090
Group*TNT		9.11		6	.167	.144
Group*Cue*TNT		4.20		6	.650	.098

4.2 Session 2 - Think/No-Think task

Participants correctly entered a replacement word rather than the original word an average of 99% (range: 93%-100%) of the time on 'No-think' trials. However, participants reported an intrusion of the original word an average of 50.8% of the time on no-think/replace trials and that they successfully thought of the original word an average of 82.5% of the time on think trials (note that participants did not always answer this question on time and these percentages are based on the number of times participants answered). This suggests that participants found no-think trials difficult to perform correctly.

4.3 Recall on session 3 (after 2 days)

Table 3: Results of main GEE analysis used to assess the effects of the TNT task, pair type and retrieval group on recall of image-word pairs

Parameter		Wald Chi Square	95% CI	df	Sig	Effect size Cramér's V
Session		25.00		1	**<.001**	.585
	Session 1		[.40, .56]			
	Session 3		[.56, .77]			
Group		1.93		3	.588	.094
	Retrieval = 0 trials		[.44, .90]			
	Retrieval = 4 trials		[.35, .64]			
	Retrieval = 18 trials		[.46, .81]			
	Retrieval = 36 trials		[.41, .71]			
Pair-Type		31.32		3	**<.001**	.378
	Beer-Beer		[.31, .47]			
	Beer-Neutral		[.49, .73]			
	Neutral-Beer		[.54, .76]			
	Neutral-Neutral		[.56, .80]			
TNT		1.45		2	.485	.100
	Think		[.43, .64]			
	No-Think		[.48, .69]			
	Baseline		[.48, .67]			
Session * group		2.60		3	.458	.109
Session * Pair-Type		0.15		3	.986	.026
Session * TNT		37.27		2	**<.001**	.505
Session * group * Pair-Type		20.66		18	.297	.125
Session * group * TNT		16.70		12	.161	.138
Session * Pair-Type * TNT		29.87		12	**.003**	.185
Session * group * Pair-Type * TNT		126.70		36	**<.001**	.220

GEE analysis was used to investigate the effect of the factors: session (1/3), TNT (think words/no-think words/baseline words), pair-type (beer-beer/beer-neutral/neutral-beer/neutral-neutral), and group (0/4/18/36 retrieval trials). This revealed session was a significant predictor of recall ($\chi^2(1)=25.00, p<.001$), indicating decreased recall on session 3 in comparison to session 1.

Think/no-think

Pairwise comparisons between session 1 and 3, on the significant session*TNT condition interaction, showed the recall of no-think and baseline items significantly reduced (p<.001). Pairwise comparisons revealed that recall of 'think' words was significantly greater than baseline words (p<.001), and no-think words (p=.001*)*, on session 3. There was no-difference between baseline and no-think conditions (p=.569) on session 3 indicating a lack of lasting suppression-induced forgetting overall.

Further investigation using separate GEE analyses for each pair type revealed the practice effect was only present in the beer-beer pair type (baseline vs. think: p<.001) and a suppression induced forgetting effect in the neutral-neutral pair-type (no-think vs. baseline: p<.047). See figure 5 and supplementary materials for more in-depth results.

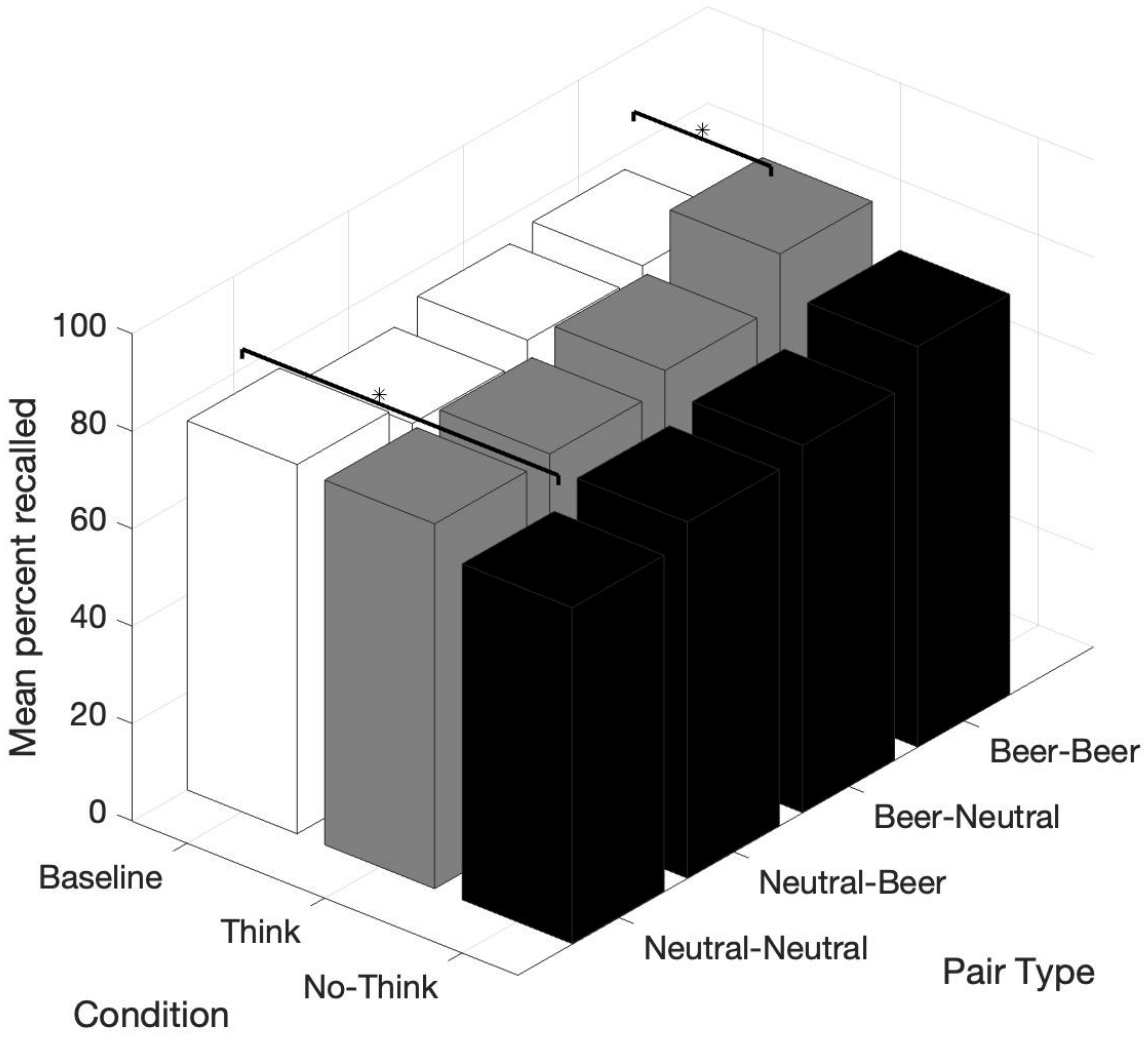

Figure 5: *Bar graph of recall percent on session 3. See supplementary materials for histograms of this data. 'Baseline' refers to baseline words not shown during the TNT task.*

Retrieval group

The significant four-way interaction of session*TNT*pair type*group ($\chi^2(36)=126.70$, $p<.001$) was explored by using separate GEE analyses on each group.

This revealed the session*TNT*pair type interaction was only significant in the groups undergoing 4 (group 4: $\chi^2(6)=40.32$, $p<.001$) and 36 retrieval trials (group 36: $\chi^2(6)=14.39$, $p<.05$; group 0: $\chi^2(6)=2.88$, $p=.824$; group 18: $\chi^2(6)=7.77$, $p=.256$). Pairwise comparisons between baseline word recall and think/no-think word recall on session 3 were used to investigate this interaction further in group '4' and '36'. In the group with 'full' retrieval (36 trials) there was no effect of the think/no think manipulation on recall, other than in the beer-beer pair types, where 'think' words were recalled significantly better than baseline words ($p=.002$); indicating a practice/rehearsal effect. In the four- cue group 'think' words were recalled significantly more than 'baseline' words on session 3 ($p<.001$) for beer-beer and neutral-beer pair types. Conversely, no-think words in neutral-neutral pair types were significantly *less* well recalled ($p=.006$), indicating a specific retrieval-suppression effect that was limited to non-alcohol-related word pairs.

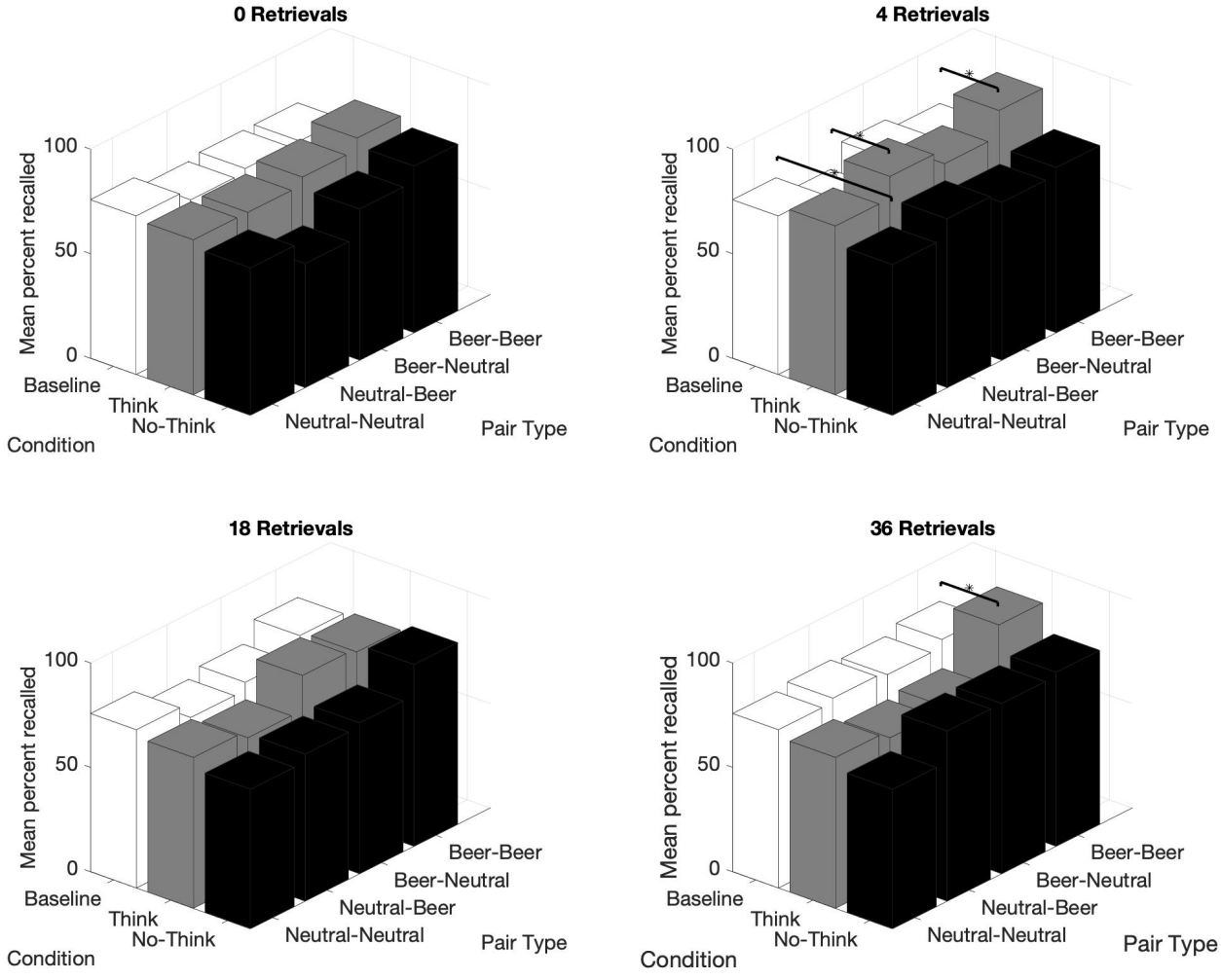

Figure 6: *Bar graph showing the mean percent correctly recalled on session 3. 'Baseline' refers to baseline words not shown during the TNT task. See the supplementary materials for histograms of this data.*

4.4 Recall on session 4 (after 7 days)

Table 4: Results of main GEE analysis used to assess the effects of the TNT task, pair type and retrieval group on recall of image-word pairs

Parameter		**Wald Chi Square**	**95% CI**	**df**	**Sig**	**Effect size Cramér's V**
Session		23.84		1	**<.001**	.571
	Session 1		[.40, .57]			
	Session 4		[.56, .77]			
Group		2.40		3	.494	.105
	Retrieval = 0 trials		[.43, .89]			
	Retrieval = 4 trials		[.36, .64]			
	Retrieval = 18 trials		[.48, .83]			
	Retrieval = 36 trials		[.40, .69]			
Pair-Type		33.04		3	**<.001**	.388
	Beer-Beer		[.31, .47]			
	Beer-Neutral		[.48, .71]			
	Neutral-Beer		[.54, .76]			
	Neutral-Neutral		[.58, .82]			
TNT		0.24		2	.885	.041
	Think		[.45, .66]			
	No-Think		[.47, .68]			
	Baseline		[.48, .67]			
Session * group		3.10		3	.377	.041
Session * Pair-Type		0.71		3	.870	.057
Session * TNT		22.38		2	<.**001**	.392
Session * group * Pair-Type		17.62		18	.481	.116
Session * group * TNT		19.47		12	.078	.149

Session * Pair-Type * TNT	24.01	12	**.020**	.166
Session * group * Pair-Type * TNT	53.68	36	**.029**	.143

GEE analysis was used to investigate the effect of the factors: session (1/4), TNT (think words/no-think words/baseline words), pair-type (beer-beer/beer-neutral/neutral-beer/neutral-neutral), and group (0/4/18/36 retrieval trials). All interaction terms that included session were included (Table 4; figure 7,8). This revealed that session was a significant predictor of recall ($\chi^2(1)=23.84$,$p<.001$), such that recall was decreased on session 4 in comparison to session 1.

Think/no-think

There was a significant interaction of session*TNT condition ($\chi^2(2)=22.38$, $p<.001$) such that the recall of no-think and baseline items was significantly reduced ($p<.001$). Pairwise comparisons of the difference between baseline (unpresented) word recall and think/no-think word recall on session 4 were inspected. Pairwise comparisons revealed think word recall was better than both baseline word recall ($p=.003$) and no-think word recall ($p=.034$) (i.e. a practice effect), but there was no difference between control and no-think conditions ($p=.317$), revealing a lack of suppression induced forgetting *overall*.

As on session 3 analyses, separate GEEs were conducted for each pair type. These revealed the practice effect was only present for the beer-beer pairs (think vs. baseline: p<.001). See figure 7 and supplementary materials for more in-depth results.

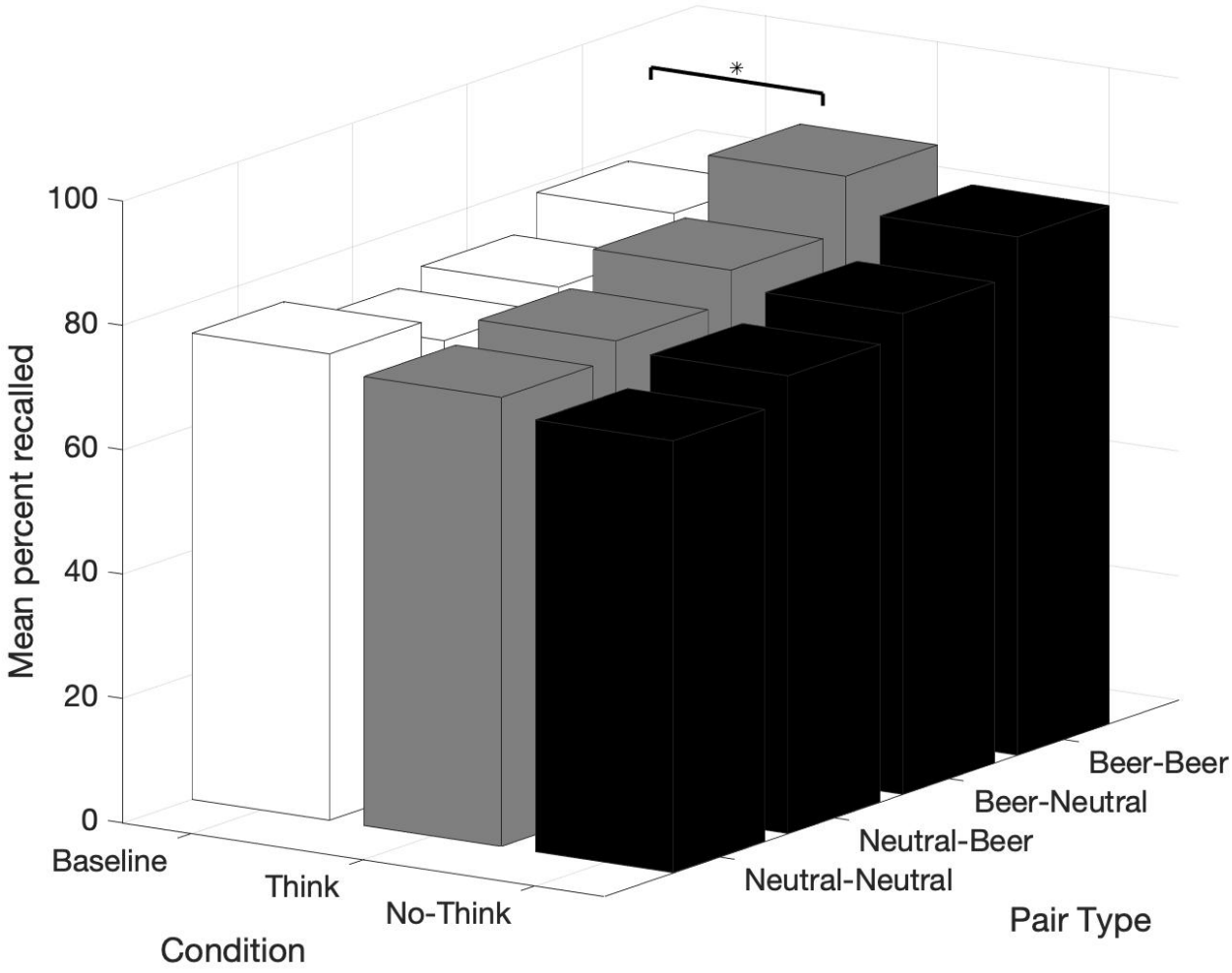

Figure 7: *Bar graph of recall percent on session 4. See supplementary materials for histograms of this data. 'Baseline' refers to baseline words not shown during the TNT task.*

Retrieval group

The significant four-way interaction of session*TNT*pair type*group ($\chi^2(36)=53,68$, $p<.05$) was explored via separate 3-way GEE analyses for each group.

The separate analyses of each group revealed the session*TNT*pair type interaction was only significant in the group with 4 retrievals (group 4: $\chi^2(6) =14.50$, $p=.024$), but not in other retrieval conditions (group 0: $\chi^2(6)=2.95$, $p=.815$; group 18: $\chi^2(6)=8.82$, $p=.184$; group 36: $\chi^2(6)=10.39$, $p=.109$). Pairwise comparisons in the 4-cue retrieval group revealed that beer-beer ($p=.001$) and neutral-beer ($p<.047$) pairs in the 'think' condition were significantly better recalled than 'control' words on session 4, with beer-neutral 'think' pairs nearing significantly greater recall ($p=.051$), but no effect on neutral-neutral pairs ($p=.886$). There was no significant difference between no-think and baseline word recall on session 4. Taken together, these findings indicate a failure of suppression-induced forgetting, but a recall-boosting effect of 'think' pairs following the 4-trial retrieval consistent with the memory strengthening role of reconsolidation and previous

research demonstrating induction of alcohol memory reconsolidation following 4-cue retrieval (Das et al, 2015, 2018, 2019, 2020).

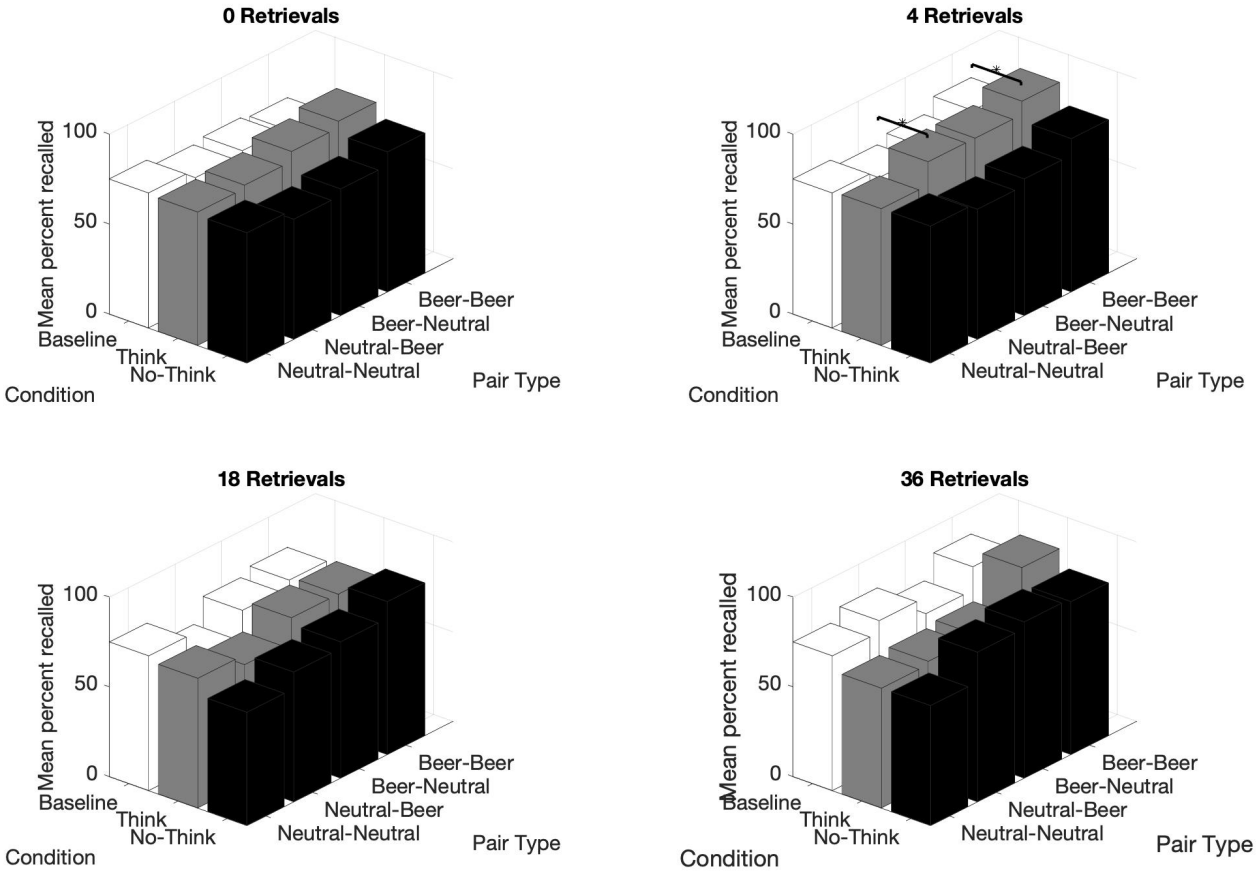

Figure 8: *Bar graph of recall percent on session 4. See supplementary materials for histograms of this data. 'Baseline' refers to baseline words not shown during the TNT task.*

5. Discussion

This study is the first to examine whether reward relevance and prior associability modulates the ability to intentionally suppress recall. We assessed 'retrieval suppression' using a modified version (online) of the Think/No-Think task to target recall of alcohol reward-relevant and neutral associates in a hazardous drinking population. We did not observe suppression effects for alcohol-related associate pairs. However, consistent with previous research, a suppression effect was seen for neutral cue/target stimuli (water image – neutral word pair associates), reducing subsequent recall and providing support for the hypothesis that alcohol-related associates would be harder to suppress in our sample of hazardous drinkers. We further sought to assess whether retrieval-suppression effects could be enhanced by first destabilising the cue-target pair memory in a reconsolidation-interference paradigm.

Only the group that received 'brief retrieval' (4 retrieval cues) prior to the T/NT task showed a significant suppression effect at subsequent test and this effect was limited to the neutral-neutral pair types on session 3 (2 days post TNT) only. A practice effect (increase in 'think' words compared to unpresented control words) was also seen in this group (at both 2- and 7-days post TNT) and in the 'full retrieval' group (all 36 pairs retrieved), at 2-days post TNT, in some alcohol-related items. The findings in the 4-trial retrieval group (enhancing and prolonging practice effects and enhancing the suppression effect in neutral associates) are consistent with reconsolidation effects and previous research demonstrating induction of alcohol memory reconsolidation following 4-cue retrieval (Das et al, 2015, 2018, 2019, 2020). In the 36-trial retrieval group a significant effect on session 3 is seen between think and baseline items. Whilst we cannot state from this data that this effect is definitely not due to memory reactivation, it seems likely that the extra presentation of stimuli during memory retrieval would have caused an increase in recall.

That the 'classic' suppression effect in the T/NT task was only seen for neutral items (and only in the 4-trial retrieval group) suggests that the study population and inclusion of alcohol-related images and words in the TNT task made it difficult for the image-word pairs to be suppressed. Past research by López-Caneda et al. (2018) has demonstrated suppression-induced forgetting of alcohol related pairs in healthy participants. As such, the lack of suppression induced forgetting in alcohol pairs may reflect a characteristic of our sample of hazardous drinkers. This is of primary relevance to the aetiology of alcohol misuse and to clinical intervention, but may equally represent a key constraint on the efficacy of retrieval-suppression that limits its potential for treating maladaptive reward memory. However, future research including a healthy control group would be crucial to confirm these suggestions. Studies have shown cognitive control deficits in alcohol use disorder (Wilcox et al., 2014) and enhanced attention bias toward alcohol cues (Field & Cox 2008), which may have made it particularly difficult for our group to 'supress' alcohol-related associates. Similarly, practice effects (increase in 'think' words compared to unpresented control words) were seen only in image-word pairs containing alcohol related stimuli. Whilst it is not possible to say rule out a contribution of memory reactivation here, the seeming specificity of this practice effect (think>baseline) to beer-beer pairs in the 36-trial retrieval group may simply reflect the prior associability of these items. Greater salience and prior semantic association between beer images and words may reduce threshold for correct retrieval

(and thus practice effects) via attentional orienting, or automatic activation of associates. Indeed, this is a population where there is an unmeasured (but presumably highly extensive and variable) history of reward-learning surrounding alcohol. We measured thought control ability in our sample using the thought control ability questionnaire (TCAQ) and scores did not indicate a reduced ability to control thoughts, with comparable scores to those obtained in studies of healthy subjects (Feliu-Soler et al., 2019).

The majority of TNT literature tests recall immediately post the TNT task. Studies that have assessed the long-term outcome of TNT suppression have tested recall after 3.5 hours (Davidson et al., 2019), after 2-3 months and after 12-13 months (Noreen & Macleod, 2014). All of which found the suppression effect dissipated over prolonged periods. Demonstrating an enduring suppression effect would be crucial if the retrieval-suppression approach was to have a clinical application. In the current study we assessed possible prolongation of the suppression effects via memory reconsolidation. The use of a 4-retrieval trial memory reactivation procedure with TNT did lead to a suppression effect 2 days post the TNT (which was not seen in any other retrieval group); however after 7 days this effect had dissipated. We did not test immediately post the TNT task, as this would have interfered with the reconsolidation manipulation. As such, it may be that if we had tested recall immediately after TNT, we would have observed more suppression effects, however if the effect were so short-lived, any clinical relevance would be severely limited.

Reconsolidation is a general memory updating process, allowing memory strengthening (as seen enhanced in practice effects in think trials) and weakening (as per the suppression effects seen in neutral associates), depending on the conditions 'destabilised' memories are exposed to. In the current study we have replicated previous findings, which demonstrated an effect of reconsolidation on paired-associate learning (Forcato et al., 2007; Forcato, Rodriguez, & Pedreira, 2011; Forcato, Fernandez, & Pedreira, 2013). Additionally, we extended these finding by testing four retrieval 'lengths', and were able to identify that four retrieval trials led to effects most consistent with reconsolidation, as it was the most effective of the four retrieval lengths tested. The retrieval lengths tested were based on prior research, but the 'optimal' retrieval for destabilisation may be somewhere between (or beyond) the lengths tested. It is likely also a function of the learning history e.g. memory strength and age, in combination with reactivation parameters. As such the findings here may not be generalisable beyond the present paradigm. In rats it has been shown that a reactivation of 3 minutes was enough to trigger reconsolidation of a 1-day old memory, but 5 minutes was necessary to reactivate a 21-day old memory. Thus far in humans a short reactivation, similar to the 4-retrieval group used in the current study, has been shown to be enough to trigger reconsolidation effects of memories (Das et al, 2015, 2018, 2019, 2020; Schiller, Raio & Phelps, 2012). The lack of reconsolidation effect seen in the longer retrieval groups is consistent with other studies that utilised longer retrieval periods (Potts and Shanks, 2012; Hardwicke et al., 2016), and with a study which measured the optimal retrieval length for motor memory reactivation (de Beukelaar, 2014). Although we can make no claims with regards to endogenous mechanisms, the pattern of effects across retrieval lengths in the current study is broadly consistent with the pattern observed in research showing the existence of a "limbo" state between reactivation and new learning (Merlo et al., 2014;2018, Vaverovka et al, 2020). This pattern is characterised

by reconsolidation-update effects at short reminders, new learning effects (e.g. extinction) with many reminders and a lack of effects between, as observed here in the 18-trial retrieval group. Together this confirms that retrieval length (i.e. N reminders) is a crucial boundary for reactivating human memories and suggests a short reactivation procedure is likely to be optimal.

Past research has demonstrated that memory reconsolidation is only triggered when the retrieval experience contains novel or surprising information (a prediction error; Pedreira et al., 2004; Morris et al., 2006; Díaz-Mataix et al., 2013). Indeed, retrieval 'length' may only be important to the extent that it represents the accrual of prediction errors. In the current study a PE occurred on every retrieval trial (adapted from Forcato et al., 2007), however many other studies utilise a single PE. Research to examine the effect of multiple PEs found a single PE triggered memory destabilisation whilst multiple PEs lead to a 'limbo' state, between reconsolidation and extinction (Sevensters et al., 2014; Merlo et al, 2014). In our study, four PEs was most consistent with memory destabilisation. However, PE can be construed at various levels (neurobiologically, behaviourally, computationally and cognitively) and the discrepancy may be due to the differing nature of the PEs under study. In Sevenster et al.'s (2014) study the PE was created by the omittance of an expected aversive outcome (a shock), in a Pavlovian conditioning paradigm. In our study, learning was explicit and participants were simply prevented from completing an answer, this does not directly give any information about the outcome word but contradicts their expectation that they should be able to enter it. Further experimental investigation of PE nature, number and magnitude is needed to determine optimal retrieval procedures. We hope that this research highlights the need to focus upon retrieval in reconsolidation research, rather than treating it as a nuisance parameter hampering the search for reconsolidation-modifying interventions.

Strengths and Limitations:

The current study had several other methodological differences to the classic TNT paradigm (Anderson & Green, 2001). One strength of the current study is that a monetary incentive was offered for the correct recall of items. This was done to create memories that were associated with a reward to be analogous with associative alcohol memories. It may be that reward related memories are protected from the suppression effects of TNT, and that the suppression effect would have been more lasting in the neutral pair word recall and present in the alcohol pair word recall had we not added this recall reward. However, if this is the case, clinical implementation of the paradigm in reward-related disorders would be precluded.

In order to facilitate the investigation of the effect of reconsolidation on TNT, pairs were learnt the day before the retrieval + TNT intervention, allowing time for the pairs to be consolidated. Most previous TNT studies involved memories that have been acquired immediately before the TNT task. One other study has investigated the suppression of consolidated memories (learnt 24 hours before) using a TNT task and did not find a reduction of no-think items in comparison to baseline items (Liu et al., 2016). In reality, most memories that an individual may want to supress are likely to be at least a day old. In the current study, we hoped to circumvent this issue by reactivating the memory of image-word pairs.

Another methodological difference in the current study was the use of the 'substitution' version of the TNT task, in which we specified that participants should substitute the originally learnt word with a new word ad-hoc at retrieval instead of just trying to suppress it. This may produce forgetting via a different mechanism to direct suppression (i.e. competing associates from a single cue; Benoit & Anderson, 2012). We used this approach because 1) pre-specifying a strategy may reduce variability due to spontaneous covert use of a substitution strategy in a suppression paradigm 2) a replacement strategy was better suited to the online nature of the current study, providing a basic check on task compliance, and 3) the response inhibition deficits and higher automatic cue reactivity that typifies hazardous drinkers may make direct suppression more difficult for this group. Due to this we are unable to disentangle the mechanisms underlying any 'forgetting' effects and comparison of the two strategies in this group is a topic for future study and potential clinical implementation. We included just six repetitions of each associate pair in the TNT trials because each trial was considerably longer and more involved than those used in other studies. This is because participants were required to first type in their substitute response and then to view the image with the replacement for a further four seconds. Piloting indicated that more repetitions of the TNT procedure felt unacceptably long to participants. However, it has been shown several times that more TNT trials lead to an increased effect of suppression (Curran, 2006). It may also be that our longer trials meant a greater degree of cognitive effort was required to inhibit the original word, and thus a greater number of ''unsuccessful' suppression attempts. To overcome this issue future studies could assess if multiple retrieval-TNT session across several days could lead to strong and lasting effects.

There are several limitations of the current study discussed above but notably this study utilised remote testing which results in many unknowns about participants' compliance with instructions. Future research will be needed to ensure these methodological differences cannot explain the findings of this study. Experimental investigation of these methodological differences is needed to examine the constraints upon the efficacy of retrieval suppression to identify conditions that are likely to benefit and to prune away translational; 'dead ends'. Additionally, a large number of statistical tests were necessarily used in the analysis of the data from this study. This increases our risk of type 1 error. As such, replication studies would be beneficial to confirm our findings.

In conclusion, this study investigated a reconsolidation enhanced TNT procedure in a sample of hazardous drinkers. The two key findings from this study are 1) a short retrieval & PE procedure produces memory effects consistent with triggering memory reconsolidation and 2) the use of reward-relevant alcohol cues diminishes suppression induced forgetting in a sample of hazardous drinkers. These findings should energise further experimental research to better elucidate the optimal memory reactivation conditions for associative memories and the potential constraints on intentional-suppression approaches.

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