Cognitive and neuropsychopharmacological processes in human drug craving
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Citation for published version (APA):

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Selective Memory for Alcohol Cues in Alcoholics and its Relation to Craving

There is evidence that alcoholics and (abstinent) alcoholics display a cognitive processing bias that may contribute to relapse and recurrence after abstinence. The current hypothesis was that abstinent alcoholics would demonstrate enhanced memory for alcohol-related pictures (memory bias) compared to non-alcoholic drinkers. In addition, it was hypothesized that there would be a positive relation between alcohol craving and this memory bias. The cognitive processing of alcohol cues was compared to general incentive cues (food) and neutral cues in a group of alcoholics (n=26) and non-alcoholic (light) drinkers (n=24). Alcoholics showed enhanced memory for alcohol cues compared to neutral or general incentive cues. Moreover, the magnitude of this bias was positively correlated with alcohol craving. This study provides evidence for the presence of a memory bias for alcohol cues in alcoholics. This memory bias possibly results in enhanced alcohol craving. Implications for further study and treatment of alcoholism are discussed.


Introduction
The cognitive processing of disorder-relevant stimuli is important in the etiology, maintenance, and treatment of psychopathological disorders\(^1\). For example, there is growing evidence that alcoholics demonstrate specific cognitive processing biases for alcohol-related information\(^2\). These studies show that alcoholics pay more attention to alcohol related information than to neutral information. This attentional bias may contribute to the chronic nature of alcoholism and the frequently reported relapse after a period of abstinence. In contrast to attentional processing, less is known about a possible memory bias in alcoholism. Associative learning mechanisms, such as the encoding and retrieval of explicit memories, may play a role in the maintenance of addictive behaviors\(^2\). A conditioned stimulus (a stimulus associated with alcohol use) can activate a specific neural network that consolidated the original memory\(^3\). Cognitive theories predict that information related to the disorder will be more readily encoded in memory and more easily accessed in recall\(^4\). For example, Hermans et al.\(^6\) showed that patients with anorexia nervosa demonstrate a strong explicit memory bias for anorexia-related words using an explicit memory test (cued recall). When confronted with alcohol related stimuli, alcoholics may experience that similar cue elicited memories exacerbate the experience of craving. It is known that this alcohol craving can result in relapse after a period of abstinence\(^5\).

Although there is some evidence that addiction may be related to altered memory functions\(^7\),\(^8\), to our knowledge, no study has investigated the concept of memory bias for alcohol cues and its relation to craving. In the present study, alcoholics and light drinkers were compared on incidental recall of alcohol versus general incentive and neutral information on a color-naming task. It was predicted that alcoholics would remember more alcohol pictures (but not more control pictures) than light drinkers. Furthermore, it was hypothesized that this memory bias correlates positively with an increase in alcohol craving. This study was part of a more comprehensive study on selective information processing in alcoholic subjects and only data on memory bias and craving are reported here.
Table 1 Means (M) and standard deviations (SD) for the recall and cue-elicited instant craving data of light drinkers (n=24) and alcoholics (n=26).

<table>
<thead>
<tr>
<th></th>
<th>Light drinkers</th>
<th>Alcoholics</th>
<th>M</th>
<th>SD</th>
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<td>1.97</td>
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<td>Recall general incentive</td>
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<tr>
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<td>Alcoholics</td>
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</table>

Method

Subjects

The alcoholic group consisted of 26 participants who were recruited from the patient population of an alcohol-free inpatient alcoholism treatment program. All subjects met the criteria for alcohol dependence. Based on the QFV-Index, all subjects of this population were excessive drinkers. Most alcoholic subjects (84.6%) drank more than 24 days a month on average and if they drank, most subjects (92.3%) drank more than 7 standard glasses. The light drinkers were recruited from treatment staff. This was done in order to control for familiarity effects on memory, as it is likely that treatment staff is frequently exposed to alcohol related cues and alcohol related problems. Based on the QFV score, 24 of the 32 subjects fulfilled the criteria for light drinkers and were included in the study. The remaining eight subjects were classified as moderate drinkers and were excluded. Informed consent was obtained for all subjects and the local medical ethical committee approved the study. On the testing day, all subjects were asked to abstain from alcohol. The persons recruited from the alcohol treatment program were at least one week detoxified and free of withdrawal symptoms. None of the alcohol subjects were positive on the breath analyzer, which is employed routinely in the alcohol clinic. Eight alcoholic subjects received acamprosate. T-testing revealed no differences between subjects with and without acamprosate on the dependent variable. Therefore, the subjects with acamprosate were not analyzed separately. The group alcoholics was older (44.0 vs. 37.4 years, t=-2.23, 48 df, p=.030), consisted of more males (80.8% vs. 50.0%, χ²=5.26, 1 df, p=.033), and had less higher education (53.8% vs. 79.2%, χ²=7.69, 1 df, p=.021). However, none of these variables had a significant effect on the dependent variable (memory bias).

Instruments

The Quantity-Frequency-Variability Index (QFV-Index) is a questionnaire for measuring drinking history. In this questionnaire three items are employed in order to determine the drinking quantity (number of glasses), frequency (drinking days) and variability (binge drinking) during the last 6 months. The classification of drinkers is described in Meerkerk, et al."

Desires for Alcohol Questionnaire (DAQ) measures instant craving and is derived from the Alcohol Craving Questionnaire (ACQ). In a recent validation study of these two alcohol craving questionnaires, the DAQ was found to have clear psychometric advantages over the ACQ. In a cue reactivity study of Schultz and Jones, the DAQ was a sensitive measure of subjective cue reactivity. The DAQ, as used in the present study, measures four dimensions of craving, strong desires and intentions, negative reinforcement craving, control, and mild desires. The Obsessive Compulsive Drinking Scale (OCDS) is a self-rating scale that measures alcohol craving over the previous week.
(chronic craving) by quantifying obsessive thoughts about alcohol use and compulsive behaviors toward drinking. This scale has been translated in Dutch language and is a valid and reliable questionnaire for measuring these two constructs\cite{21,22}.

**Stimuli**

The stimulus material consists of color pictures with neutral (n=10), food related (n=10) and alcohol related (n=10) content. The food and neutral pictures used in this memory task where chosen from the International Affective Picture Set (IAPS) database\cite{23}. The alcohol pictures were taken by one of the authors (MR) and were rated in a pilot study on their valence and arousal properties. For this rating, the Self Assessment Manikin (SAM; Bradley & Lang)\cite{24} was employed. The SAM was used in order to quickly assess reports of affective response on the alcohol pictures. The SAM is a non-verbal pictorial assessment technique that directly measures the valence and arousal associated with a person's affective reaction to emotional stimuli. In this pilot study, 20 healthy participants (other persons than the main experiment) were asked to rate a set of 30 alcohol pictures on those two dimensions (60 items). Ten alcohol pictures with the highest valence and arousal ratings were chosen for the present study. The neutral cues were pictures of inanimate objects (e.g. garbage can, plate, book), the general incentive cues consisted of food pictures (e.g. candy, chocolate) and the alcohol cues were pictures of beer and liquor.

In order to avoid explicit selective encoding (i.e. deliberate encoding a specific category of pictures) an incidental learning task was used. In this task, every picture is placed in front of a colored circle (red, green, yellow or blue) and the participant was instructed to name the color of the circle as quickly as possible. The picture stayed on the screen until a response was made. Subjects were not told about the recall procedure in advance in order to exclude explicit encoding of specific cues.

There were 120 color naming trials and each stimulus was presented four times in a different color. The appearance of pictures and colors was random, the only restriction being that, the same color could not appear more than three times in succession.

**Apparatus**

The pictures were presented with use of the Experimental Run Time System (ERTS)\cite{25} run on an IBM 300 GL personal computer. The stimuli were presented on an IBM G54 15" color monitor in a 320 x 240 resolution with 256 colors.

**Procedure**

After the participants were provided with information about the test and the aim of the study, they were asked to sign informed consent. First, participants completed the baseline DAQ, OCDS and QFV. Then, after a short instruction, the pictures were presented. After this task, the participants were asked to complete the DAQ again. After this questionnaires subjects were asked to name as many pictures from the memory task as possible (free-recall procedure).

**Analysis**

The number of recalled pictures was separately analyzed using a 2x3 mixed design repeated measurement ANOVA for Group (light drinkers vs. alcoholics) x Cue type (neutral, alcohol, general incentive pictures) with Greenhouse-Geisser corrected degrees of freedom for sphericity correction\cite{26}. Tests of Within-Subjects Contrasts were performed in order to determine in which cue category the differences were present. In addition, differences in alcohol memory bias (recall of alcohol cues minus recall of neutral cues) and general incentives bias (recall of food cues minus recall of neutral cues) were tested with use of paired t-tests. Differences in craving were tested using independent t-tests. In addition, correlations between craving change (post craving score minus baseline craving scores) and memory bias were calculated.

**Results**

**Memory bias**

Means and standard deviations for the recall and craving data are summarized in table 1. No difference was observed be-
between light drinkers and alcoholics on the overall number of recalled pictures (F=.001, 1/48 df, p=.972). However, there was a significant main-effect of Cue type on recall. Analysis of within subjects contrast showed that all subjects recalled more pictures with alcohol content than neutral content (F=41.00, 1/48 df, p<.001). In addition, analysis of interaction effects showed that alcoholics remembered significantly more alcohol cues than light drinkers (F=5.487, 1/48 df, p=.023). Post-hoc paired t-tests analysis showed that within the group of alcoholics there was a better memory recall for alcohol vs. general positive incentive stimuli (t=-5.79; p<.001) and alcohol vs. neutral stimuli (t=-5.35; p<.001). In figure 1, the mean recall scores are displayed by Cue type and Group. An independent t-test showed that there was a difference in bias scores between alcoholics and light drinkers for alcohol information (t=-2.34; p=.023). No difference in bias between the two groups was observed for general positive incentive information (t=1.03; p=.31).

Figure 1. Mean number of recalled pictures by Group and Cue type. NEUT = neutral picture; ALC = Alcohol-picture; POS = General incentive picture.

Craving and memory bias
Alcoholics experienced significantly higher pre-experimental instant craving on the scales "strong desires and intentions to drink" (t=2.3; p=.02), "negative reinforcement craving" (t=4.5; p<.001). Post-experimental negative reinforcement craving was also higher for alcoholics, (t=4.3; p<.001). For the total group, memory bias was positively correlated with the post-task DAQ scales "strong desires and intentions to drink" (r=.42; p=.003), "negative reinforcement craving" (r=.29; p=.042), and "mild desires to drink" (r=.37; p=.009). Higher craving was associated with increased memory bias for alcohol related pictures. None of the OCDS scales were significantly correlated with memory bias (obsessive thoughts scale, r=.24; ns; compulsive behaviors scale, r=.10). Correlation analysis revealed that memory bias was positively correlated with increased craving (r=.44; p=.029) in alcoholics, but not in the control group (r=-.11; ns). This indicates that stronger memory bias is associated with an increase in cue-elicited craving.

Conclusions
The aim of the present study was to investigate the presence of a memory bias for alcohol related pictures in alcoholics. It was shown that this memory bias was present in alcoholics. The results specifically indicated that alcoholics have a biased memory for alcohol related pictures compared to light drinkers. This memory bias was not the effect of differences in general memory ability nor the effect of an enhanced memory for incentive cues in general. It is suggested that alcohol cues are more readily encoded by alcoholics than light drinkers, probably because of the stronger associative links between alcohol related memories and the presented cues.

Furthermore, the present study found that instant alcohol craving (strong desire) was significantly associated with memory bias for alcohol stimuli. This supports the view that in high cravers, the cognitive processing of drug cues is biased. Although no correlation was found between chronic craving (as measured by the OCDS) and memory bias, the current study showed that in alcoholics, memory bias was associated with increased (instant) cue-elicited craving (as measured by the DAQ). Although the present research design does not allow to draw causal relationships, it can be speculated that the presence of a memory bias increases craving experiences. By this specific mechanism, a memory bias may result
in relapse of drinking behavior in alcoholics. Research is needed that addresses the causality of this relationship.

The present findings are in line with neurobiological accounts of addiction. Frequent alcohol use may change neural circuits involved in memory\(^1\). Grant and colleagues already demonstrated that the memory circuits of cocaine addicts are involved during the experience of cocaine craving. The current finding that memory bias is related to increased craving supports White's (1996) view that memory processes are essential to the analysis of changes in behavior produced by addictive drugs.

A limitation of the present study is that the amount of time spent processing the cues may differ between the groups. A time limit would have helped to equate this amount of time spent processing the cues, and would have lent stronger support to the conclusion that memory bias accounted for the findings.

This is the first demonstration of a memory bias for pictorial alcohol cues in alcoholics. The present study shows that this memory bias is associated with the experience of craving, which may subsequently result in a relapse. However, research is needed that specifically targets the causal role of cognitive processing biases in alcoholism.

References

Chapter 7


