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ORIGINAL ARTICLE

Impaired Generalization of Associative Learning in Patients with Alcohol Dependence After Intermediate-term Abstinence

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Abstract — **Aims:** We used an associative learning task in order to investigate cognitive dysfunctions in alcohol dependence. This test is suitable for the assessment of stimulus–response learning and memory generalization (acquired equivalence), which is related to medial temporal lobe functioning. **Methods:** Twenty patients with alcohol dependence (abstinence: >6 months) and 20 matched healthy controls participated in the study. In the task, antecedent stimuli were cartoon faces (girl, boy, man and woman) and consequent stimuli were color cartoon fishes. The task was to learn face–fish associations using feedback. In the transfer phase, the fish–face pairs were generalized to new associations. **Results:** There was no significant difference between patients and controls during the acquisition phase of fish–face associations. In the transfer phase, patients were impaired relative to controls. We found no association between task performance and intelligence quotient. **Conclusion:** These results suggest that abstinent patients with alcohol dependence show marked dysfunctions in the generalization of associations, which may indicate the dysfunction of the medial temporal lobe.

INTRODUCTION

The impairment of cognitive functions is a well-known consequence of alcohol misuse; even acute alcohol abuse causes some reversible mild dysfunctions (McKinney and Coyle, 2004). The chronic effect of alcohol misuse may lead to significant impairments, sometimes as severe as Korsakoff syndrome (Alcohol-Induced Persisting Amnestic Disorder) (e.g. Jacobson and Lishman, 1987; Kopelman *et al*., 2009) or Alcohol-Induced Persisting Dementia (for a review see Martin *et al*., 1986). The etiology of this process is complex, and genetic, nutritional and drinking behavioral factors can all be relevant (Butterworth, 1995; Smith and Fein, 2010). Although alcohol causes diffuse neurodegeneration, both human and animal studies suggest that certain parts of the brain (e.g. the prefrontal cortex and the medial temporal lobe) are specifically vulnerable (Fadda and Rossetti, 1998; White *et al*., 2000; Kubota *et al*., 2001; Sullivan and Pfefferbaum, 2005). Some cognitive functions are particularly sensitive for the deteriorating effect of alcohol (Sullivan *et al*., 2002; Fein *et al*., 2006; Loeber *et al*., 2009). It is pertinent to note that after abstinence cognitive recovery can be detected (Sullivan *et al*., 2000; Rosenbloom *et al*., 2004; Fein *et al*., 2006). Although the precise mechanism of abstinence-related cognitive recovery raises many questions, hippocampal neural stem cells proliferation and neurogenesis may be among the key factors of regeneration (Crews and Nixon, 2009).

In this study, we focus on memory system impairments, which are one of the most consistently reported cognitive abnormalities in alcohol-related disorders. The classic division of long-term memory distinguishes declarative (explicit) and non-declarative (implicit or procedural) memory (Squire and Zola, 1996; Gabrieli, 1998), but recent data suggest that these systems interact (Ashby *et al*., 1998; Kéri, 2003; Poldrack and Packard, 2003). From the classic 'modular' point of view, the medial temporal lobe (hippocampus, dentate gyrus and rhinal cortex) and the diencephalic structures are responsible for explicit processes, whereas the neuronal substrates of implicit memory include the basal ganglia, cerebellum and sensory cortex. The basal ganglia also play a pivotal role in stimulus–response associative learning, sequence learning and category learning (Yin and Knowlton, 2006). Although it is likely that the medial temporal lobe is not directly involved in all forms of stimulus–response learning, it has a major role in the generalization of previously learned information in a novel context (Manns and Eichenbaum, 2006).

To investigate the impairment of basal ganglia- and medial temporal lobe-dependent processes, we used an associative learning test, which has not previously been examined, to our knowledge, in alcohol research. The first phase of this task investigates basal ganglia-dependent associative learning, in which the participant acquires stimulus–stimulus connections using feedback after each decision. The second, putatively medial temporal lobe-dependent part of the test is transfer generalization (acquired equivalence) because, in this phase, the previously learned associations should be generalized in novel situations. In acquired equivalence, prior training to handle two stimuli as equivalent, linking them to the same outcome, increases generalization between them: animal studies indicated that lesions to the medial temporal lobe interrupt transfer generalization and acquired equivalence learning (Coutureau *et al*., 2002). Patients with Parkinson's disease with basal ganglia pathology exhibited slower feedback-guided stimulus–stimulus associative learning, but they were able to generalize the acquired associations (Myers *et al*., 2003). In contrast, elderly individuals with hippocampal atrophy, patients with Alzheimer's disease and patients with schizophrenia with hippocampal abnormality displayed successful feedback-guided learning but deficient transfer generalization and acquired equivalence (Myers *et al*., 2003; Kéri *et al*., 2005; Bódi *et al*., 2009). Functional

magnetic resonance imaging has revealed that generalization of associations appears to be related to coupled changes in acquisition-phase activity in the hippocampus and midbrain (Shohamy and Wagner, 2008).

The aim of this study was to compare the impairment of putatively basal ganglia- and medial temporal lobe-dependent processes in patients with alcoholism after intermediate-term abstinence. We hypothesized that patients with alcoholism show more pronounced deficits on the medial temporal lobe-dependent phase of the task, detectable even after intermediate-term abstinence.

METHODS

Participants

We enrolled 20 patients with DSM-IV alcohol dependence (American Psychiatric Association, 1994) participating in Alcoholic Anonymous (AA) groups. Inclusion criteria included abstinence for >6 months (average: 9.8 months, SD = 3.1) and scores <10 on the Beck Depression Inventory (BDI) (Beck, 1987). None of the patients showed any sign of alcohol intoxication and relapse. General psychosocial functions were assessed with the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 1994). Patients were evaluated with the Addiction Severity Index (ASI) semi-structured interview (McLellan *et al.*, 1980) (Table 1) and with the MINI International Neuropsychiatric Interview Plus (Sheehan *et al.*, 1998). General cognitive functions were assessed with the revised version of the Wechsler Intelligence Scale (Wechsler, 1981). Individuals with concurrent DSM-IV Axis I disorders, history of brain injury, neurological disorders, drug abuse and dependence, and delirium did not participate in the study. The patients did not receive psychotropic medications.

Table 1. Demographic and illness-related characteristics of the participants

	ALC ($n = 20$)	HC ($n = 20$)
Age (years)	37.2 (11.5)	36.3 (10.1)
Education (years)	12.2 (3.3)	11.4 (3.8)
Wechsler Adult Intelligence Scale	109.2 (10.8)	112.7 (14.2)
GAF	71.2 (14.8)	74.4 (10.7)
BDI	7.8 (2.3)	7.4 (2.1)
ASI severity profile: personal health (medical)	2.8 (1.4)	–
ASI severity profile: personal health: psychiatric	1.1 (0.5)	–
ASI severity profile: social functioning: employment	3.4 (1.2)	–
ASI severity profile: social functioning: family/social	3.2 (1.4)	–
ASI severity profile: social functioning: legal	1.2 (0.4)	–
Alcohol-related characteristic of addicted population (from ASI)		
Age started drinking – alcohol any use at all	15.3 (3.7)	–
Age at first heavy use – alcohol to intoxication	23.4 (4.1)	–
Hospitalized due to alcohol withdrawal	4.2 (3.1)	–
Ambulate alcohol detoxification	4.2 (3.9)	–
Duration of abstinence (month)	9.8 (3.1)	–
ASI severity profile: alcohol use (at present)	0.0 (0.0)	–
ASI severity profile: substance use (at present)	0.0 (0.0)	–

Data are mean (SD). ALC, patients with alcohol dependence; HC, healthy controls; ASI, Addiction Severity Index. Patients and controls did not differ in paired measures ($P > 0.1$, t tests).

The patients were compared with 20 healthy volunteers matched for age, education, intelligence quotient (IQ), BDI and GAF scores (Table 1). The control volunteers were also screened with the MINI International Neuropsychiatric Interview Plus (Sheehan *et al.*, 1998) in order to exclude Axis I mental disorders and drug abuse/dependence. They were social drinkers and scored zero on the cut down on drinking, annoyed by criticizing drinking, guilty about drinking, eye-opener alcohol-screening questionnaire (Ewing, 1984). After being given a description of the study, participants were asked to give their consent. The institutional ethics committee approved the study.

The acquired equivalence associative learning task

Stimuli were presented and responses were collected using a Macintosh Power-Book laptop. The antecedent stimuli were four drawings of faces (man, woman, girl and boy). The consequents were drawings of fishes colored red, orange, purple and pink. Faces and fishes were randomly assigned as antecedent and consequent stimuli. At the start of the experiment, the following instruction appeared on the screen: 'Welcome to the experiment. You will see drawings of people who each have some pet fish. Different people have different kinds of fish. Your job is to learn which kinds of fish each person has. At first, you will have to guess.' On each trial, a face and two fish drawings were displayed on the computer screen along with the prompt: 'Which fish does this person have? Use the Left or Right key to choose.' The participant responded with pressing one of two separate keys labeled as 'LEFT' and 'RIGHT' to indicate whether the fish on the left or the fish on the right was associated with the face. The selected fish drawing was circled and corrective feedback was given (Fig. 1). In the case of an incorrect response, an alert beep sounded. The acquisition phase included three phases (Table 2). Stages 1 and 2 terminated after 8 consecutive correct responses, whereas stage 3 terminated after 12 consecutive correct responses in order to make sure that the participant successfully acquired the increasing number of associations from stage 1 to stage 3.

After the termination of the acquisition phase, a new instruction appeared on the screen, informing the participant that the task would remain the same but feedback would no longer be provided. We did not inform the participant on the appearance of new associations. The transfer phase consisted of 48 trials. Twelve trials were new associations for the testing of learned equivalence, and 36 trials were old associations trained during the acquisition phase. In this phase, the participant was requested to recall previously acquired associations and to generalize this knowledge to new associations. Given that there was no feedback, participants could not acquire new associations via a feedback-guided learning.

The dependent measures were the average number of errors in the acquisition phase and the proportion of incorrect responses in the transfer phase (for methodological details, see Myers *et al.*, 2003).

RESULTS

All patients were able to complete both phases of the task. There was no significant difference between patients and

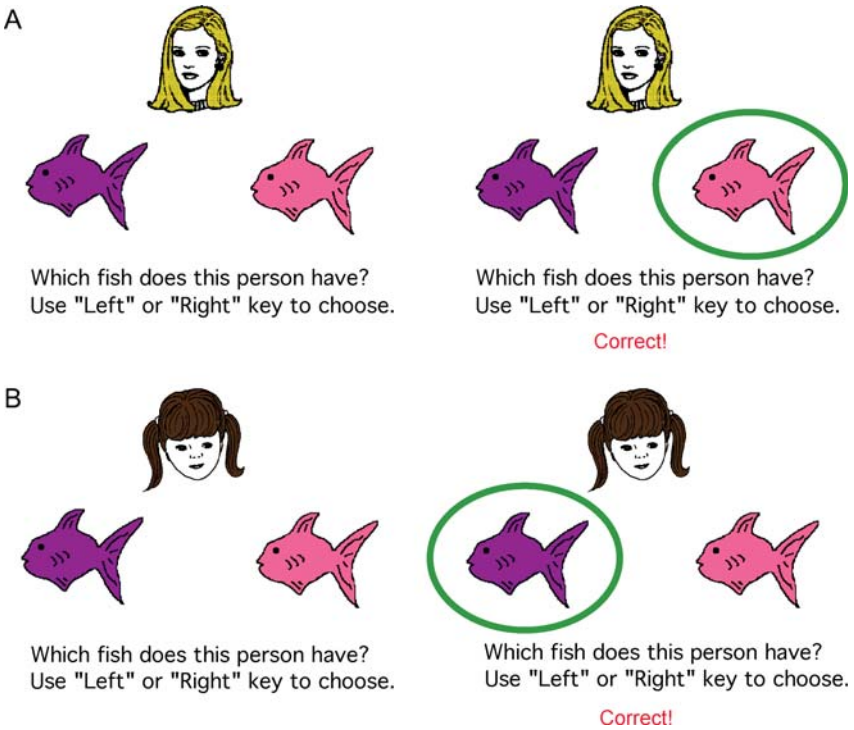

Fig. 1. Example of an experimental trial. First, stimuli appeared on screen. Second, the participant responded, the chosen fish was circled and corrective feedback was given.

Table 2. The acquired equivalence associative learning task

Acquisition stage 1: shaping	Acquisition stage 2: equivalence training	Acquisition stage 3: new consequences	Transfer phase: equivalence testing
A1–X1	A1–X1	A1–X1	A2–X2?
	A2–X1	A2–X1	
		A1–X2	
B1—Y1	B1–Y1	B1–Y1	B2–Y2?
	B2–Y1	B2–Y1	
		B1–Y2	

During stage 1, participants learn the first 2 associations between different persons (A, B) and fishes (X, Y). During phase 2, different persons are associated with the same fishes (stimulus equivalence), whereas, during stage 3, new consequences are added. During the transfer phase, participants are tested on the associations learned in stages 1–3 and also on new associations that are not learned during stages 1–3, but are the consequences of stimulus equivalence (Myers *et al.*, 2003).

controls regarding the mean number of errors in the acquisition phase (controls: 8.9, SD = 2.3; patients: 10.1, SD = 2.6; $t(38) = 1.51$, $P = 0.14$), and the total number of acquisition trials (controls: 35.6, SD = 14.0; patients: 40.2, SD = 16.7, $t(38) = 0.94$, $P = 0.35$).

We conducted an analysis of variance on the proportion of incorrect responses in the transfer phase with group (patients vs. controls) as the between-subjects variable and association type (old vs. new) as the within-subjects variable. There were significant main effects of group ($F(1,38) = 27.49$, $P < 0.001$, $\eta^2 = 0.42$) and association type ($F(1,38) = 37.01$, $P < 0.001$, $\eta^2 = 0.49$). The interaction between group and association type was also significant ($F(1,38) = 29.65$, $P < 0.001$, $\eta^2 = 0.44$). Scheffé's *post hoc* tests indicated that patients had a selective impairment in the case of new associations

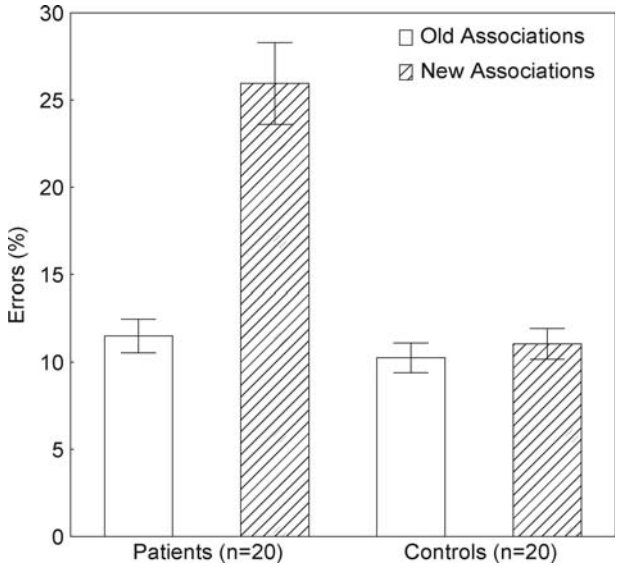

Fig. 2. Mean performance in the transfer phase in abstinent patients with alcohol dependence and healthy controls. Error bars indicate standard error of the mean. *$P < 0.001$, Scheffé's test (old vs. new associations in patients).

($P < 0.001$) but not in the case of old associations ($P = 0.9$) (Fig. 2).

We calculated Pearson's product moment correlation coefficients between test performance (mean errors from the acquisition phase, proportion of incorrect responses for old and new associations in the transfer phase), IQ and BDI scores. These analyses yielded non-significant results either when we analyzed patients and controls together or when we separated the two groups ($-0.2 < r < 0.02$, $P > 0.1$).

DISCUSSION

The findings of this study indicate that abstinent patients with alcohol dependence display preserved stimulus–stimulus associative learning, whereas the generalization of this information was severely impaired. These results may indicate that medial temporal lobe functions remain impaired even after intermediate-term abstinence, whereas basal ganglia-related processes are spared.

In accordance with previous research, the present findings suggest that several months of alcohol abstinence is required for the improvement of cognitive functions. Fein *et al.* (1990) distinguished three periods of abstinence: (i) acute detoxification (up to 2 weeks of abstinence), (ii) intermediate period (3 months of abstinence) and (iii) long-term abstinence (from 2 months to 5 years). In their review, they found that even in the long-term phase some cognitive impairments still existed, especially in abstract reasoning, visuospatial ability, short-term memory and mental flexibility, whereas other cognitive functions improved much earlier (attention and concentration, reaction time, verbal learning, abstract reasoning and verbal short-term memory) (Fein *et al.*, 1990). Later, Fein *et al.* (2006) investigated a very long-term abstinent group (average abstinence time: 6.7 years) with a complex cognitive battery. They found that most of the neurocognitive deficits, including memory impairments, resolved, although spatial processing was still impaired.

The most serious limitations of the present study were the small sample size and the fact that we used only a single test for the assessment of memory. The patients included in this study were not fully representative for the general population of patients with alcohol dependence because of their young age, spared IQ and high general functioning.

For example, Schottenbauer *et al.* (2007) showed that performance on the Block Design test, an indicator of nonverbal IQ, decreased with the increasing age of patients with alcohol-related disorders, and this decline in IQ was associated with brain shrinkage. In contrast, vocabulary did not decrease with age and was related to premorbid brain size, suggesting that lower verbal IQ precedes alcohol-related disorders. The young, well-functioning patients in this study without comorbidity still exhibited transfer generalization impairments, suggesting that this phase of the associative learning test is highly sensitive for memory impairments. In more severely affected patients, we expect an extensive impairment of associative learning, probably including the feedback-guided acquisition phase of stimulus–stimulus associations. Further studies are warranted in order to explicitly test this hypothesis.

It is also necessary to rule out the possibility that transfer generalization impairment is a consequence of the dysfunction of the prefrontal cortex. Kéri *et al.* (2005) used this test in patients with schizophrenia who exhibit severe prefrontal deficits. In this study, transfer generalization dysfunctions correlated with performance on the California Verbal Learning Test (declarative verbal memory) but not with performance on the *n*-back task, which is a working memory test assessing prefrontal functions (Kéri *et al.*, 2005). These results are against the possibility that prefrontal pathology caused transfer generalization dysfunctions.

In the present study, we applied the disease model of addiction, which interprets addiction as a lifelong disorder with biological and environmental origins. This model is also the basis of AA movement, from which we recruited the patients. The choice of this population was justified by the fact that from the AA group we could easily enroll drug-free and abstinent patients. The treatment protocol at our psychiatric department is based on the Minnesota model with a close cooperation with the local AA movement.

The results can be interpreting two different ways. First, it can be hypothesized that memory generalization impairments may occur before the development of alcohol-related disorders. In other words, it can be a vulnerability factor similar to novelty and sensation seeking, impulsivity, extraversion (Nees *et al.*, 2012) and even alterations in brain oscillations (Porjesz and Rangaswamy, 2007). Second, taking into consideration previous reports of hippocampal dysfunctions in patients with alcohol-related disorders and associated animal models (Fein *et al.*, 1990, 2006; White *et al.*, 2000; Crews and Nixon, 2009; Tokuda *et al.*, 2011), the present results can be explained with the long-term toxic effect of alcohol. Nevertheless, given that memory generalization dysfunctions were present together with a reasonably good long-term outcome, it is less likely that this cognitive dysfunction is a predictor of relapse. Future studies should investigate the issue of premorbid vulnerability marker status vs. toxic consequences, similarly to the effect of shorter and more prolonged abstinence on memory generalization and medial temporal lobe functions.

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