

COGNITIVE EFFECTS

Impairment of Cognitive Abilities and Decision Making after Chronic Use of Alcohol: The Impact of Multiple Detoxifications

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Abstract — Aims: In the present study, the effect of previous detoxifications on prefrontal function and decision making was examined in alcohol-dependent patients. Further, we examined whether the length of abstinence affects cognitive function. **Methods:** Forty-eight alcohol-dependent patients were recruited from an inpatient detoxification treatment facility and cognitive function was compared to a control group of 36 healthy controls. The patient population was then divided into a group of patients with less than two previous detoxifications (LO-detox group, $n = 27$) and a group of patients with two or more previous detoxifications (HI-detox group, $n = 21$) and cognitive function was compared. In addition, cognitive function of recently (i.e. less than 16 days; median split) and longer abstinent patients was compared. We assessed prefrontal function, memory function and intelligence. **Results:** Alcoholics, when compared to healthy controls, performed worse with regard to the performance index Attention/Executive function. Cognitive impairment in these tasks was pronounced in recently abstinent patients. We found no significant differences between HI-detox and LO-detox patients with regard to the Attention/Executive function. However, in the IOWA gambling Task, the HI-detox group seemed to be less able to learn to choose cards from the more advantageous decks over time. **Conclusions:** Our results provide additional evidence for cognitive impairment of alcohol-dependent patients with regard to tasks sensitive to frontal lobe function and underline the importance of abstinence for these impairments to recover. We found only little evidence for the impairing effects of repeated withdrawal on prefrontal function and we suggest that executive function is affected earlier in dependence.

INTRODUCTION

Severe chronic use of alcohol has been consistently associated with neuropsychological impairments with respect to cognitive flexibility, problem solving, decision making, risky behaviour and further aspects of cognitive function (for a review, see Moselhy *et al.*, 2001; more recent studies, for example, by Bechara *et al.*, 2001; Fein *et al.*, 2004; Davies *et al.*, 2005; Noël *et al.*, 2007; Glass *et al.*, 2009). In addition, an association between drinking-related variables (e.g. the frequency and duration of alcohol consumption) and a decline of frontal lobe function of alcohol-dependent patients (e.g. Fein *et al.*, 1990) as well as an association of cognitive impairment with frontal lobe function (Noël *et al.*, 2001; Chanraud *et al.*, 2007) has been reported. Although cognitive deficits may also be a risk factor for the development of drug and alcohol dependence, a longitudinal study by Tapert and Brown (1999) suggested that continued substance involvement in adolescence leads to greater neurocognitive difficulties. Taken together, these findings suggest that chronic alcohol use induces neurotoxicity (Moselhy *et al.*, 2001).

Although a large number of studies have demonstrated cognitive impairment in alcohol-dependent patients, only few studies have assessed the influence of repeated withdrawal from alcohol on cognitive function. With regard to animal studies demonstrating an impairment of cognitive abilities and learning after repeated withdrawal (e.g. Stephens *et al.*, 2001; Borlikova *et al.*, 2006), it is reasonable to suggest that an association between the number of previous detoxifications and cognitive impairment in alcoholic patients should exist. In a recent review, Stephens and Duka (2008) have presented cumulative evidence from animal and human studies for altered function of prefrontal cortex and amygdala as the result of aberrant plasticity induced by repeated periods of alcohol exposure.

While the acute administration of alcohol disrupts glutamatergic neurotransmission by reducing the sensitivity of the NMDA receptor (Lovinger, 1993), the prolonged inhibition of NMDA receptors by ethanol leads to an increase in glutamate release. The cessation of chronic alcohol consumption in combination with glutamate release can result in acute excitotoxicity (Tsai and Coyle, 1998). As the frontal lobes are particularly rich in glutamatergic pathways (Kril *et al.*, 1997), this glutamate-mediated excitotoxicity induced by the withdrawal from alcohol may especially affect frontal lobe function. However, only a few studies have assessed the influence of repeated withdrawal from alcohol on cognitive function. In 1989, Glenn *et al.* demonstrated that the number of withdrawals (defined as the number of 24-h periods of abstinence following a drinking day in the last year) was affecting both immediate and delayed semantic and figural memory in alcohol-dependent patients. More recently, Duka *et al.* (2003) provided evidence that the repeated experience of withdrawal (i.e. periods of abstinence under medical supervision) is associated with impaired cognitive function in alcohol-dependent patients in a reward delay task, a Porteus maze task and a vigilance task. The fact that these effects were confounded with the age of starting heavy drinking and the years of problem drinking suggests that susceptibility to cognitive impairment associated with multiple detoxifications increases with an earlier start of regular alcohol use. Further evidence for the impact of withdrawal on cognitive functioning can be derived from a small literature on human adolescents (see Tapert *et al.*, 1999, 2002; Brown *et al.* 2000) relating recent and lifetime alcohol withdrawal symptoms assessed with the lifetime version of the Customary Drinking and Drug Use Record (Brown *et al.*, 1998) to cognitive deficits especially with regard to performance in tests of visual motor integration, visuoperception and retrieval of verbal and nonverbal information (Brown *et al.* 2000).

In the present study, the effect of previous detoxifications on cognitive function including performance in a gambling task was examined in order to enhance our knowledge on the impact of withdrawal on cognitive impairment. As not all alcohol-dependent individuals may manifest cognitive impairment depending for example on the severity and chronicity of their dependence (e.g. Fein *et al.*, 1990), we initially compared cognitive functioning of our alcohol-dependent patient group with a sample of healthy controls matched for age, gender and demographic variables. We administered a battery of cognitive tasks sensitive to cognitive abilities related to frontal lobe function including performance in a gambling task (Bechara *et al.*, 2001), general cognitive abilities and memory function. Then we divided the patient group according to the findings of Duka *et al.* (2003) into a group of patients with two or more previous detoxifications (HI-detox group) and a group of patients with fewer than two previous detoxifications (LO-detox group) and compared performance of these two patient groups. Furthermore, we examined whether cognitive performance improves in early abstinence as described by a number of studies (e.g., Mann *et al.*, 1999; Sullivan *et al.*, 2000; Fein *et al.*, 2006) to provide a further understanding of the time course of recovery of cognitive deficits. In addition, findings from a recent study (Noël *et al.*, 2007) have suggested that impairment in a gambling task might recover under continued abstinence.

MATERIALS AND METHODS

Study population

Eighty-four volunteers participated in the study. Forty-eight alcohol-dependent patients (27 males, 21 females) were recruited from diagnosed alcoholics (DSM-IV criteria) seeking extended inpatient detoxification treatment at the Department of Addictive Behaviour and Addiction Medicine at the Central Institute of Mental Health, Germany. All patients fulfilling the study criteria and providing written informed consent were included. A total of 61% of the patients had been medically supported during withdrawal with standard detoxification treatments. Of all medicated patients, 57% had received the nonbenzodiazepine sedative clomethiazole, 32% had received diazepam and 11% clonidin. The average dose of clomethiazole given was 384 mg, four times daily, gradually reducing over a 3-day period. Diazepam was given at an average dose of 8 mg three times daily, gradually reducing over 3 days. Clonidin was given once daily (125 mg) over 3 days. As part of the extended detoxification treatment programme, patients took part in group therapy and relapse-prevention training based on motivational interviewing techniques and cognitive behaviour therapy (Mann *et al.*, 2006).

The patient population was divided into two groups based on the number of previous medically supervised detoxifications using information obtained from a structured interview. Medically supervised detoxifications were defined as periods of abstinence under medical supervision. Based on the findings from Duka *et al.* (2003) that after two previous detoxifications patients are more impaired with regard to their performance in a reward delay task and a vigilance task when compared to patients with less than two detoxifications, the number of two previous detoxifications was chosen to split the patients

into two groups. Thus, the LO-detox group ($n = 27$) consisted of those patients with fewer than two medically supervised detoxifications, whereas the HI-detox group ($n = 21$) comprised those patients with two or more detoxifications.

The control group consisted of 36 healthy controls (23 males, 13 females) recruited from the community via newspaper advertisements. Volunteers had no alcohol-related problems based on information obtained from semi-structured interviews, questionnaires and biological alcoholism markers (serum gamma-glutamyl transpeptidase, serum aspartate aminotransferase and serum alanine aminotransferase). They were paid for their study participation.

Inclusion and exclusion criteria

Study participants aged between 21 and 65 and fluent in the German language were recruited for participation in the study. Exclusion criteria for both samples were current drug abuse or dependence other than nicotine or alcohol for the patients, severe somatic, neurological or psychiatric diseases, serious complications in detoxification for the patients, pregnancy, lactation period or suicidal tendencies. We also excluded participants taking any pharmacological agents. The study was approved by the Ethics Committee of the University of Heidelberg (Medical Faculty Mannheim) and adhered to the Declaration of Helsinki. All participants signed informed consent.

General procedures

For patients as well as healthy controls, the data assessment comprised questionnaires on demographic and drinking-related variables. Information on past and recent alcohol consumption was obtained from the Life Time Drinking History (LDH; Skinner and Sheu, 1982) and the Time Line Follow Back Interview (TLFB; Sobell and Sobell, 1995). The duration of dependence, defined as the number of years since the criteria for alcohol dependence according to DSM-IV were fulfilled for the first time, was also assessed in an interview. The Alcohol Dependence Scale (ADS; Skinner and Allen, 1982) was used to assess the severity of alcohol dependence. Further, the Fagerström Test for Nicotine Dependence (FTND; Fagerström *et al.*, 1991) was administered to assess smoking and the Beck Depression Inventory (BDI; Beck *et al.*, 1996) was used to assess depressive symptoms. A number of neuropsychological tests were administered to assess impairment of frontal executive functioning and decision making (see below). IQ performance and memory function were assessed to control for interfering variables. The test session lasted about 2–3 h and was conducted by a clinical psychologist trained in neuropsychological test administration. Patients were allowed smoke breaks. For patients, the mean duration of abstinence prior to the test session was 15.65 days ($SD = 6.69$, range 4–37).

Neuropsychological assessment

Vocabulary test (WST). The WST assesses verbal intelligence and provides an indicator of premorbid intelligence (Schmidt and Metzler, 1992). The WST consists of 42 rows of words. In each row a real word is presented with five distractors of non-existent words. The subjects' task is to mark the correct word in each row. The reliability (Cronbach's alpha) of this test according to Schmidt and Metzler (1992) is $r = 0.94$.

The number of correctly identified words was transformed into an IQ-score according to the tables provided in the test manual.

Reduced Wechsler Intelligence Scale (WIP). The WIP (Dahl *et al.*, 1986) is a short version of the Wechsler Adult Intelligence Scale (Wechsler, 1997) and designed as a comprehensive test of cognitive ability. The reliability (Cronbach's alpha) of the four different subscales (general knowledge, similarities, picture completion, block design) ranges from $r = 0.71$ to $r = 0.96$. As a dependent measure, an IQ-score based on the results from the four subscales was used.

Auditory verbal learning test (TME). The TME (Rey, 1964; Roether *et al.*, 1984) was used to provide a measure of memory function. A list of 20 words is read to the participant reading one word every 2 s. Afterwards the participant is asked to say back as many words as he or she can remember (immediate recall). After the immediate recall is finished, the list is repeated once and the participant is again required to recall the words he/she remembers (second recall). The test-retest reliability of this test is $r = 0.79$. As dependent measures, we used the number of words remembered in the first and the second recall.

We have used the TME previously and demonstrated that patients with a longer duration of their alcohol dependence were more impaired with regard to memory function than patients with a shorter duration of their dependence (Loeber *et al.*, 2009).

Benton Visual Retention Test (BVRT). The BVRT (Benton, 1992) assesses visual perception, visual memory and visual constructive abilities. Ten images (one showing for example a square and a rectangle of the same size and a smaller circle in the upper-right part of the image) are presented one at a time for 10 s to the participants. After each presentation of an image, participants are asked to draw the image from memory. For the evaluation of the drawings, each drawing is rated as correct or incorrect (e.g. with regard to the number of objects, their relative size and alignment) and the number of errors in each incorrect drawing is assessed, whereby the results are supposed not to rely on drawing abilities. The test-retest reliability of the BVRT is $r = 0.85$. As a dependent measure, we used the number of correct drawings and the number of errors made in all incorrect drawings. Several studies have used the BVRT previously (e.g. John *et al.*, 1991; Goldstein *et al.*, 2004) and demonstrated that the BVRT is a valid measure to assess impairment of memory function in alcohol-dependent patients.

Trail Making Test Part B (TMT-B). The TMT-B (Reitan, 1992) is a measure of visual-conceptual and visual motor tracking skills, with a focus on divided attention, the ability to shift and mental flexibility. The participant is instructed to connect circles each containing either a number from 1 to 13 or a letter from A to L as quickly as possible thereby alternating in sequence between numbers and letters. The dependent measure is the total time (in seconds) required to complete the task.

Previous studies using the TMT demonstrated that this measure is related to prefrontal functioning (Chanraud *et al.*, 2007) and that cognitive performance of alcohol-dependent patients is especially impaired in Part B of the TMT (Davies *et al.*, 2005; Chanraud *et al.*, 2007).

Wisconsin Card Sorting Test (WCST). The WCST is a measure of prefrontal cortical function (executive function, abstract conceptual skills, concept formation, cognitive flexibility, working memory) (Tien *et al.*, 1996). A computerized version (Loong, 1990) was used in the present study, with procedures

similar to those described by Grant and Berg (1948). The task requires sorting of 128 cards according to predetermined rules. There are three possible ways to sort a card—by the colour of the items on the card, by the number of the items on the card and by the shape of the items. Feedback of accuracy is given after each trial. The criterion for correct categorization changes whenever 10 consecutive cards are sorted correctly. The reliability of the WCST (Cronbach's alpha) is $r = 0.96$. We used perseverative errors and number of categories completed as dependent measures.

Previous studies using the WCST (e.g. Chick *et al.*, 1989; Goldstein *et al.*, 2004; Chanraud *et al.*, 2007; Glass *et al.*, 2009) demonstrated an impairment of alcohol-dependent patients.

IOWA Gambling Task (IGT). The IGT is a measure of ventromedial prefrontal cortex function and detects impairment in decision making based on the evaluation of long-term consequences (Bechara *et al.*, 1994, 2000, 2001; Noël *et al.*, 2007). In the present study, we used a computerized version similar to the procedure described by Bechara *et al.* (2000). Four card decks appeared on the screen and the participants were instructed to accumulate as much facsimile money as possible by picking one card at a time from any of the four decks. Each card choice provided a reward of a certain amount of money or a potential penalty (loss of a certain amount of money), which was revealed only after turning up the card. Original amounts in dollars were replaced by amounts in euros, divided by 2. Two of the decks were considered as advantages decks (C, D) that provided smaller rewards more frequently with lower penalties, while the disadvantages decks (A, B) generated larger rewards, albeit less frequently, and the punishment was two times as high. The task ended when the participant had selected a total of 100 cards. For the analysis of the results, the total of 100 trials were organized in five consecutive blocks (block 1: trials 1–20, block 2: trials 21–40, block 3: trials 41–60, block 4: trials 61–80 and block 5: trials 81–100). As dependent measures, we used the net outcome $((C + D) - (A + B))$ for each of the five blocks. Further, we made a distinction between the initial phase of the task (the first 10 trials), in which subjects learn to make choices, but have not yet any explicit knowledge about the contingencies (decision under ambiguity), and the late phase (the last 10 trials), in which decisions become more influenced by explicit knowledge about the risks associated with each choice (decision under risk; Brand *et al.*, 2007).

Previous studies using the IGT (e.g. Bechara *et al.*, 2001; Fein *et al.*, 2004; Goudriaan *et al.*, 2005; Noël *et al.*, 2007) demonstrated deficits of alcohol-dependent patients when compared to controls with regard to decision making and feedback processing.

Statistical analysis

T-tests (two-sided) and chi-square analyses using Fisher's exact test were used to examine differences between patients and controls, and between patients of the HI-detox group and the LO-detox group with respect to demographic and drinking-related variables (i.e. the age of onset of regular alcohol consumption, the duration and severity of alcohol dependence, the amount of lifetime alcohol consumption, the number of previous detoxifications and the duration of abstinence prior to testing). With regard to performance in the different neuropsychological tasks related to attention, executive function and memory, two

performance indices were calculated by standardizing each outcome variable (with the sample mean and standard deviation for each individual variable) and averaging each of the variables for each participant. If necessary, variables were recoded thus that higher values indicated better performance. Thus, the index *Memory* comprises performance in the TME and the BVRT, while the index *Attention/Executive function* comprises performance in the TMT and the WCST. Performance in the IGT as a measure of decision making was analysed separately.

Differences between patients and controls and between HI-detox and LO-detox patients with regard to cognitive function were analysed using multivariate analysis of variance. In the case of significant baseline differences between the patient groups, multivariate analysis of covariance was conducted with group (e.g. HI-detox group versus LO-detox group) as a between-group factor and the baseline variable as covariate or, in the case of a dichotomous variable, as a second between-group factor to control for confounding effects. In addition, as it has been demonstrated previously (e.g. Chick *et al.*, 1989) that the total amount of lifetime alcohol consumption is associated with brain damage, this variable was entered as a covariate as well. For the analysis of the IGT, a repeated measures ANOVA was performed with group (patients versus controls or LO-detox versus HI-detox) as a between-group factor and with the block (1, 2, 3, 4 and 5) as a within-group factor. For significant main effects, *post hoc* analyses with Bonferroni-corrected *t*-tests were used. Data of five patients for the IGT were lost due to technical problems with the recording of the results.

In order to analyse the impact of abstinence length on recovery of cognitive function, we divided the patient group in a group with recently abstinent patients (i.e. <16 days) and with patients with longer abstinence (i.e. 16 or more days of abstinence) based on the median of the distribution and compared these two patient groups with controls using multivariate analysis of variance with least significant difference (LSD) *post hoc* tests.

For all analyses, SPSS for windows (Statistical Package of the Social Science, 15.0.) was used.

RESULTS

Comparison of alcohol-dependent patients and healthy controls

Population characteristics. Table 1 shows the sample characteristics for alcohol-dependent patients and for healthy controls. The groups were well matched for age, gender and premorbid IQ (vocabulary test). As expected, we found a significantly higher amount of lifetime alcohol consumption for the alcohol group compared to the control group ($t(48) = 5.85$, $P < 0.001$) as well as a significantly higher score on the ADS (severity of dependence) ($t(53) = 14.48$, $P < 0.001$). Further, patients reported significantly more depressive symptoms than controls in the BDI ($t(67) = 5.59$, $P < 0.001$), and we found a significantly higher number of smokers in the patients' group ($\chi^2(1) = 24.89$, $P < 0.001$).

Cognitive tasks

Table 2 shows the means for the alcohol and control group with regard to the Attention/Executive function (performance

index), decision making, Memory (performance index) and intelligence.

Multivariate analysis indicated a significant main effect of group ($F(3, 80) = 3.51$, $P < 0.05$) and univariate analysis indicated that patients performed significantly worse than controls with regard to the Attention/Executive function ($F(1, 82) = 10.63$, $P < 0.05$), while the groups did not differ with regard to Memory ($F(1, 82) = 0.96$, $P = 0.33$) and intelligence ($F(1, 82) = 2.65$, $P = 0.11$).

We found no significant differences between patients and controls in the IGT. Both groups showed an increase in the net outcome from blocks 1 to 5 (main effect of block: $F(4, 308) = 15.05$, $P < 0.001$). Single comparisons (corrected for multiple comparisons) between performances in each block revealed that there was a significant difference between block 1 and block 2 ($t(78) = -2.57$, $P < 0.05$), but not between block 2 and block 3, block 3 and block 4, or block 4 and block 5. Neither the group effect ($F(1, 77) = 0.89$, $P = 0.35$) nor the interaction block \times group ($F(4, 308) = 0.20$, $P = 0.94$) was significant.

Analysis of moderating variables

Separate correlation analysis for the patient and control group indicated that depression scores were not significantly associated with cognitive performance in alcohol-dependent patients (all $P \geq 0.30$). In contrast, for healthy controls, we found that a higher depression score was associated with a poorer outcome in the Memory index ($r = -0.33$, $P < 0.05$) and a marginally significant negative correlation between the depression score and the Attention/Executive function ($r = -0.32$, $P = 0.056$) indicated that a higher depression score was associated with poorer performance with regard to the tasks averaged in this index. However, entering the depression score as a covariate in the multivariate analysis of variance still indicated a significant difference between patients and controls with regard to the performance index Attention/Executive function ($F(1, 81) = 8.95$, $P < 0.05$). Thus, group differences with regard to depressive symptoms did not account for differences between patients and controls with regard to attention and executive function.

To assess if performance in the cognitive tasks might be related to smoking, correlation analysis was performed for smokers only using the FTND score as an indicator of severity of nicotine dependence. As only eight participants of the control group were smokers, this analysis was not performed separately for patients and controls. For the whole sample, the mean for the FTND score was 4.93 (SD = 2.51). Our results indicated that the severity of nicotine dependence was not significantly associated with performance in any of the cognitive measures (all $P \geq 0.20$).

Comparison of patients with a low and high number of previous detoxifications

Population characteristics. Patients of the HI-detox group reported a longer duration of alcohol dependence ($t(46) = -3.39$, $P < 0.001$) and a higher severity of alcohol dependence (ADS) ($t(46) = -2.19$, $P < 0.05$) than patients of the LO-detox group (Table 3). We also found a significant difference between the two groups with respect to gender

Table 1. Demographic and substance-related characteristics of alcohol-dependent patients and healthy controls

	Alcoholics (<i>n</i> = 48)	Controls (<i>n</i> = 36)	Level of significance
Gender			
Women [<i>N</i> (%)]	21 (43.6)	13 (36.1)	ns
Men [<i>N</i> (%)]	27 (56.3)	23 (63.9)	
Age (years) [mean (SD)]	46.5 (8.2)	44.4 (9.9)	ns
Patients in a relationship [<i>N</i> (%)]	10 (20.8)	12 (33.3)	ns
Patients employed [<i>N</i> (%)]	26 (54.2)	23 (63.9)	ns
Premorbid IQ (vocabulary test) [mean (SD)]	103.9 (11.1)	108.2 (14.0)	ns
Age of onset of regular alcohol consumption [mean (SD)]	19.4 (4.5)	18.2 (7.9)	ns
Amount of lifetime alcohol consumption (number of standard drinks) [mean (SD)]	91,987.6 (102,845.9)	4967.6 (6755.2)	<i>P</i> < 0.001
Alcohol Dependence scale (ADS; summary score) [mean (SD)]	15.2 (6.8)	0.5 (1.5)	<i>P</i> < 0.001
Beck Depression Inventory (BDI; summary score) [mean (SD)]	10.0 (8.1)	2.8 (3.4)	<i>P</i> < 0.001
Smoking status			
Smokers [<i>N</i> (%)]	37 (77.1)	8 (22.2)	<i>P</i> < 0.001
Non-smokers [<i>N</i> (%)]	11 (22.9)	28 (77.8)	

ns: not statistically significant group difference; 1 standard drink = 10 g ethanol.

Table 2. Cognitive function of alcohol-dependent patients and healthy controls

	Alcoholics (<i>n</i> = 48)	Controls (<i>n</i> = 36)
Attention/Executive functioning (performance index)		
TMT-B, total time to complete (s) [mean (SD)]	97.1 (41.3)	78.3 (27.9)
WCST, no. of preservative errors [mean (SD)]	16.5 (10.3)	10.7 (7.7)
WCST, no. of categories completed [mean (SD)]	5.6 (2.6)	6.8 (2.2)
Decision making ^a		
IGT, net outcome block 1 [mean (SD)]	−3.2 (5.2)	−2.3 (4.7)
IGT, net outcome block 2 [mean (SD)]	0.7 (5.9)	0.0 (6.1)
IGT, net outcome block 3 [mean (SD)]	1.2 (9.2)	2.2 (6.8)
IGT, net outcome block 4 [mean (SD)]	2.5 (9.3)	3.1 (7.6)
IGT, net outcome block 5 [mean (SD)]	3.3 (9.5)	5.4 (8.3)
Memory (performance index)		
TME, no. of correct words part 1 [mean (SD)]	11.4 (3.4)	12.1 (2.6)
TME, no. of correct words part 2 [mean (SD)]	10.9 (3.2)	11.3 (2.4)
BVRT, no. of correct cards [mean (SD)]	7.4 (1.9)	7.7 (1.7)
BVRT, no. of errors [mean (SD)]	3.5 (2.8)	3.2 (2.4)
Intelligence		
WIP, IQ score [mean (SD)]	120.8 (14.6)	126.1 (15.0)

^aData of five patients are missing.

($\chi^2(1) = 5.0$, $P < 0.05$) indicating a higher proportion of women in the LO-detox group. The groups did not differ with respect to demographic or smoking-related variables.

Depressive symptoms. Table 4 shows that patients of the HI-detox group reported a higher number of depressive symptoms than the LO-detox group. However, separate correlation analysis for patients of the HI-detox and LO-detox groups indicated that the BDI summary score was not significantly correlated with any of the cognitive variables (all $P \geq 0.09$).

Cognitive tasks. An analysis of covariance showed that the two groups differed with respect to their performance in the IGT. We found a significant block \times group interaction referring to a greater increase of cards taken from advantageous decks from the first to the last ten trials for the LO-detox group in contrast to the HI-detox group ($F(1, 35) = 4.48$, $P < 0.05$). As shown in Fig. 1a, patients of the HI-detox group started the task taking more cards from the advantageous decks, although this difference just failed to reach statistical significance ($t(41) = -1.92$, $P = 0.06$). However, the LO-detox group improved their performance during the task ($t(18) = -2.89$, $P < 0.05$) while this improvement marginally failed to reach significance for the HI-detox group ($t(23) = -2.04$, $P < 0.10$) indicating that the significant group \times block interaction effect is due to a greater improvement of the LO-detox group

when compared to the HI-detox group. Both groups performed equally in the last 10 trials ($t(41) = -0.07$, $P = 0.94$).

We found no differences between the HI-detox and the LO-detox group with regard to the other outcome variables of the IGT (i.e. net outcome in the different blocks; see Fig. 1b).

In addition, patients of the HI-detox group did not perform worse than patients of the LO-detox group with regard to the Attention/Executive function, Memory and intelligence; multivariate analysis of covariance indicated no significant main effect of group ($F(2,39) = 1.94$, $P = 0.16$).

Comparison of recently and longer abstinent patients

Population characteristics. Table 5 indicates that there were no significant differences between recently and longer abstinent patients with respect to demographic and drinking-related variables (all $P > 0.41$). In addition, recently and longer abstinent patients did not differ with regard to their classification into the LO-detox and HI-detox groups.

Table 4 also shows that recently and longer abstinent patients did not differ with regard to depressive symptoms.

The multivariate analysis of variance with group (recently versus longer abstinent patients versus controls) as a fixed factor revealed a significant main effect of group ($F(2, 158) = 1.89$, $P < 0.05$). Univariate analysis of variance indicated that

Table 3. Demographic and substance-related characteristics of alcohol-dependent patients with two or more previous detoxifications (HI-detox group) compared to patients with fewer than two previous detoxification (LO-detox group)

	HI-detox (<i>n</i> = 27)	LO-detox (<i>n</i> = 21)
Gender		
Women [<i>N</i> (%)]	8 (29.6)	13 (61.9)*
Men [<i>N</i> (%)]	19 (70.4)	8 (38.1)
Age (years) [mean (SD)]	47.8 (8.8)	45.0 (7.2)
Patients in a relationship [<i>N</i> (%)]	5 (18.5)	5 (23.8)
Patients employed [<i>N</i> (%)]	11 (54.2)	15 (63.9)
Premorbid IQ (vocabulary test) [mean (SD)]	105.7 (12.2)	101.6 (9.2)
Number of previous detoxifications [mean (SD), range]	7.1 (11.0), 2–56	0.2 (0.4), 0–1*
Duration of alcohol dependence (years) [mean (SD)]	17.4 (9.4)	9.4 (6.0)*
Age of onset of regular alcohol consumption [mean (SD)]	19.6 (5.2)	19.1 (3.3)
Amount of lifetime alcohol consumption (number of standard drinks) [mean (SD)]	98,694.3 (85,205.3)	83,364.6 (123,611.9)
Alcohol dependence scale (ADS; summary score) [mean (SD)]	17.0 (7.1)	12.9 (5.8)*
Length of abstinence prior to testing [mean (SD)]	16.2 (8.0)	14.9 (4.6)
Smoking status		
Smokers [<i>N</i> (%)]	20 (74.1)	17 (81.0)
Non-smokers [<i>N</i> (%)]	7 (25.9)	4 (19.0)

* $P < 0.05$; 1 standard drink = 10 g ethanol.

Table 4. Depressive symptoms of patients with two or more previous detoxifications (HI-detox group), patients with fewer than two previous detoxification (LO-detox group), recently abstinent (R-abstinent group) and longer abstinent (L-abstinent group) patients and healthy controls

	HI-detox (<i>n</i> = 27)	LO-detox (<i>n</i> = 21)	R-abstinent (<i>n</i> = 28)	L-abstinent (<i>n</i> = 20)	Controls (<i>n</i> = 36)
Beck Depression Inventory [mean (SD)]	12.6 (8.4) ^{a,b}	6.8 (6.6) ^b	10.1 (8.1) ^b	10.0 (8.4) ^b	2.8 (3.4)

^aDifferent from the related patient group; ^bdifferent from the control group (social drinkers).

Table 5. Demographic and substance-related characteristics of recently abstinent (R-abstinent group) and longer abstinent (L-abstinent group) alcohol-dependent patients compared to healthy controls

	R-abstinent (<i>n</i> = 28)	L-abstinent (<i>n</i> = 20)	Controls (<i>n</i> = 36)
Gender			
Women [<i>N</i> (%)]	13 (46.4)	8 (40.0)	13 (36.1)
Men [<i>N</i> (%)]	15 (53.6)	12 (60.0)	23 (63.9)
Age (years) [mean (SD)]	45.3 (7.3)	48.3 (9.2)	44.4 (9.9)
Patients in a relationship [<i>N</i> (%)]	6 (21.4)	4 (20.0)	12 (33.3)
Patients employed [<i>N</i> (%)]	16 (57.1)	10 (50.0)	23 (63.9)
Premorbid IQ (vocabulary test) [mean (SD)]	104.1 (11.0)	103.6 (11.6)	108.2 (14.0)
Length of abstinence prior to testing [mean (SD), range]	11.5 (3.8), 4–16 ^a	21.4 (5.5), 17–37	N/A
Age of onset of regular alcohol consumption [mean (SD)]	19.3 (4.4)	19.6 (4.6)	18.2 (7.9)
Duration of alcohol dependence (years) [mean (SD)]	13. (9.2)	15.2 (8.7)	N/A
Amount of lifetime alcohol consumption (standard drinks) [mean (SD)]	93,313.9 ^b (117925.1)	90,130.6 ^b (79981.5)	4967.6 (6755.2)
Alcohol dependence scale [mean (SD)]	16.2 (7.3) ^b	13.8 (6.0) ^b	0.5 (1.5)
Number of previous detoxifications [mean (SD)]	4.4 (10.7)	3.6 (5.5)	N/A
Classification of previous detoxifications			
HI-detox patients [<i>N</i> (%)]	15 (53.6)	12 (60.0)	N/A
LO-detox patients [<i>N</i> (%)]	13 (46.4)	8 (40.0)	
Smoking status			
Smokers [<i>N</i> (%)]	19 (67.9) ^b	18 (0.9) ^b	8 (22.2)
Non-smokers [<i>N</i> (%)]	9 (32.1)	2 (0.1)	28 (77.8)

^aDifferent from the related patient group ($P < 0.05$), ^bdifferent from the control group ($P < 0.05$); N/A, not applicable; 1 standard drink = 10 g ethanol.

the groups differed significantly with regard to the performance index Attention/Executive function ($F(2, 81) = 5.88, P < 0.05$), but not with regard to the performance index Memory ($F(2, 81) = 0.70, P = 0.50$) or intelligence ($F(2, 81) = 1.39, P = 0.25$). The *post hoc* test indicated for the performance index Attention/Executive function that recently abstinent patients performed significantly worse than controls ($t(62) = 3.62, P < 0.05$), while we found only a marginal significant difference between longer abstinent patients and controls ($t(54) = 1.77, P = 0.09$).

In the IGT, we found a significant main effect of group ($F(2, 76) = 3.31, P < 0.05$) and block ($F(4, 304) = 14.56, P < 0.001$), while the block \times group interaction failed to reach significance ($F(8, 304) = 1.61, P = 0.12$). *Post hoc t*-tests indicated that recently abstinent patients had a lower total net outcome in the IGT compared to controls ($t(59) = 2.15, P < 0.05$) and to longer abstinent patients ($t(41) = 2.17, P < 0.05$; see Fig. 2b).

However, when we compared the performance of the three groups in the first 10 trials as well as in the last 10 trials, we

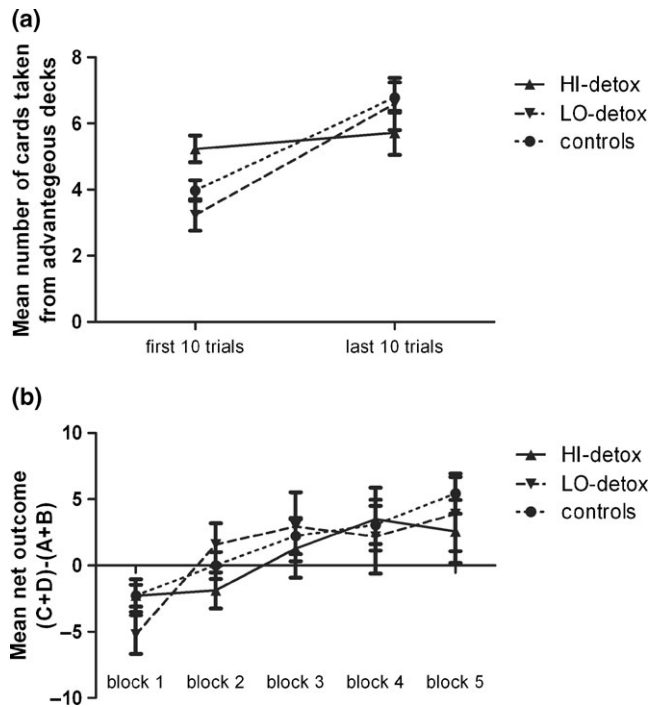


Fig. 1. Performance of patients with two or more previous detoxifications (HI-detox group) compared to patients with fewer than two previous detoxification (LO-detox group) and controls in the IGT (covariate adjusted mean and SEM): (a) number of cards taken from advantageous decks; (b) net outcome measurement.

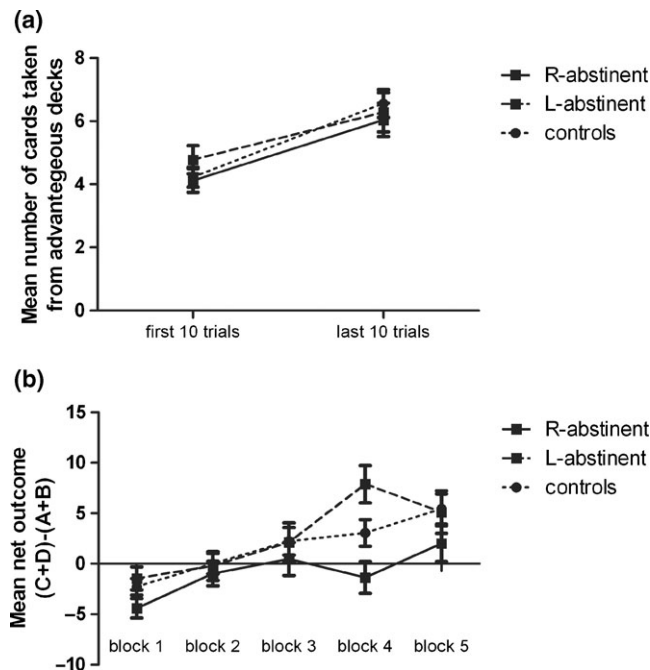


Fig. 2. Performance of recently and longer abstinent patients in the IGT in contrast to controls (mean and SEM). (a) Number of cards taken from advantageous decks; (b) net outcome measurement.

found only a significant effect of block ($F(1, 76) = 24.80$, $P < 0.001$), but neither a significant group ($F(2, 76) = 0.46$, $P = 0.63$) nor a significant block \times group interaction ($F(2, 76) = 0.40$, $P = 0.67$; see Fig. 2a).

DISCUSSION

The main aim of the present study was to assess in alcohol-dependent patients the impact of multiple withdrawals from alcohol on prefrontal function and decision making in a gambling task (IGT).

In line with previous studies, our results indicated first of all that alcohol-dependent patients performed significantly worse than healthy controls in tasks related to prefrontal function. Alcoholics, when compared to healthy controls, were impaired with regard to the performance index Attention/Executive function that comprised tasks assessing the ability to shift (TMT-B) as well as executive function and cognitive flexibility (WCST). This impairment was found despite an IQ score in the alcohol-dependent patients above average and in the range of healthy controls, and intact auditory and visual memory functioning. These results are in line with recent findings from Chanraud *et al.* (2007), who reported that alcohol-dependent patients were impaired with regard to their performance in the TMT-B and the WCST, but not in the Letter-Number-Sequencing Test (Wechsler, 1997), which provides a measure of working memory. Using magnetic resonance imaging morphometry, Chanraud *et al.* (2007) further demonstrated an association between cognitive impairment in the TMT-B and decreases in grey matter volume in the frontal and temporal cortices, the insula and the hippocampus, while WCST scores were related to grey matter volumes in the middle temporal gyri, thalamus and cerebellum. The authors therefore suggested that subcortical shrinkage within cerebello-thalamo-cortical circuits adversely affects frontal functioning and thereby impairs executive function. Our results provide further evidence for the adverse effects of chronic alcohol consumption on these processes.

Comparing recently to longer abstinent patients indicated that the observed impairment of executive functions was especially pronounced in early abstinence. This result is in line with previous studies (e.g. Mann *et al.*, 1999; Fein *et al.*, 2006) who reported a recovery of cognitive impairment under abstinence. With regard to decision making (IGT), we found an impairment only in recently detoxified alcohol-dependent patients that is in contrast to previous studies reporting an impairment of decision making not only in recently, but also in longer abstinent alcohol-dependent patients (e.g. Fein *et al.*, 2004; Goudriaan *et al.*, 2005). However, Noël *et al.*, (2007) suggested only recently that performance of alcohol-dependent patients in the IGT might recover after a period of abstinence. While our results are in line with this suggestion, further studies are warranted to systematically address this question as there might be several explanations for divergent findings (e.g. sample differences with regard to the number of previous detoxifications, brain atrophy or stress-hormone-induced alterations in monoaminergic function).

While our results thus indicated an impairment of alcohol-dependent patients with regard to attention and executive function, we found only little evidence that repeated withdrawal from alcohol has deleterious effects on frontal lobe function.

Comparing patients with two or more previous detoxifications (HI-detox group) to patients with less than two previous detoxifications (LO-detox group) revealed no significant differences between the two groups with regard to the performance index Attention/Executive function and Memory, as well as with regard to general cognitive abilities (WIP). These results are in contrast to a previous study by Duka *et al.* (2003) that found that patients with two or more previous detoxifications were more impaired than patients with only a single or no previous detoxification. However, differences between the results of the current study and the results of Duka *et al.* (2003) may be due to sample differences as well as differences with regard to the cognitive abilities examined. The most important sample differences are the lower age of onset of problem drinking in the HI-detox sample of Duka *et al.* (2003) in contrast to the present study and the inclusion of alcohol-dependent patients with concurrent illicit drug abuse problems in the Duka *et al.* study. Both aspects might be associated with higher cognitive impairment and an analysis of covariance performed by Duka *et al.* (2003) indicated that some of the effects of repeated withdrawal on cognitive function were confounded by the age of starting heavy drinking and the years of problem drinking. However, after controlling for confounding factors (i.e. age of starting heavy drinking, years of problem drinking, severity of dependence, alcohol consumption in the 6 months prior to hospitalization) Duka *et al.* (2003) still found that performance in the delay task was significantly related to the number of previous detoxifications. Thus, differences with regard to the cognitive abilities examined might explain divergent findings between the present study and Duka *et al.* (2003). The tasks administered by Duka *et al.* (2003) were concentrating on the ability to follow goals (i.e. the Porteus maze), the ability to disinhibit a prepotent response (the vigilance task in the Gordon diagnostic battery of tasks) and the ability to wait before a response to receive a reward (the delay task from the Gordon Diagnostic System), while in contrast to the present study no tasks on attention, the ability to shift, working memory and mental flexibility were administered. Thus, tasks that assess response inhibition or are incorporating aspects of reward might be more sensitive to the impairing effects of repeated withdrawal. In line with this assumption, we found preliminary evidence for a greater impairment of the HI-detox group with regard to decision making in a gambling task (IGT). Our results indicated that the LO-detox group picked in the first trials more cards from the disadvantageous decks, providing not only higher rewards but also higher losses, and switched to the advantageous decks to receive a higher reward in the long-term. In contrast, patients in the HI-detox group started the task taking more cards from the advantageous decks but showed less improvement from the first to the last 10 trials when compared to patients from the LO-detox group. In our view, this behaviour might refer to a decision-making strategy of the HI-detox group based on safety considerations or avoidance of punishment in the initial phase of the task, while later on they persist on the first decks that were chosen. However, future studies are necessary to further investigate this preliminary finding. In general, the IGT seems to be an interesting task to assess the effects of repeated withdrawal because decision-making performance has been linked to serotonergic innervation of the prefrontal cortex (e.g. Rogers *et al.*, 2003), and serotonin transporter availability was found reduced in alcoholics in association with detoxification-related

increases in cortisol (Heinz *et al.*, 2002). In line with this, our results indicated a higher depression score for patients of the HI-detox group compared to patients of the LO-detox group. Thus, future studies are warranted to assess if the IGT is sensitive to the effects of repeated withdrawal.

However, apart from differences with regard to the tasks administered, further aspects might explain why we found only little evidence that repeated withdrawal affects cognitive performance. Defining withdrawal as the number of 24-h periods of abstinence following a drinking day in the last year, Glenn *et al.* (1988) demonstrated that the number of repeated withdrawals was related to poor immediate and delayed semantic and figural memory in alcohol-dependent patients. It is reasonable to assume that divergent findings between Glenn *et al.* (1988) and the present study are accounted for by differences with regard to the definition of withdrawal. Thus, withdrawal defined as medically supervised detoxification might not be an adequate measure to assess the impact of withdrawal from alcohol on prefrontal function as impairment might occur earlier in dependence, for example in association with personal attempts to abstain from alcohol or special drinking patterns. While the medically supervised detoxification can be described as a major event with respect to the cessation of alcohol consumption, drinking patterns characterized by alternating phases of loss of control associated with the consumption of high amounts of alcohol (i.e. binge drinking) and intervals of abstinence might as well induce cognitive impairment due to an excess of glutamate release and associated biochemical changes or oxidative stress from proinflammatory enzymes during intoxication [for recent reviews on alcohol-related brain damage, see Crews and Nixon (2009) and Ward *et al.* (2009)]. In social drinkers, previous studies (Weissenborn and Duka, 2003; Townshend and Duka, 2005) reported an association between binge drinking and impaired cognitive function, albeit more commonly in female binge drinkers. Thus, drinking patterns leading to high levels of intoxication alternating with phases of abstinence might be a major component for the development of impaired prefrontal function.

In addition, it should be taken into account that the impact of repeated withdrawal on cognitive function might be modulated by other variables. For example, Duka *et al.* (2003) demonstrated previously that the age of start drinking and years of problem drinking are affecting cognitive functioning and are modulating the effects of repeated withdrawal. It is known that the frontal lobe develops later in life (Crews *et al.*, 2007), and thus, early age of drinking alcohol or having problems with alcohol would increase the frontal lobe susceptibility to the damaging effects of repeated detoxifications. In line with this, the serotonergic system that regulates prefrontal functioning (e.g. Rogers *et al.*, 2003) has been shown to be affected in relation to the amount of lifetime alcohol intake (Heinz *et al.*, 2000, 2001).

Further, there might be a number of other factors such as blackouts, head injuries or nutritional deficiencies that might be linked to the number of detoxifications and modulate cognitive function. Thus, the number of previous detoxifications may primarily serve as a kind of marker or mediator of these effects.

There are some limitations that should be taken into account when interpreting the results of the present study. First, except the verbal IQ as an indicator of premorbid intelligence, no data are available in the current study with regard to premorbid

prefrontal functioning of alcohol-dependent patients. Cognitive deficits can be a risk factor for the development of drug and alcohol dependence (Moriyama *et al.*, 2006) and some studies described differences between healthy subjects with and without a family history of alcoholism with regard to cognitive functioning (Drejer *et al.*, 1985; Tarter *et al.*, 1989; Corral *et al.*, 2003). Although there are also longitudinal studies (e.g. Tapert and Brown, 1999) suggesting that substance abuse in adolescents leads to cognitive impairment, we cannot exclude that the patients of our study were impaired with regard to executive functioning prior to the development of alcohol dependence.

Second, smoking status differed significantly between patients and controls and as demonstrated previously by Duka *et al.* (2003), smoking can be a confounding factor in the assessment of cognitive impairment. However, in the present study, performance in the cognitive tasks in which patients and healthy controls differed significantly with regard to their performance, was not significantly associated with the severity of nicotine dependence (FTND score). Further, the different patient groups compared (i.e. HI-detox versus LO-detox, and recently versus longer abstinent patients) did not differ with respect to smoking status or the severity of nicotine dependence. In addition, the testing procedure allowed participants to smoke until the start of the session and after completion of single tasks; thus, it is unlikely that subjects were nicotine deprived when performing the tasks. Nevertheless, there are further studies (Durazzo *et al.*, 2006, 2007) that demonstrated that comorbid chronic cigarette smoking modulates cognitive functioning in alcohol-dependent patients and further research is necessary for a better understanding of the consequences of chronic smoking in alcoholism.

Nevertheless, our results provide additional evidence for cognitive impairments in frontal lobe functions in alcoholics compared to healthy controls and initial evidence is found for an effect of repeated withdrawals on decision making in a gambling task, suggesting an inability to adjust behaviour to newly learned rules in patients with two or more previous detoxifications compared to alcoholic patients with less than two previous detoxifications. In addition, the present study has shown that cognitive impairment is especially pronounced in early abstinence and might recover with longer duration of abstinence.

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