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ORIGINAL ARTICLE

Effects of Repeated Withdrawal from Alcohol on Recovery of Cognitive Impairment under Abstinence and Rate of Relapse

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Abstract — Aims: Several authors suggest that withdrawal from alcohol could cause neurotoxic lesions in the frontal lobe and thereby affect cognitive function. In line with this, previous studies have demonstrated greater cognitive impairment of alcohol-dependent patients with two or more previous detoxifications (Hi-detox) compared with patients with less than two detoxifications (Lo-detox). The aim of the present study was to investigate whether repeated withdrawal from alcohol affects recovery of cognitive function and is related to relapse. **Methods:** Forty-eight alcohol-dependent patients (Hi-detox: $n = 31$, Lo-detox: $n = 17$) and 36 healthy controls underwent a comprehensive neuropsychological test-battery. Patients were tested after completion of detoxification (T1) and 3 (T2, $n = 35$) and 6 (T3, $n = 28$) months after discharge. Healthy controls were tested at T1 ($n = 36$) and T2 ($n = 16$). Drinking behaviour was assessed at all times. **Results:** Patients performed significantly worse than controls at T1 as well as T2 with regard to attention/executive function. Recovery of attention/executive function was observed within the second 3 months after discharge, but the Hi-detox group performed worse than the Lo-detox group. No association with relapse was observed. **Conclusion:** This study provides first evidence, that repeated withdrawal from alcohol might be associated with reduced brain plasticity as indicated by a delay of recovery from impairment of attention/executive function. However, little evidence was found for a direct influence of cognitive impairment on treatment success.

INTRODUCTION

It is well known that severe chronic use of alcohol induces neurotoxicity and is associated with cognitive impairment, especially related to tasks which involve prefrontal function (for a review see, for example, Moselhy *et al*., 2001). Thus, alcohol-dependent patients compared with healthy controls show impaired performance in tests of attention, mental flexibility, decision-making, reward delay, problem solving and related aspects of executive function (e.g. Chanraud *et al*., 2007; Noël *et al*., 2007). Importantly, a longitudinal study by Tapert *et al*. (1999) demonstrated that continued substance involvement in adolescence leads to greater cognitive deficits, thus suggesting that the observed cognitive deficits are not merely a risk factor for the development of drug and alcohol dependence, but a consequence of factors related to addicted behaviour. In addition, there are also some studies which demonstrated that cognitive impairment of alcohol-dependent patients is associated with a higher rate of relapse after treatment. For example, Noël *et al*. (2001) found that the risk of short-term relapse after detoxification is related to an impairment of executive functions and deficits of inhibitory control (Noël *et al*., 2002).

There is also a vast body of literature demonstrating that cognitive impairment of alcohol-dependent patients is, at least partly, reversible (e.g. Brandt *et al*., 1983; Fein *et al*., 2006; Mann *et al*., 1999). For example, already in 1977 O'Leary *et al*. demonstrated that within the first year of abstinence, performance of alcohol-dependent patients in the Trail Making Test (TMT), a measure of attention and executive function, improved significantly. In a more recent study, Fein *et al*. (2006) demonstrated that long-term abstinent patients (i.e. abstinent on average for 6.7 years) performed similarly to healthy controls on a wide range of neuropsychological measures assessing abstraction/cognitive flexibility, attention, working memory, psychomotor function, reaction time and verbal skills. Impairment was only observed with regard to deficits in the spatial processing domain. In our own study, we found evidence for recovery of cognitive impairment even within the first 3 weeks of abstinence: patients abstinent for less than 16 days compared with patients abstinent for 16 or more days were found to differ significantly from healthy controls with regard to performance in the IOWA gambling task (IGT) (Loeber *et al*., 2009a,b). This result is in line with a finding from Noël *et al*. (2007) who also reported a positive association between the duration of abstinence and performance in a gambling task. Neurogenesis of the brain after alcohol-induced neurodegeneration was also demonstrated in animal studies, which showed that after months of abstinence bursts of proliferating cells occur across multiple brain regions with many new microglia across the brain and many new neurons in the neurogenic hippocampal dentate gyrus (Crews and Boettiger, 2009). In contrast, there are also human studies which demonstrated that some cognitive abilities might be more resistant to recovery than others. Thus, Mlinarics *et al*. (2009) as well as Munro *et al*. (2000) reported that executive function especially, seems to be resistant to recovery.

However, it is less clear which factors contribute to cognitive deficits of alcohol-dependent patients and even less is known about factors that affect recovery of the observed deficits (Harper, 2009). While some authors reported 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), some authors argued that the repeated withdrawal form alcohol causes neurotoxic lesions in the frontal lobe and that the resulting cognitive deficits should negatively influence treatment outcome after detoxification (De Witte *et al*., 2003). Chronic alcohol consumption disrupts

glutamatergic neurotransmission in the brain and leads to a prolonged inhibition of the N-methyl-D-aspartate (NMDA) receptor (Lovinger, 1993). Consequently, as a homeostatic mechanism an increase in glutamate release can be observed. Thus, the abrupt cessation of alcohol consumption can cause excitotoxicity due to the increased glutamate release (Tsai and Coyle, 1998). As the frontal lobes are particularly rich in glutamatergic pathways (Kril *et al.*, 1997), the glutamate-mediated excitotoxicity may especially affect the frontal lobes, and deficits of frontal lobe function can be the consequence.

While several animal studies demonstrated that repeated withdrawal is associated with an impairment of cognitive abilities and learning (e.g. Borlikova *et al.*, 2006; Stephens *et al.*, 2001), only a few studies have assessed the influence of repeated withdrawal from alcohol on cognitive function in humans and the results are less clear. For example, Duka *et al.* (2003) found that patients with two or more previous medically supervised detoxifications performed worse than patients with less than two detoxifications in a Porteus maze task, a reward delay task and a vigilance task. In addition, in our previous study (Loeber *et al.*, 2009a,b) comparing cognitive performance of patients with two or more previous medically supervised detoxifications with performance of patients with less than two detoxifications we found that patients with two or more detoxifications showed less improvement of reward-related learning in the IGT than patients with less than two detoxifications indicating possibly an impairment of plasticity. Thus, the repeated withdrawal from alcohol might especially affect learning processes and inhibitory control mechanisms (assessed in the Duka *et al.* study with the reward delay task) and it might be associated with reduced brain plasticity. This assumption is supported by a recent review by Stephens and Duka (2008) in which the authors present cumulative evidence for reduced plasticity (long-term potentiation) in amygdala and hippocampus from animal and human studies, which was accompanied by both impaired associative learning and inappropriate generalization of previously learned associations to irrelevant stimuli as the result of repeated withdrawal form alcohol. Based on these findings, it can be assumed that the repeated withdrawal from alcohol affects recovery of cognitive impairment due to its effects on brain plasticity. Thus, in the present study, we set out to test whether patients with two or more previous medically supervised detoxification treatments show less recovery of cognitive impairment than patients with only one previous detoxification. In addition, as suggested by De Witte *et al.* (2003), we questioned whether the repeated withdrawal from alcohol is associated with the frequency of, and time, to first relapse after discharge from treatment.

MATERIALS AND METHODS

Study population

Forty-eight patients (29 male, 19 female) who were alcohol-dependent according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria and sought extended inpatient detoxification treatment at the Department of Addictive Behaviour and Addiction Medicine at the Central Institute of Mental Health, Mannheim, Germany were initially recruited for the study. Extended inpatient detoxification treatment in Germany comprises medically supervised detoxification as well as group therapy and relapse prevention training based on motivational interviewing techniques and cognitive-behaviour-therapy (Mann *et al.*, 2006). In a previous study, we demonstrated that in contrast to standard detoxification this 3-weeks program is associated with a reduced risk of relapse (Loeber *et al.*, 2009a,b). To assess the impact of repeated withdrawal from alcohol on recovery of cognitive impairment, we divided the patient population into two groups based on the number of previous medically supervised detoxifications using information obtained from a structured interview in accordance with our previous study on the effects of repeated withdrawal (Loeber *et al.*, 2009a,b). This criterion was derived from findings form Duka *et al.* (2003) who reported an impairment of cognitive function in patients with two previous detoxifications compared with patients with less than two detoxifications. Thirty-six healthy control participants matched for age, gender and premorbid intelligence assessed with the Vocabulary Test (Schmidt and Metzler, 1992) were recruited from the general population of Mannheim and served as control group. They were paid for their study participation. Exclusion criteria for both samples were current drug abuse or dependence other than nicotine or alcohol for the patients. Healthy controls had no alcohol-related problems according to information obtained from semi-structured interviews, questionnaires and biological alcoholism markers. Further exclusion criteria were severe somatic or neurological diseases, mental disorder, serious complications in detoxification for the patients, pregnancy, lactation period or suicidal tendencies. The study was approved by the Ethics Committee of the Medical Faculty Mannheim at the University of Heidelberg and adhered to the Declaration of Helsinki. All participants signed informed consent.

General procedures

A comprehensive neuropsychological test battery was administered at study inclusion to patients ($n = 48$) as well as healthy controls ($n = 36$). The first assessment with the patients took place during inpatient treatment after cessation of withdrawal symptoms and at least 5 days after termination of medication. Thirty-five patients of the initial sample as well as 16 participants of the control group were tested with the same battery 3 months later and 28 patients were tested once more 3 months later, i.e. 6 months after the first testing. Patients lost for follow-up could either not be contacted or denied a further test session. A third test session with healthy controls was not performed as no changes of cognitive function were assumed. At both the second and third testing, patients were interviewed about their drinking behaviour. For a total of $n = 32$ follow-up data with regard to drinking behaviour are available. When abstinence appeared questionable to the interviewer (e.g. several appointments are needed to meet the patient for the interview, inconsistent reports in the interview), biological alcoholism markers were assessed to verify self-reported data ($n = 12$). No inconsistencies were observed between self-reported data and the results of blood analysis.

Questionnaires and neuropsychological measures

Several questionnaire measures and structured interviews were used to assess demographic and drinking-related variables.

The Life Time Drinking History (Skinner and Sheu, 1982) and the Time Line Follow Back Interview (Sobell and Sobell, 1995) were administered to gain information on past and recent alcohol consumption. The Alcohol Dependence Scale (ADS; Skinner and Allen, 1982) was used to assess the severity of alcohol dependence. In addition, the Beck Depression Inventory (Beck *et al*., 1961) was administered to assess depressive symptoms. Impairment of cognitive function was assessed using a comprehensive neuropsychological test battery including tests sensitive to attention and executive function (TMT Part B, Reitan, 1992; Wisconsin Card Sorting Test, WCST, Loong, 1990), decision-making and risk-taking behaviour (IGT, Bechara *et al.,* 2000) and memory (Auditory Verbal Learning Test, TME, Rey, 1964; Benton Visual Retention Test, BVRT, Benton, 1992). The test session lasted ~2–3 h and was conducted by a clinical psychologist trained in neuropsychological test administration.

Statistical analysis

Differences between patients and controls and between patients of the HI-detox group and the LO-detox group with regard to confounding demographic and substance-related characteristics were analysed using chi-square analyses (Fisher's exact test) and non-parametric tests (two-sided) due to the small sample size of the LO-detox group and uneven group sizes. Recovery of cognitive impairment was analysed first by calculating a repeated measures analysis of variance (ANOVA) with cognitive function at T1 and T2 as the repeated measures and patients versus healthy controls as group factor. Secondly, to assess the impact of repeated withdrawal on recovery of cognitive function, repeated measures ANOVAs were performed with patients only entering Lo-detox versus Hi-detox as group and cognitive function at T1 and T2 or T2 and T3 as repeated measures factor. The repeated measures ANOVAs were performed separately for the first and the second 3 months period to avoid loss of data from patients who took part in T2 but not T3 ($n = 7$). All of the variables analysed met the assumptions of normal distribution and variance homogeneity. However, to rule out possible confounding effects of the small sample size of the Lo-detox group and uneven group sizes, non-parametric analysis (Friedman ANOVA) were performed for significant findings. As in our previous study (Loeber *et al*., 2009a,b) two different performance factors were calculated from the various measures of neuropsychological functioning to reduce multiple testing. Thus, the raw values from each neuropsychological test outcome measure were standardized (with the sample mean and standard deviation for each individual variable) and, if necessary, variables were recoded so that higher values indicate better performance. Then, the variables were summed up to build two different performance factors. The factor attention/executive function summarizes performance in the TMT (time needed to finish the task) and the WCST (number of categories identified correctly, number of errors), while Memory function comprises performance in the TME (number of words remembered correctly) and the BVRT (number of pictures remembered correctly). Performance in the IGT (risk-taking behaviour) was analysed separately using the net outcome. To assess the impact of repeated withdrawal on time to first relapse the survival curves of patients from the Lo-detox and Hi-detox groups were compared by calculating a log rank test. In addition, to analyse differences with regard to the frequency of relapse a chi-square analysis was performed as well as a logistic regression analysis with relapse as the dependent variable and the number of previous detoxifications and cognitive performance at baseline as independent variables. For the analyses, PAWS Statistics 18 was used; only non-parametric statistics were calculated with Statistical Analysis Software (SAS), version 9.2.

RESULTS

Patients and controls did not differ significantly with regard to age, gender, IQ and employment status, but the patients reported a significantly higher amount of lifetime alcohol consumption, achieved a higher score in the ADS-questionnaire assessing severity of alcohol problems and dependence and reported more depressive symptoms (see Table 1 for descriptive data). Patients with two or more previous detoxifications ($n = 31$) did not differ significantly from patients with less than two previous detoxifications

Table 1. Demographic and drinking drinking-related variables of patients and healthy controls

	Hi-detox ($n = 31$)	Lo-detox ($n = 17$)	Controls ($n = 36$)
Gender			
Women [*n* (%)]	6 (24.0)	5 (50)	7 (43.7)
Men [*n* (%)]	19 (76.0)	5 (50)	9 (56.3)
Age (years) [mean (SD)]	47.4 (8.4)	44.9 (7.7)	44.4 (9.1)
Patients in a relationship [*n* (%)]	6 (24.0)	0 (0.0)	5 (31.3)
Patients employed [*n* (%)]	13 (52)	7 (70)	11 (68.8)
Premorbid IQ (vocabulary test) [mean (SD)]	105.0 (11.8)	101.8 (9.7)	108.2 (14.0)
Age of onset of regular alcohol consumption [mean (SD)]	19.4 (5.0)	19.4 (3.5)	18.2 (7.9)
Amount of lifetime alcohol consumption (alcohol units) [mean (SD)]	94065.5 (80793.8)[a]	88198.4 (137141.7)[a]	4967.6 (6755.2)
Daily amount of alcohol consumption in the last 90 days prior to admission (alcohol units) [mean (SD)]	160.4 (126.0)[a]	107.4 (114.5)[a]	3.7 (3.8)
Number of drinking days in the last 90 days prior to admission [mean (SD)]	51.7 (20.2)	50.7 (26.5)	n/a
Number of previous detoxifications [mean (SD)]	7.3 (10.4)[b]	1.00 (0.00)[b]	n/a
Alcohol dependence scale [mean (SD)]	16.7 (6.8)[a]	12.6 (6.1)[a]	0.5 (1.5)
Beck depression inventory [mean (SD)]	11.7 (8.4)[a]	7.1 (6.9)	2.8 (3.4)

Note: Non-parametric statistics were used (Kruskal–Wallis one way ANOVA, median test).
[a]Significantly different from control group; n/a, not applicable.
[b]Significantly different from related alcohol group.

($n = 17$) with regard to demographic variables, premorbid IQ, depressive symptoms as well as the age of starting drinking regularly, the amount of lifetime or recent alcohol consumption or the number of drinking days in the last 90 days prior to admission. We found only a tendency for a higher summary score of the Hi-detox group on the ADS ($P = 0.07$); however, as the severity of alcohol dependence was not significantly correlated with any of our measures of executive function (all rs ≤ 0.29; all Ps ≥ 0.12), this variable was not entered as a covariate in the subsequent analyses.

Cognitive performance and recovery of cognitive deficits of alcohol-dependent patients compared with healthy controls

The results of an ANOVA with the factor attention/executive function at T1 and T2 as repeated measures factor indicated a significant main effect of group [$F(1,48) = 6.23$, $P = 0.016$, observed power = 0.83], while neither the main effect of time [$F(1,48) = 0.02$, $P = 0.90$, partial $\eta^2 = 0.00$] nor the time by group interaction [$F(1,48) = 0.23$, $P = 0.63$, partial $\eta^2 = 0.01$] was significant. *Post hoc* comparisons indicated that patients performed worse than controls at T1 [$t(49) = -3.10$, $P = 0.001$] as well as T2 [$t(49) = -2.23$, $P = 0.03$]. Thus, patients did not show any improvement of their performance within the first 3 months after discharge with regard to tasks assessing attention and executive function. Healthy controls performed equally well at T1 and T2.

With regard to risk-taking behaviour, the repeated measures ANOVA yielded neither significant main nor interaction effects for the net outcome in the IGT administered at T1 and T2 (all Fs ≤ 0.94, all Ps ≥ 0.34, all partial $\eta^2 \leq 0.05$), indicating that patients and healthy controls did not differ with regard to their risk-taking behaviour at T1 and T2 and that both groups did not show any changes of their performance.

When we entered the index memory function at T1 and T2 as repeated measures factor in the ANOVA we found again neither significant main nor interaction effects (all Fs ≤ 0.57, all Ps ≥ 0.54, all partial $\eta^2 \leq 0.01$) indicating no significant impairment of patients when compared with healthy controls and no significant changes over time for all participants.

Impact of repeated withdrawal from alcohol on recovery of cognitive deficits

Descriptive data with regard to the different indices of cognitive function are shown in Table 2. The repeated measures ANOVA with attention/executive function at T1 and T2 and Hi-detox versus Lo-detox as group factor indicated a main effect of the groups, which marginally failed to reach significance ($F(1,32) = 3.24$, $P = 0.08$, partial $\eta^2 = 0.08$), but tended towards better performance of the Lo-detox-group. However, the main effect of time [$F(1,32) = 1.87$, $P = 0.18$, partial $\eta^2 = 0.02$] as well as the time by group interaction [$F(1,32) = 0.08$, $P = 0.77$, partial $\eta^2 = 0.02$] were not significant, indicating improvement of cognitive function for neither of the groups. The Friedman ANOVA (non-parametric statistics) indicated as well an only marginally significant main effect of group [$F(1,82) = 2.92$, $P = 0.09$]. In contrast, when we entered the attention/executive function score at T2 and T3 in the repeated measures ANOVA we now found a significant main effect of time [$F(1,26) = 4.41$, $P = 0.048$, partial $\eta^2 = 0.15$, observed power = 0.53], which indicated significant improvement of cognitive function for both groups. In addition, a significant main effect of group [$F(1,26) = 5.48$, $P = 0.027$, partial $\eta^2 = 0.17$, observed power = 0.62] indicated overall better performance of the Lo-detox group within the second 3 months after discharge. The interaction time by group slightly failed to reach statistical significance [$F(1,26) = 3.16$, $P = 0.087$, partial $\eta^2 = 0.11$]. A significant main effect of group was also observed, when non-parametric statistics (Friedman ANOVA) were calculated [$F(1,62) = 5.24$, $P = 0.03$].

Table 2. Results of the neuropsychological testing at T1, T2 and T3

	T1	T2	T3
Hi-detox	($n = 31$)	($n = 25$)	($n = 20$)
Attention/executive [mean (SD)]	−0.70 (2.26)	−1.02 (2.64)	−0.45 (2.66)
Memory [mean (SD)]	0.11 (1.96)	−0.22 (1.70)	−0.07 (1.73)
IGT (net outcome) [mean (SD)]	5.48 (24.10)	23.90 (38.01)	22.80 (39.35)
Lo-detox	($n = 17$)	($n = 10$)	($n = 8$)
Attention/executive [mean (SD)]	−0.67 (2.83)	0.71 (2.22)	1.13 (1.77)
Memory [mean (SD)]	−0.42 (1.79)	0.31 (1.48)	0.19 (1.42)
IGT (net outcome) [mean (SD)]	−0.75 (32.90)	13.80 (42.87)	15.14 (39.31)
Healthy controls	($n = 25$)	($n = 16$)	n/a
Attention/executive [mean (SD)]	0.92 (1.92)	1.15 (2.15)	
Memory [mean (SD)]	0.11 (1.48)	0.14 (1.73)	
IGT (net outcome) [mean (SD)]	8.56 (20.84)	13.14 (29.30)	

Note: Controls were only tested at T1 and T2; n/a, not applicable.

With regard to risk-taking behaviour, our results indicated no significant differences between the Lo-detox compared with the Hi-detox group for the first- or second 3-month period after discharge, nor did we observe any significant changes of performance from T1 to T2 or from T2 to T3 (all Fs ≤ 1.24, all Ps ≥ 0.28, all partial $\eta^2 \leq 0.09$).

When we entered the factor Memory function at T1 and T2, we found no evidence for better performance or greater improvement of the Lo-detox group; the main effect of group [$F(1,32) = 0.05$, $P = 0.83$] as well as the interaction time by group [$F(1,32) = 1.36$, $P = 0.25$] were not significant. In addition, the overall effect of time was not significant [$F(1,32) = 0.004$, $P = 0.95$] indicating no changes of performance over time for the patients (all partial $\eta^2 \leq 0.04$). The same results were observed, when Memory functions at T2 and T3 were entered in the repeated measures ANOVA (all Fs ≤ 2.25, all Ps ≥ 0.15, all partial $\eta^2 \leq 0.08$).

As recovery of cognitive function might depend on abstinence during follow-up, we repeated the analyses reported above entering relapse (yes, no) as a second group factor. However, this did not change any of the reported findings.

Association of repeated withdrawal with frequency of relapse and time to first relapse

Table 3 shows the number of patients from the Lo-detox and the Hi-detox groups who relapsed within the first 6 months after discharge. A Chi-square analysis indicated no significant differences [$\chi^2(32) = 0.08$, $P = 1.00$]. The same result was observed when we performed a conservative analysis

Table 3. Patients of the Lo-detox and the Hi-detox groups did not differ with regard to the frequency of relapse within the first 6 months after discharge from treatment

	Number of previous detoxifications		
Relapse	Lo-detox group ($n = 9$)	Hi-detox group ($n = 23$)	Total
No	4	9	13
Yes	5	14	19

and coded also patients who could not be contacted after T2 ($n = 3$) as relapsed [$\chi^2(35) = 0.05$, $P = 1.00$].

In line with this, a log rank test of the survival curves of the Lo-detox and the Hi-detox groups indicated no significant differences [$\chi^2(1) = 0.16$, $P = 0.69$; see Fig. 1].

When we entered the number of previous detoxifications together with attention/executive function, Memory function and risk-taking behaviour in a logistic regression analysis, our results for the overall model evaluation indicated a significant improvement over the intercept null model, when these predictors were included [$\chi^2(1) = 7.05$, $P = 0.008$]. However, the net outcome achieved in the IGT was the only significant predictor of relapse in this sample ($P = 0.033$, odds ratio = 1.05) and our results indicated that patients who achieved a higher net outcome in this task at the first testing were more likely to relapse within the first 6 months after discharge (all other Ps ≥ 0.40).

DISCUSSION

Several authors suggested previously that the withdrawal from alcohol could cause neurotoxic lesions in the frontal lobe due to glutamate-mediated excitotoxicity, and that the resulting cognitive deficits should influence treatment outcome after detoxification (De Witte *et al.*, 2003). While there are several animal studies demonstrating cognitive impairment due to the repeated withdrawal from alcohol, human studies investigating the effect of repeated withdrawal on brain function and neuroplasticity are rare. In the few studies performed, impairment seemed to be more associated with learning and executive function, in particular, inhibitory control, which supports the assumption of an impairment of neuronal plasticity. The present study aimed to take these initial findings further by investigating whether repeated withdrawal from alcohol affects not only cognitive function during early abstinence but also recovery of cognitive impairment. Such recovery of impairment was reported in several studies (e.g. Fein et al., 2006) but it is unclear which factors affect this recovery. In addition, we questioned whether the repeated withdrawal from alcohol is related to the frequency and time to first relapse.

The results of the present study demonstrate that 3 months after discharge from detoxification treatment alcohol-dependent patients still perform worse than healthy controls with regard to tasks related to attention capacities and executive function as measured by the TMT and the WCST. There was no evidence for any improvement of attention capacities and executive function within the first 3 months after discharge. In contrast, within the second 3-month period after discharge our results indicated a significant improvement of attention and executive function. Although due to limited resources we did not assess cognitive performance of healthy controls at T3, we do not think that this represents merely an effect of repeated task administration as no such effects were observed from T1 to T2 for either group. It seems reasonable to assume that improvement of cognitive function due to familiarity with the testing procedures should have already occurred at T2 and we thus suggest that in the second 3 months period after discharge an improvement of deficits of attention and executive function took place.

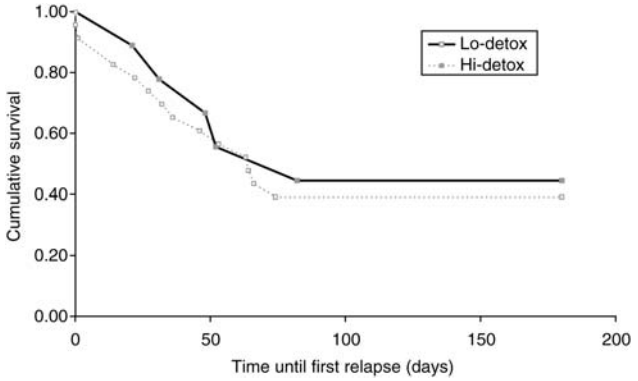

Fig. 1. The Lo-detox and the Hi-detox groups did not differ significantly with regard to the cumulative survival.

With regard to the effect of repeated withdrawal we found within the first 3 months after discharge a difference between the Lo-detox and the Hi-detox groups which was only nearing significance, but tending towards a better performance of the Lo-detox group. However, as this difference was not significant, only limited conclusions can be drawn. In contrast, in the second 3 months after discharge, patients of the Lo-detox group performed significantly better than patients of the Hi-detox group. These findings imply that especially within the second 3 months after discharge, recovery of cognitive function can be observed in patients with less than two previous detoxifications, while impairment is still observed in patients with two or more previous detoxifications. Subsequent analyses indicated that this result was not affected by abstinence during follow-up as also reported by Donovan *et al.* (1984), who found that the individual's age was the only factor affecting resistance to recovery of cognitive function 6 months after discharge. Interestingly, Munro *et al.* (2000), who investigated a sample of older alcoholics (i.e. aged between 55 and 83), reported that in this sample deficits with regard to executive function were still observed after 6 months of complete abstinence. Thus, higher age and a higher number of previous detoxifications might be two independent factors affecting recovery of executive function.

Although we found evidence for an impact of the repeated withdrawal from alcohol on recovery of attention and executive function, our results did not indicate any differences between patients with less than two previous detoxifications and patients with two or more previous detoxifications with regard to relapse and the time until first relapse. In line with this, Noël *et al.* (2002) reported that alcohol-dependent patients who relapsed did not differ from those who abstained with regard to the number of previous detoxifications. Within this context, it is interesting to consider that attention and executive function as measured in the present

study were not significant predictors of relapse. Thus, although the repeated withdrawal from alcohol affects recovery of attention and executive function, deficits of attention and executive function seem not to be the mechanism underlying relapse and therefore repeated withdrawal might not affect relapse. Along the same line of thinking, it is important to consider that the mean time until first relapse was 39.3 days (SD = 24.3), which is well within the first 3 months. However, significant differences between patients of the Lo-detox group and patients of the Hi-detox group with regard to recovery of cognitive function were only observed in the second 3 months period. Thus, other factors than the repeated withdrawal and deficits of attention and executive function seem to account for relapse within the first few weeks after discharge from treatment. One such factor that emerged in our logistic regression analysis was the net outcome achieved in the IGT. While previous studies reported differences between alcohol-dependent patients and healthy controls with regard to performance in this task (e.g. Goudriaan *et al*., 2005; Noël *et al*., 2007), we are aware of only one study investigating the predictive value of performance in this task for treatment outcome. Bowden-Jones *et al*. (2005) reported that alcohol-dependent patients relapsed early if their choices in the task were guided by immediate gain irrespective of a lower net outcome. However, in the present study, our results indicated that a lower net outcome was associated with a lower frequency of relapse. Thus, patients following a safety strategy by preferring cards with lower immediate gains but fewer losses were more likely to relapse. We think that this finding—like subjective reports of craving during inpatient treatment—might be influenced by social desirability and may reflect problems of generalizability of the test-situation to real life situations. As an alternative to the gambling task used here, it might thus be useful to assess impairment of cognitive function by administering tasks sensitive to automatic processes and cognitive control mechanisms like response inhibition and delay discounting, as these might be related more closely to relapse. As proposed by Goldstein and Volkow (2002), impairment of cognitive control and cue-reactivity might be two processes mediating relapse. In addition, these authors propose that an impairment of cognitive control should be especially pronounced when one is confronted with substance-related cues. Thus, it would be helpful for future studies to implement tasks incorporating substance-related cues to measure these processes more directly. However, apart from task significance, there might be other factors explaining difficulties to assess the predictive value of cognitive impairment for relapse. One such factor in the present study might be the rather small sample size with regard to patients for whom complete follow-up data were available. Nevertheless, previous studies have also reported limitations of neuropsychological testing in predicting treatment outcome and suggested that there might be a number of factors affecting the relationship between cognitive impairment and treatment outcome (e.g. Bates *et al*., 2006; Donovan *et al*., 1984). For example, Bates *et al*. (2006) reported that cognitive impairment led to less treatment compliance and self-efficacy, both of which were associated with negative treatment outcome.

Taken together, the present study adds to new knowledge by demonstrating for the first time that the repeated withdrawal from alcohol might be associated with a delay of recovery from impairment of attention and executive function. However, this effect was not associated with relapse occurring within the first few weeks after discharge from treatment. In general, little evidence was found for a direct influence of cognitive impairment on treatment success, which might be due to less sensitivity of common cognitive tasks to assess cognitive mechanisms related to addictive behaviour and relapse.

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