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Decreased verbal learning but not recognition performance in unmedicated alcohol-dependent patients during early abstinence

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Abstract

Objective. Alcoholism leads to a decrease in cognitive functions, e.g., memory. Cognitively impaired alcoholics may have difficulties to remember and implement newly learned skills during therapy. The primary aim of this study was to investigate cognitive performance such as, verbal learning during early withdrawal in unmedicated patients. We assumed that alcoholics, although without clinical apparent withdrawal symptoms and therefore often discharged, may still be impaired in higher-order cognitive functions.

Methods: 34 severely ill alcohol-dependent patients and 20 matched healthy controls were tested with the Verbal Learning and Memory Test which includes 7 measurement points including free recall after distraction, after 30 min delay, and one recognition task. Testing was performed between day 7 and day 10 exclusively after the beginning of abstinence and clinical withdrawal symptoms have ceased.

Results. The patient group performed worse in free recall ($F(1,50)=14.28$, $p<.001$, partial $\eta^2=.22$) but not in recognition compared to healthy controls. Further the patients showed a declined total verbal learning efficiency ($F(1,52) = 14.17$, $p < .001$, partial $\eta^2 = .21$). Memory loss after distraction was associated with years of being diagnosed for alcohol dependence ($r=.39$, $p=.01$).

Conclusions. Our results provide evidence that alcohol dependent patients without obvious withdrawal symptoms and medication show an impaired verbal recall but not recognition performance during days 7-10 of their abstinence. This deficit may lead to poorer treatment outcomes due to lower implementation of newly learned skills during this time period.

INTRODUCTION

Clinical evidence shows that chronic alcohol consumption as well as early alcohol withdrawal leads to long term cognitive impairment and decrease of memory function (Brown et al., 2000; Seifert et al., 2003; Seifert et al., 2004). Cognitive deficits related to alcohol consumption have been found in several areas like problem solving, verbal and non-verbal abstraction learning, or memory consolidation (Parsons, 1998; Davies et al., 2005).

A number of studies have compared memory capabilities such as verbal recall and verbal recognition performance in alcoholics to outcomes of different clinical groups as well as healthy controls and reported impairments(table 1). Most of the studies indicate that alcoholics perform worse in recall than in recognition tasks (Tivis et al., 1995; Uekermann et al., 2003; Seifert et al., 2003) compared to different clinical groups as well as healthy controls (Davies et al., 2005; Pitel et al., 2007).

Studies that have focussed on the memory dimension of verbal recall in alcoholics revealed impairments in alcoholics on the first day of acute alcohol withdrawal (Seifert et al., 2003), and an impaired cognitive efficiency as well as a declined verbal short-term memory capacity seems to be deteriorated compared to healthy controls even up to five weeks after alcohol consumption has ceased (eg. Mann et al., 1999). Furthermore, verbal recall performance was impaired in free recall performance compared to patients with depression (e.g. Uekermann et al., 2003). However, although performance is deteriorated alcoholics show fewer deficits than patients suffering from both, polysubstance abuse and concurrent alcohol abuse (Medina et al., 2006). With regard to the quality of verbal recognition, alcoholics perform worse than controls (Sullivan et al., 1997), as well as in order recognition compared to schizophrenic patients and healthy controls (Sullivan et al., 1997). Even so, not all studies that have been carried out show significant differences in recognition memory in alcoholic patients compared to polysubstance abusers (Medina et al., 2006).

---------- *insert table 1 (synopsis of articles)* ----------

The findings in alcoholics described above are comparable to results that target on the loss of verbal memory in patients with dementia, amnesia, Alzheimer´s disease or Korsakoff´s syndrome. Findings indicate that recall performance of amnesic patients is lower than those of controls (Giovanello and Verfaellie, 2001), and patients with alcohol-related dementia exhibit more deficits in delayed verbal recall as well as verbal recognition performance than patients with subcortical vascular dementia (Schmidt et al., 2005). The pattern of greater deficits on recall than on recognition memory in alcohol-dependent patients impresses as similar to the initiation-retrieval difficulties of patients with subcortical dysfunction (Bondi et al., 1998). Patients suffering from alcohol dementia seem to be more impaired on free recall, though, they do not differ from controls in verbal recognition memory compared to patients with Alzheimer´s disease who also do show declines on recognition memory (Saxton et al., 2000). Finally, a study on patients with Korsakoff ´s syndrome provides evidence that learning names of objects, verbal generation facilitates recognition, whereas verbal generation as well as performing a specific action facilitate recall performance (Mimura et al., 2005). Therefore, action memory might be of interest regarding consolidation processes in alcoholics.

General findings indicate that in healthy people new acquired memories persist in a fragile state and consolidate over time (McGaugh, 2000). This slow consolidation of memories may serve as an adaptive function and enables physiological processes that modulate memory strength (McGaugh, 2000; Nielson and Powless, 2007) which may be disturbed in alcoholics, thus impairing consolidation, rather than retrieval (Sherer et al., 1992).

When focussing on the second part of verbal memory, the recognition performance, dual-process models (Jacoby, 1991; Mandler, 1980) have postulated two independent processes that can be used to investigate recognition. First, recollection that refers to a conscious, effortful process in which a prior aspect of an experience is retrieved, and second, familiarity that seems to be a subjective feeling that arises when fluent processing of a stimulus is attributed to prior experience with that stimulus (Jacoby and Dallas, 1981; Giovanello and Vaerfaellie, 2001; Gardiner, 1988). Studies show disproportionate deficits in amnesic

patients during recollection of newly acquired memory contents (Aggleton and Shaw, 1996; Mayes et al., 1995; Verfaellie and Treadwell, 1993; Yonelinas et al., 1998). However, there is evidence that both axes, i.e., recollection and familiarity, are equally impaired in this group (Reed and Squire, 1997, 1998; Squire and Knowlton, 1995). A similar finding that might emerge in alcoholics as well but has not jet been proven.

A number of studies have been investigating the neuropsychological performance of intoxicated and abstinent alcoholics at different time points during abstinence (table 1). However, data on verbal recall and recognition performance of severely ill but drug free patients collected immediately after acute withdrawal symptoms have ceased are lacking. This time point is critical because patients are often discharged from intense treatment and have to implement newly learned strategies to maintain their abstinence. To our knowledge there is only one study that examined memory deficits as episodic memory in alcoholics during early abstinence, however, with a comparably large standard decviation (Pitel et al., 2007).

The objective of our study was to investigate cognitive deficits as verbal memory during the first days of abstinence. Because the cognitive dysfunction found in alcoholics is related to tasks of higher-order cognitive function (Noel, et al., 2001; for a review see Moselhy et al., 2001) we used tasks that measure the ability to recall and recognize words without a specific context (VMLT test, Helmstaedter et al., 2001). Based on previous studies, our predictions were that compared to healthy controls, the group of alcoholics are impaired in their learning abilities, and that there are differences regarding the task complexity (free recall vs. recognition). We assumed that alcoholics show a better performance in recognition than in free recall, because recognition should be a lower-order cognitive function than free recall.

METHODS

Study population and diagnostic procedures

The local ethics committee approved the study according to the declaration of Helsinki and written informed consent was obtained from all participants after the procedures had been

fully explained. All patients were inpatients and recruited in the Psychiatrische Universitätsklinik of the Charité, in the St. Hedwig Hospital Berlin as well as in the Jewish Hospital, Berlin. Each patient was examined physically and psychometric with the structured clinical interview for DSM disorders (SCID-I, First et al., 2001). Patients fulfilled DSM-IV criteria for alcohol dependency, had no other axis I disorder, and no active substantial medical or neurological disorder. The alcoholic group included 34 severely ill alcohol-dependent inpatients. The mean age for the alcoholic group was 44.09 years (SD = 8.16). Twenty-eight patients were male, 6 female. The average years of school education were 10.06 years (SD = 1.37). After school, 27 completed vocational education, 5 finished their academic degrees, 1 patient started attending university and 1 did not respond. Patients reported having had their first drink at an average age of 14.85 years (SD = 3.87), and their first intoxication at a mean age of 23.50 years (SD = 9.12). Twenty-five patients reported a mean of 8.64 (SD = 9.74) prior detoxications in an inpatient setting. Patients had an average of 18.41 years (SD = 9.99) of being diagnosed with alcohol dependence. The mean amount of pure alcohol intake during the past 5 years was 218.99 kg (SD = 172.42 kg) alcohol per patient. All patients underwent acute alcohol detoxication including complete alcohol abstinence in an inpatient setting starting 7-10 days before inclusion into the study. Acute alcohol withdrawal symptoms were measured up to a maximum of 12 times a day according to the alcohol withdrawal scale (AWS, Wetterling et al., 1997). Medication supported withdrawal was performed at an AWS score of 10 or higher. At admission, patients had a mean of 7.5 points (SD = 3.20) on the AWS. 20 patients surpassed the AWS cut-off score, thus medication to treat withdrawal symptoms had to be started. In these cases, patients were treated with diazepam, clomethiazole, or carbamacepine for a mean of 4.72 days (SD = 3.89). In the case of seizures or delirium in the past medical history during previous withdrawal, medication was given individually at the lower AWS score of 6 to 8. Overall only the following medications were used: Diazepam, clomethiazole or carbamacepine for treatment of acute withdrawal symptoms, haloperidole for the treatment of visual hallucinations and clonidine for the treatment of high blood pressure. Once a treatment was

started, the medication was reduced stepwise during the following days. 12 of the 34 patients reported having had a delirium, and 12 reported having had seizures. Of these, 2 patients reported having had a delirium but no seizures, and 1 patient reported having had seizures but no delirium. During our inpatient program, no patient had a delirium or seizures. The day before the assessments, no patient showed clinical symptoms of alcohol withdrawal syndrome. Only patients without psychotropic medication or those who at least discontinued four half-lifes before study begin were allowed to enter the study.

The comparison group included 20 healthy subjects with no lifetime psychiatric diagnosis, no clinically significant medical or neurological history, no acute medication and no history of alcohol abuse or alcohol dependency according to DSM-IV and ICD-10. The mean age was 44.40 years (SD = 13.13), 13 were male, 7 female. The average years of school education was 10.04 years (SD = 1.54). After school 12 participants finished vocational education, 5 finished their academic studies, 2 started with their university program, and 1 did not respond to this question. The comparison group was matched for age, sex, schooling and vocational education.

Assessment of verbal memory

Participants were tested with the Verbal Learning and Memory Test (VLMT, Helmstaedter et al., 2001), a test for serial word learning. The test encompasses two word lists: a learning list and a distraction list. Each list consists of 15 different, and semantically independent words. Furthermore, the test comprises a recognition list which includes all words from the learning list as well as from the distraction list and additional 20 new distraction words, which are semantically (10 words) and phonetically (10 words) similar. With the VLMT it is possible to assess different parameters of the declarative verbal memory like learning efficacy and long-term encoding as well as decoding processes. This test is especially made for differentiation in the lower range of performance. It takes a patient about 50 - 55 min to complete the test. In general, the assessment with the VLMT is composed of 7 measurement points. The measurement points 1 to 5 represent the learning phase. In each session, the investigator

reads out the word list, following a 2 second rhythm for the presentation of each word. After each read-out, the subject gives a free oral reproduction of the words remembered (immediate memory, short-term memory). The number of correct recalls was noted for each of the 5 runs. In every of the first 5 sessions, the same sequence of words were presented. After the 5th run, the investigator reads out the list with the distraction words. The subject has to recall the distraction list once. Afterwards, the learning list has to be recalled by the subject without a renewed presentation (6th measurement point). After a delay of 30 minutes from the 6th run, while each subject is busy with non stressful personal interaction, the subject is being asked to give a recall of the original word list (learning list) without another former read out of the word list by the investigator (7th measurement point; delayed memory). Immediately after the 7th run, the investigator presents a blended list including all 15 words of the original list (learning list), the 15 words of the distraction list and 20 new, distracting words. The subject is now asked to recognize the words of the original learning list, given a dichotomy (yes-no) response format. Table 2 explains the different VLMT scores according to Helmstaedter and colleagues (2001) and indicates their calculation. In this study, we focus on four main outcomes: total learning efficiency, recall performance after distraction, recall performance after delay, and recognition. Finally, we set the 5th run to define 100% of the active reproducible words learned from the learning list, the ratio between *loss after distraction* and *learning efficiency* as well as *loss after delay* and *learning efficiency* may be used as markers for the relative loss of memory contents from the learning list in percent after distraction as well as delay.

---------- *please insert* ***table 2*** ----------

Statistical Analysis

Data were analyzed using SPSS Version 15.0 for Windows. Data of the memory test were analyzed using a repeated measures analysis of variance (ANOVA), with “time” as the repeated-measures factor and “group” (patients-controls) as the between subjects factor. A

total N of 54 was reduced to 52 with the deletion of cases missing a score in the 6th session and another one who canceled the test after the 4th session. The first step in the repeated measures analysis of variance was to calculate the Mauchly test for sphericity. To correct for violation of sphericity, we used the Huynh-Feldt correction which alters the degrees of freedom, thereby altering the significance value of the *F*-ratio. This test is appropriate for small sample sizes. Univariate post-hoc tests were conducted with Bonferroni correction. The effect-size for the analysis of variance is partial eta squared (partial η^2). Furthermore, correlations were conducted with one-tailed Spearman Roh for non parametric tests among the four main variables (total learning efficiency, recall performance after distraction, recall performance after delay, recognition) and former delirium, seizures, years of being diagnosed for alcohol dependency, and number of prior detoxications.

RESULTS

Group-differences in verbal memory

A repeated-measure analysis of variance was performed with the dependent variable "correctly recalled words" with time (1 through 7) as the repeated measure factor and group as the between-subject factor (**Figure 1)**. Because of a significant Mauchly test for sphericity (W= 0.27, appoximate chi-square = 62.65, df = 20, $p < .001$), we used the Huynh-Feldt correction. Results showed a significant within subject effect for time i.e. verbal learning memory (correctly recalled words) was affected by the amount of learning cycles (runs) ($F = 144.44$, df = 4.23, $p < .001$). The higher the number of learning cycles the higher the memory performance. Results reflected a strong association for both groups between measurement points and number of correctly reproduced words, partial $\eta^2 = .74$. Furthermore, a time * group interaction was found ($F = 3.37$, df = 4.24, $p = .01$, partial $\eta^2 = .06$). Healthy controls showed a more linear development in verbal memory performance than the alcoholic patient group. Also, results showed that patients performed worse in averaged free recall than healthy controls ($F(1,50) = 14.28$, $p < .001$, partial $\eta^2 = .22$). There was no overall group difference in verbal learning memory between alcoholics with a past medical history of former

seizures or delirium (n = 10) compared to alcoholics without reported former seizures or delirium (n = 24). Setting a family-wise Type-I Error corrected significance level at $p < .006$, univariate post-hoc tests indicated one significant difference between alcoholics with former seizures/delirium compared to alcoholics without former seizures/delirium in the 6th run (recall after distraction). Patients with former seizures/delirium performed lower in recall after distraction ($F(1,32) = 8.51$, $p < .006$, partial $\eta^2 = .21$).

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Univariate post-hoc tests with Bonferroni correction were computed for each measurement point. There was a significant group difference regarding the *learning efficiency* (5th run) ($F(1, 52) = 12.09$, $p < .001$, partial $\eta^2 = .19$) as well as *total learning efficiency* (sum of the recalled words 1st to 5th run) ($F(1,52) = 14.17$, $p < .001$, partial $\eta^2 = .21$). Alcohol-dependent patients recalled significantly less words of the learning list than healthy controls after five learning cycles (learning efficiency, 5th run). In addition, alcoholics recalled less words than healthy controls in total when the performance of every learning cycle of the five learning cycles was taken into account (total learning efficiency, sum 1st to 5th run). Furthermore, there was a significant group difference for the *recall performance after distraction* (6th run; $F(1,52) = 9.73$, $p = .003$, partial $\eta^2 = .16$) as well as for the *recall performance after delay* (7th run; $F(1,52) = 11.07$, $p = .002$, partial $\eta^2 = .18$). Compared to the alcoholics the healthy controls were able to recall significantly more words at these two measurement points.

However, there were no significant group differences a) at the first learning cycle (1st run), b) for *loss after distraction* (difference between 5th and 6th run), and c) for the correctly recalled items after 30 min delay (*loss after delay*) calculated using the difference between the 5th and the 7th run. Furthermore, univariate post-hoc ANOVAs with Bonferoni correction showed no group difference for the dependent variables "*recognition efficiency*" and "*correctly reproduced words of the distraction list*". Reproducing words of the distraction list is a similar task as reproducing the learning list for the first time (1st run) in which also no group

difference were detected. The verbal memory test for alcohol-dependent patients compared to healthy controls were shown in means and standard-errors in **Figure 1**.

An analysis of covariance with verbal memory as the dependent variable was computed. The between-subject factor was once again group (alcoholics vs. healthy controls). Covariate was the 1st run i.e. working memory capacity. After adjustment by the covariate (capacity for short-term memory), verbal memory varied significantly by group ($F(1, 49) = 16.68$, $p < .001$). Even if we corrected for working memory capacity, patients showed lower performance in free recall than healthy controls. The strength of the relationship was strong with partial $\eta^2 = .25$. A statistically significant main effect of TIME (2nd to 6th run) with performance increasing in later runs (Huynh-Feldt $F = 8.23$, $df = 3.63$, $p < .001$, partial $\eta^2 = .14$). But there was no significant TIME by group interaction (2nd to 6th run) after adjustment for covariate.

Associations between severity of alcohol dependency and verbal memory

Tested with one tailed Spearman Roh with 17 of the 20 alcohol dependent patients (3 missings), the *loss after distraction* (difference between 5th and 6th run) was positively associated with former delirium ($n = 12$, $r = .34$, $p = .04$), seizures ($n = 12$, $r = .46$, $p = .01$), and years of being diagnosed for alcohol dependency ($r = .39$, $p = .01$). The *loss after delay* (correctly recalled items after 30 min delay) was associated with former seizures ($r = .34$, $p = .04$). There was no significant association between number of prior detoxications and verbal memory performance.

DISCUSSION

Clinical evidence shows a decline of cognitive performance and a decrease of memory function during early alcohol abstinence (e.g. Seifert et al., 2003, 2004; Pitel et al., 2007). These impairments may be due to a number of different but synergistic neurobiological adaptations during withdrawal (Tsai et al., 1995; Inder et al., 1995; Abi-Dargham et al., 1998; Oscar-Berman and Marinkovic, 2003; Kiefer and Wiedemann, 2004; Heinz et al., 2005). The

decrease of memory function may negatively affect the ability of alcoholics to transfer their psychotherapeutic intervention into daily routine and increase their risk for relapse (Miller et al., 2003; Breese et al., 2005; Sinha, 2007).

We confirmed the hypothesis that compared to healthy controls, alcohol dependent patients during early withdrawal show a decreased verbal memory performance in recall but not in recognition. Furthermore, our data indicated that verbal memory consolidation increased as a function of time i.e. multiple learning sessions. This result was in accordance with the work of Pitel and colleagues who have included patients with a broader range of days of abstinence (Pitel et al., 2007). Other studies indicated that consolidation of newly learned items, which have a declarative quality, are time dependent (McGaugh, 2000). Considerable evidence suggests that the slow consolidation of memories serves an adaptive function by enabling endogenous processes activated by an experience to modulate memory strength (McGaugh, 2000; Nielson and Powless, 2007). In our study, alcoholics showed a worse performance compared to healthy controls not only when they were asked to give a free recall of all items they remembered from the verbal learning list a few seconds after the list was orally presented (*learning-* and *total learning efficiency*) but also when they were asked to give a free recall immediately after having reproduced a verbal distraction list (*recall performance after distraction*) as well as after a delay of 30 minutes (*recall performance after delay*). A decrease in verbal learning efficiency in alcoholics has been found in a number of studies (Nixon et al., 1987, 1998; Sherer et al., 1992; Mann et al., 1999). It has been suggested that memory deficits in alcoholics may be produced by inferior acquisition processes, rather than inferior retrieval (Sherer et al., 1992). In our study, we were not able to confirm the presence of an inferior acquisition process. No evidence for a group difference in *word recognition efficiency* could be detected in our data, which contributes to the findings of Sullivan et al. (1997). Moreover, we found a significantly higher level of word recognition (retrieval) compared to the ability of free recall in both alcoholic patients and healthy controls. We suggest that low memory consolidation may not be detectable in recognition performance because it is a less complex cognitive function, whereas a high memory consolidation should

be indicated by the individuals' ability of free reproduction (McGaugh, 2000). Our findings showed that in alcoholics, an impairment of the basal ability of word acquisition and immediate retrieval (after the 1st run) may be less affected during early alcohol withdrawal. However, we found a difference between alcoholics and healthy controls in the ability of further memory consolidation indicated by impaired free memory reproduction between runs 2 and 7 in the alcoholic group. Contradictory findings exist about verbal memory acquisition and retrieval capacity in alcoholics during early abstinence (Nixon et al., 1987; Sherer et al., 1992; Sullivan 2000; Pitel et al., 2007, Seifert et al., 2003). The divergent study results may be explained by differing study designs with differences in severity of alcoholism, medication, and the variable time period defined for early withdrawal.

In accordance with Müller and Pilzecker´s early preservation-consolidation theory of memory (1900), which postulates that newly learned information will be disrupted by the learning of other information shortly after the original learning, we found a decrease of verbal memory recall performance in all subjects in both conditions, i.e. when participants reproduced a verbal distraction list (*recall performance after distraction, loss after distraction*) as well as after a time delay of 30 minutes (*recall performance after delay, loss after delay*). The disruption of learning and cognitive interference may weaken short-term memory capacity (Lechner et al., 1999; McGaugh, 2000) and inhibit working memory performance (Unsworth and Engle, 2007).

When the learning efficiency (after 5th run) of each group was set to 100%, the alcoholic group showed a relatively larger decrease of reproducible words compared to healthy controls. This effect may be due to a withdrawal induced declined memory consolidation process in alcoholics. However, there was no group difference for word reproduction after the first learning session (1st run, and reproduction of the distraction list). Regarding this finding, we assume that the efficacy of working memory might be comparable in both groups. Other studies also did not find impairment in working memory in alcoholics (Hildebrandt et al., 2004; Sullivan et al., 1997). However, the slope of the learning curve was steeper for healthy controls than for alcoholics.

Furthermore, we did not find a group difference when subjects were asked to recognize the words from the learning list from a longer list blended with new distractors (*recognition efficiency*). In this task, all subjects were able to recognize a significantly higher number of words in total compared to free recall as reported above what might be due to hidden memory assets. This finding points in the direction of studies in Korsakoff patients which have also shown a better recognition performance compared to free verbal recall performance (Cermak and Stiassny, 1982). The authors conclude that the encoding ability may be impaired in Korsakoff patients. These deficits would be most evident in the "acquisition" of new material since both encoding and reconstructive deficits operate and are less evident in retrieval from remote memory (Cermak and Stiassny, 1982).

On an exploratory level, we found that *loss after distraction* was positively associated with former delirium, seizures and years of being diagnosed for alcohol dependency whereas the loss after delay was associated with former seizures. It has been assumed that a decreased hippocampal volume corresponds to an increased risk for alcohol-related seizures in alcoholics (Sullivan et al., 1996). However, these findings have to be replicated by further studies.

Limitations of our study include the time-dependency of group differences. Memory improvement depends on temporal conditions. Neuropsychological recovery is not only time-dependent, but also experience-dependent (Mann et al., 1999). And the question of whether disruption of reconsolidation causes permanent or transient erasure of memory is still open. Another limitation is that we did not examine biochemical as well as imaging variables corresponding to verbal memory consolidation, recall, or recognition during early alcohol withdrawal. Furthermore, we did not measure and control for other recreational drug use such as use of ecstasy or marijuana. Although, there is evidence that use of these drugs is associated with poorer memory performance (Hoshi et al., 2007; Laws and Kokkalis, 2007). Future research should consider different recreational drugs as covariates. In addition, studies which investigate the difference between recall and recognition performance within

all-day memory, such as prospective memory versus everyday might yield further insights (see Heffernan and Bartholomew, 2006).

To conclude, our results provide evidence that alcoholism has detrimental effects on verbal memory recall immediately after acute withdrawal symptoms have ceased. This time point is very critical because once patients do not show objective withdrawal symptoms their access to intense treatment facilities is limited. However, discharge at this point may be too early for severely ill patients. Due to memory impairment, they might need more time and therapeutic care to strengthen their ability to implement e.g. coping strategies into their daily routines to maintain abstinence post discharge. The deficit in verbal learning is likely associated with poorer treatment outcomes in alcohol-dependent patients possibly due to decreased vigilance, mindfulness, and memory capacity. The results of our study may help to identify cognitive impairments that may be responsible for the comparably low ability to consolidate and transfer psychotherapeutic intervention into daily routine and thus may help to explain the high relapse rate in alcohol dependent patients especially during early abstinence.

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