

Cognitive performance of detoxified alcoholic Korsakoff syndrome patients remains stable over two years

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Excessive alcohol consumption is assumed to promote cognitive decline, eventually increasing the risk of dementia. However, little is known about the time course of cognitive functions in patients with chronic alcoholic Korsakoff syndrome (KS). Therefore, we assessed neuropsychological performance in 20 detoxified chronic KS inpatients at time 1 (T1) with a follow-up after two years (T2). The neuropsychological tests assessed verbal and visual short- and long-term memory, working memory, basic executive functions, language, general knowledge, and visual-spatial abilities. Surveys with caregivers and medical records provided information about current and previous disease-related parameters, drinking history, additional pathologies, as well as psychosocial and cognitive therapy within the two-year period. At both sessions, the majority of the KS patients' results were inferior to those of normal subjects. Comparing T1 and T2 revealed no significant decline in any of the investigated functions. Instead, general knowledge, visual long-term memory, and verbal fluency improved slightly after two years, though they still remained within pathological range. Comparing most improved and most deteriorated patients, better outcome occurred more frequently in men than women and was associated with higher premorbid education and fewer detoxifications in the past. In this sample of detoxified KS patients there was no indication of accelerated cognitive decline or onset of dementia-like symptoms over two years.

INTRODUCTION

Alcoholism is a major public health problem in modern societies. Long-term excessive alcohol abuse can lead to cognitive-behavioral disturbances and significant brain damage. One of the most devastating clinical pathologies caused by chronic and excessive alcohol consumption is the alcoholic Korsakoff syndrome (KS), often preceded by a sudden-onset episode of Wernicke encephalopathy (WE) (Victor, Adams, & Collins, 1989). Whereas peripheral neurological symptoms (ophthalmoplegia, ataxia) and confusion prevail in the WE state, the chronic phase of KS is dominated by profound amnesia (Kopelman, 1995;

Victor et al., 1989). Further cognitive and behavioral disturbances of KS patients concern emotional-motivational changes such as apathy, lack of initiative or agitation, and depressive mood (Talland, 1965), sometimes accompanied by confabulations (Dalla Barba, Cipolotti, & Denes, 1990) and executive dysfunctions (Joyce & Robbins, 1991; see below).

Thiamine (vitamin B1) deficiency resulting from severe malnutrition is regarded as the major etiological factor for KS and WE; this deficiency is probably facilitated by a genetic or age-related vulnerability (Heap et al., 2002; Pitkin & Savage, 2004). Neurotoxic effects of alcohol itself further contribute to the pathology (Homewood &

We would like to thank Martina Konrad (Haus Grefrath), Sabine Kühn (Haus Eller), Andrea Schwerdt (Therapiezentrum Germersheim), and Markus Mendt (TPR Köln) for arranging the examination of the patients and valuable help with medical and therapeutical records.

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Bond, 1999; Lishman, 1990). Resulting structural and metabolic changes in brains of alcoholic KS patients usually affect cerebellum, upper brainstem, periaqueductal and periventricular grey matter, and diencephalic regions such as the mediodorsal and anterior thalamic nuclei, the medial/paratenial nuclei, and the mammillary bodies (Harding, Halliday, Caine, & Kril, 2000; Kopelman, 1995; Mair, Warrington, & Weiskrantz, 1979; Reed et al., 2003; Victor et al., 1989). Damage to the diencephalon is most closely related to the pronounced memory deficits of KS patients (Harding et al., 2000). Further alcohol-related brain damage predominantly affects frontal lobe regions (Goldstein, Volkow, Wang, Fowler, & Rajaram, 2001; Kril, Halliday, Svoboda, & Cartwright, 1997). Accordingly, additional neuropsychological deficits of KS patients that exceed the often overwhelmingly severe memory disturbances are consistently seen in frontal-lobe-associated executive functions (Brand et al., 2003; Brokate et al., 2003; Joyce & Robbins, 1991; Stanhope, Guinan, & Kopelman, 1998).

Although alcohol-induced cerebral atrophy and associated cognitive dysfunctions are partially reversible after prolonged phases of abstinence (Mann, Mundle, Strayle, & Wakat, 1995; Nicolas et al., 1997; Trabert, Betz, Niewald, & Huber, 1995), prognosis of the chronic phase of the KS is generally regarded as poor (cf. Parsons & Nixon, 1993). Reported recovery rates in KS populations, however, show a considerable range from 0% (Malamud & Skillicorn, 1956) through 50% (Siebert, 1933) to more than 75% (Victor et al., 1989). Cutting (1978) identified KS subtypes with differential outcomes of the disease in a sample of 50 patients recruited from hospital admission lists and followed up for 6.5 years. Whereas 21 patients with classical, acute onset KS improved in only 14% of the cases, 12 gradual-onset KS patients and 11 patients with a wider range of more pronounced deficits ("alcoholic dementia") improved in more than 60% of the cases. Most favorable factors in terms of outcome included: belonging to the group of older female individuals, shorter duration of drinking history, and, having had KS-associated symptoms for a longer time prior to admission, the latter of which corresponding to patients with gradual onset KS and alcoholic dementia. Improvement was measured by criteria such as "return to work" or "being able to live alone"; formal cognitive assessment was available for the nonimproved group only. From these data, the actual time course of cognitive changes was not derived within the groups (classical acute

onset KS, gradual onset KS, alcoholic dementia) and potential deteriorations were not evaluated. Beyond the discussion whether KS consists of several subtypes, separating it from alcoholic dementia (Cutting, 1978; Horvath, 1975; Lishman, 1990) or invalidating the concept of primary alcoholic dementia altogether (Victor, 1994), it seems likely that a history of severe alcohol abuse leads to a general vulnerability to accelerated cognitive decline (cf. Ryback, 1971). A number of risk factors are known to promote the development of cognitive decline and eventually increase the risk of dementia such as low pre-morbid education (Meyer et al., 1998; Satz, 1993), history of central nervous diseases such as traumatic brain injuries (Jellinger, Paulus, Wrocklage, & Litvan, 2001), cerebrovascular diseases (Riekse et al., 2004), or depression (Modrego & Ferrandez, 2004). Excessive alcohol consumption has likewise been proposed as a possible risk factor for cognitive impairment and dementia, although previous studies revealed mixed results. Whereas some have found no association between alcohol consumption and cognitive impairment or Alzheimer's disease (Cervilla, Prince, & Mann, 2000; Rosen et al., 1993), others have shown a heightened probability of heavy drinkers to later develop dementia or mild cognitive impairment (Anttila et al., 2004; Mukamal et al., 2003; Saunders et al., 1991; Thomas & Rockwood, 2001). Also, the time course of cognitive decline may be altered by former alcohol abuse. For instance, Teri, Hughes, and Larson (1990) noted that Mini-Mental State Examination scores of Alzheimer dementia patients who were alcohol abusers dropped over five points per year faster than did those of nonabusers. These and similar findings are derived from studying alcohol consumption within normal ranges in the normal population; little is known about the time course of cognitive functions in individuals who definitely experienced alcohol-related damage to the central nervous system. It can be reasoned that these individuals might show even earlier onset of deterioration and/or steeper decline than alcohol abusers without previous history of alcohol-related central nervous diseases, including those with alcoholism but no resulting neurological disorder. Therefore, we aimed to investigate whether cognitive abilities of detoxified chronic phase KS patients—i.e., individuals who were previously exposed to excessive intake of alcohol with probable neurotoxic effects—change over time. Specifically, we were interested whether accelerated cognitive decline or dementia-related symptoms would develop in this time period, and which factors would account for potential cognitive changes.

For this purpose, we studied neuropsychological test performance in the same KS patients on two consecutive test sessions. As the patients lived in a highly controlled clinical environment between both sessions, the influence of ongoing alcohol consumption could be excluded, allowing us to study effects of prior alcohol-induced brain damage on cognitive performance over time.

METHODS

Subjects

At the first test session (T1: May to August 2000), 41 patients with alcoholic KS were recruited. Patients were permanent residents in four different socio-therapeutical nursing homes of the Allgemeine Hospitalgesellschaft (AHG) (Germany), which specialized in the treatment of chronically multi-impaired alcohol-addicted individuals. These patients have previously been described in Brand et al. (2003). All patients underwent extensive neurological and psychiatric examination, conducted by physicians in the different cooperating institutions. On the basis of these examinations two patients were excluded: one patient had previously suffered a stroke and one had a schizophrenic psychosis. In the remaining 39 patients, alcoholic KS was formally diagnosed as "Alcohol-Induced Amnesic Syndrome" according to ICD-10 (F 10.6: World Health Organization, 1994) or "Alcohol-Induced Persisting Amnesic Disorder" following DSM-IV criteria (291.1: American Psychiatric Association, 1994), respectively. The diagnoses were derived from clinical data and did not include neuroradiological investigation. Patients did not exhibit typical signs of dementia, and therefore alcohol-related dementia according to the criteria of Oslin, Atkinson, Smith, and

Hendrie (1998) was not diagnosed in any of the patients. All patients had a documented history of a Wernicke episode, which preceded the chronic state of the Korsakoff pathology. Except for one patient with unilateral amblyopia, no residual neurological symptoms from the Wernicke encephalopathy (eye signs, ataxia) were reported in any of the patients. Of the 39 patients, 20 subjects were available for the second test session after two years (T2: May to August 2002). The patients who did not participate in T2 dropped out for the following reasons: 5 patients had been admitted to other nursing homes, and 5 patients had been discharged. All 5 patients who had been discharged were women; one received subsequent professional ambulant care, the others were taken care of by relatives. None of them returned to work after discharge. Documentation of 2 patients' medical and addiction history (see below) was incomplete, which led to the exclusion of these individuals from the final dataset. Furthermore, on the day of T2, 2 patients declined to participate, and 4 patients were unavailable for other reasons (e.g., were working outside the nursing home at time of test, had visitors on the testing day, etc.). As a comparison group, 20 healthy comparison subjects without neurological or psychiatric history participated in the study. The comparison group was tested on one occasion only to provide a basis for evaluating the patients' general neuropsychological status. The comparison group consisted of administrative personnel and members of staff at the cafeteria of the University of Bielefeld and their relatives and friends. Before examination, all participants were informed about the procedure of the study and gave written consent. Neither patients nor comparison subjects received any financial incentive for participation.

As can be seen in Table 1, the 20 KS patients and the comparison group (CG) were well matched

TABLE 1
Demographic variables of KS patients and comparison subjects

	<i>Korsakoff patients (N = 20)</i>			<i>Comparison subjects (N = 20)</i>			<i>Significance</i>
	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>	
Age at T2		59.70	5.72		59.30	6.46	$t = 0.21 (p = 0.84)$
Gender							$\chi^2 = 0.96 (p = 0.33)$
Female	6			9			
Male	14			11			
Years of education		9.75	1.45		9.8	1.44	$t = -0.11 (p = 0.91)$
Professional background							$\chi^2 = 1.33 (p = 0.51)$
Unskilled	7			5			
Apprenticeship	12			12			
Academic	1			3			

Note. *SD* = standard deviation.

on gender, age, years of education, and professional background.

In order to avoid selection effects, we compared demographic variables and neuropsychological test performance at T1 of the 5 female patients who were discharged home with that of the 6 female patients who stayed in the sample at T2. Results indicated no significant differences in any of these variables (χ^2 test for professional background, Mann-Whitney *U* Tests for all other variables; all *ps* > .05). Therefore, it seems improbable that the group of discharged patients consisted of individuals with a more favorable course of the disease.

Characteristics of the KS group

We obtained characteristics of the patients' medical and addiction history via questionnaires completed by the personnel and directors of the four nursing homes. The KS patients had lived abstinely in the nursing homes for between 2 and 17 years at the time of the second investigation (mean = 10.25, *SD* = 5.19 years); their duration of alcohol addiction before admittance had been between 10 and 46 years (mean = 25.83, *SD* = 10.07 years). Between T1 and T2, one of the 20 patients had two relapses, each lasting a day; 19 patients had no relapse. The number of documented detoxifications prior to admittance was between 0 and 10 (mean = 2.05, *SD* = 2.37). As the patients enrolled in this study were in chronic stage KS at both test sessions, none of them received medical treatment or nutritional supplement for KS symptomatology. Additionally to symptoms of KS, at T2 9 of the 20 patients were reported to suffer from cardiac problems (e.g., high blood pressure, heart rhythm disturbances), 2 patients had cancer (gastrointestinal, prostate), 1 patient had recovered from anorexia, and 1 patient had concomitant depressive symptoms. Of the 9 patients with cardiac problems, 3 started having their complaints between T1 and T2; all other patients with additional diseases had suffered from their symptoms before T1. To summarize: 9 patients were being treated with antihypertensives at T2 (6 at T1) and 1 patient was taking tricyclic antidepressants at the time of both test sessions.

Socio-therapeutical treatment

All patients received socio-therapeutical treatment during their entire stay at the nursing homes. With respect to the time period between T1 and T2, we obtained the following details from the questionnaires: All 20 patients participated in

TABLE 2

Average number of hours per month of socio-therapeutical treatment between T1 and T2

	<i>Mean^a</i>	<i>SD^a</i>
Group meetings	6.63	1.65
Home duties	36.47	39.8
Training in daily living activities	12.0	12.43
Occupational therapy	34.25	23.2
Neuropsychological training	4.4	2.48
Total number of hours of supervised activities	93.74	48.59

Note. *SD* = standard deviation.

^aSee text for median and range.

group meetings (4–12 hours per month) and carried out basic home duties such as cleaning their private rooms (4–6 h/month); 10 patients were additionally involved in more extensive home-related duties—they worked, for instance, shifts in the kitchen or laundry (37–128 h/month); 15 patients participated in activities of daily living training, which included going shopping, biking, short leisure trips, and the like (4–46 h/month). Almost all of the patients (*n* = 18) received occupational therapy comprising metalwork, woodwork, painting, garden work, and similar activities (6–64 h/month). Finally, 16 patients had sessions of neuropsychological training once or twice a week (4–8 h/month).

Table 2 summarizes the average number of hours per month of organized and supervised activities calculated for the entire group of 20 patients.

Neuropsychological test battery

To compare neuropsychological status at T1 and T2, we administered the following test battery: The general cognitive state was screened by the German version (Kessler, Markowitsch, & Denzler, 1990) of the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). Verbal short-term memory was assessed with “Digit Span Forward” from the German version of the Wechsler Memory Scale–Revised (WMS–R; Härting et al., 2000) and “Immediate Recall” of words from the Memo Test, a verbal selective reminding task (Schaaf, Kessler, Grond, & Fink, 1992). Verbal working memory was assessed with “Digit Span Reversed” (WMS–R; Härting et al., 2000). Verbal long-term memory was measured with a delayed recall of the Memo Test after 15–20 minutes, and visual long-term memory was measured by a 30-minute delayed recall of the Rey–Osterrieth Complex Figure (Osterrieth, 1944). Speed of information processing

was studied with reading speed of the “Word Trial” of the Word Color Interference Test of the Nürnberger–Alters-Inventar (Oswald & Fleischmann, 1997), developed on the basis of the Stroop Test (Stroop, 1935). Susceptibility to interference was examined with the “Interference Trial” of the Word Color Interference Test (Oswald & Fleischmann, 1997). To assess executive functions and language abilities, the Word Naming Task (FAS) (Spreeen & Strauss, 1998) of verbal fluency was administered. Visual–spatial abilities were measured by copying of the Rey–Osterrieth Complex Figure. Finally, we administered the subtest “Information” of the German version of the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Tewes, 1991) to measure general verbal knowledge. Although our selection of tests did not assess higher executive functions such as planning and decision-making, some of the employed tests cover subsets of executive functions. For instance, verbal fluency and inhibition of interference can well be seen in the realms of executive functions. Both successfully discriminated between controls and several patient groups with executive dysfunctions in the study of Hanes, Andrewes, Smith, and Pantelis (1996). Therefore, we conclude that our test battery assessed at least basic subsets of executive functions.

At T2, we additionally assessed premorbid intelligence with a German adaptation of the National Adult Reading Test (Nelson, 1982) (“Mehrfachwahl-Wortschatz-Intelligenztest”, MWT; Lehrl, Merz, Burkhard, & Fischer, 1991). To illustrate discrepancies between memory performance and intellectual abilities, the difference between estimated MWT–IQ and the two assessed long-term memory measures was calculated. For this purpose, we transformed the results in delayed recall of words from the Memo Test and delayed recall of the Rey–Osterrieth Complex Figure into IQ-scaled standard scores, calculated their sum, and divided the result by two. This “Memory Index” was then subtracted from MWT–IQ assessed at T2. Usually, these kinds of IQ–MQ difference measures are derived from Full Scale WAIS–IQ and Wechsler Memory Scale Memory Quotient (MQ); they have been used in KS patients to illustrate the specificity of amnesia in the absence of general cognitive decline (cf. Butters, Lewis, Cermak, & Goodglass, 1973). Given the limited selection of tests employed here, the discrepancy between MWT–IQ and our “Memory Index” serves as a rough approximation of this measure.

Each test session lasted about 1–1.5 hours; breaks were given on demand of the patient.

Statistical analyses

All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS) for Windows (Release 12.0.0, 4 September 2003; Chicago: SPSS Inc.). Statistical comparisons of normally distributed data were conducted with parametric methods (*t* tests). In case of significant deviations from the normal distribution (indicated by the Kolmogorov–Smirnov Test, $p < .05$), we used the corresponding nonparametric Mann–Whitney *U* Tests, or Wilcoxon Signed Rank Tests for pairwise comparisons. Differences in nominal parameters were analyzed by χ^2 tests. To adjust for multiple comparisons, results were Bonferroni-corrected within scores of the same test (e.g., statistics with the Word Trial, Color Trial, and Interference Trial of the Stroop Test were divided by three) but not between tests.

RESULTS

Neuropsychological status at T1 and T2

Table 3 gives an overview of the KS group’s neuropsychological status at T1 and T2 and of the comparison group (CG) at T1.

At both test sessions, in the majority of the neuropsychological tests the KS patients’ performances were inferior to those of the comparison subjects or normative populations. However, Mini-Mental State Examination was within normal range at both test sessions and nonindicative of dementia-related deterioration. The patients also showed a normal premorbid intelligence level (average IQ estimated by MWT = 104.83, $SD = 13.22$) as tested at T2. To derive a total performance score, all raw scores in neuropsychological tests were *z*-transformed on the basis of the comparison subjects’ results or normative data. Table 4 summarizes comparisons between KS and CG, total performance scores and discrepancies between MWT–IQ and “Memory Index”.

The group showed most pronounced deficits in long-term memory measures ranging down to $z = -2.61$ in delayed recall of words from the Memo Test in T1 ($z = -2.58$ in T2) and $z = -2.62$ in delayed recall of the Rey–Osterrieth Complex Figure in T1 ($z = -2.30$ in T2). Additionally, at both test sessions patients showed significantly lower performance in some executive functions (e.g., verbal fluency, working memory) compared to healthy individuals (see Table 4). General knowledge as assessed with subtest “Information” from the WAIS–R was likewise inferior to that of

TABLE 3
Raw scores in the neuropsychological test battery

	<i>KS patients at T1</i>		<i>KS patients at T2</i>		<i>Comparison group at T1</i>	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Mini-Mental State Examination	25.0	1.73	25.5	2.12	> 26	
MWT	—	—	104.83 ^a	13.22	—	
Information (WAIS-R)	12.4	4.27	13.8	4.24	17.20	3.19
Stroop (Word Trial)	16.75 ^b	3.73	16.45 ^b	2.98	—	
Rey-Osterrieth Figure (copy)	29.78	5.80	30.03	4.96	31.0	3.79
Digit Span forward	5.70	0.80	5.57	0.84	6.41	1.24
Digit Span reversed	3.75	0.97	3.89	0.80	4.75	1.21
Memo Test (immediate)	5.05	0.95	5.05	0.72	7.05	0.83
Memo Test (delayed)	1.05	1.47	1.10	1.24	6.0	1.97
Rey Osterrieth Figure (delayed)	2.45	2.68	4.08	4.02	16.21	5.47
Stroop (Interference)	29.20 ^b	23.65	32.65 ^b	21.55	—	
FAS Test	24.5	8.36	30.70	11.76	43.25	10.90

Note. SD = standard deviation. KS patients at T1 and T2, comparison group at T1. MWT: Mehrfachwahl-Wortschatztest (Lehrl et al., 1991); WAIS-R; Wechsler Adult Intelligence Scale-Revised.

^aIQ-scaled score; ^btime in seconds.

TABLE 4
Neuropsychological status of KS patients at T1 and T2 contrasting comparison group data

	<i>KS patients</i>				<i>Comparison group – KS</i>			
	<i>T1</i>		<i>T2</i>		<i>T1</i>		<i>T2</i>	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>t/U statistic</i>	<i>significance</i>	<i>t/U statistic</i>	<i>significance</i>
Information (WAIS-R)	-1.75	1.41	-1.29	1.43	<i>t</i> = -4.53	<i>p</i> < .001	<i>t</i> = -3.30	<i>p</i> = .002
Stroop (Word Trial)	-0.35 ^a	0.88	-0.58 ^a	1.13	—	—	—	—
Rey-Osterrieth Figure (copy)	-0.40	1.59	-0.34	1.36	<i>t</i> = -0.91	<i>p</i> = .37	<i>t</i> = -0.80	<i>p</i> = .44
Digit Span forward	-0.54	0.66	-0.65	0.69	<i>U</i> = 99.5	<i>p</i> = .16	<i>U</i> = 86.5	<i>p</i> = .09
Digit Span reversed	-0.84	0.85	-0.72	0.71	<i>t</i> = -2.66	<i>p</i> = .01	<i>t</i> = -2.42	<i>p</i> = .02
Memo Test (immediate)	-2.36	1.13	-2.35	0.86	<i>t</i> = -7.0	<i>p</i> < .001	<i>t</i> = -7.91	<i>p</i> < .001
Memo Test (delayed)	-2.61	0.80	-2.58	0.68	<i>U</i> = 10.5	<i>p</i> < .001	<i>U</i> = 7.0	<i>p</i> < .001
Rey Osterrieth Figure (delayed)	-2.62	0.52	-2.30	0.78	<i>t</i> = -10.0	<i>p</i> < .001	<i>t</i> = -7.56	<i>p</i> < .001
Stroop (Interference)	-0.24 ^a	1.03	-0.85 ^a	0.97	—	—	—	—
FAS Test	-1.60	0.68	-1.09	0.95	<i>t</i> = -5.91	<i>p</i> < .001	<i>t</i> = -3.54	<i>p</i> = .001
<i>z</i> -total score ^b	-1.37	0.57	-1.24	0.57	—	—	—	—
MWT-IQ minus “Memory Index” ^c	45.11 ^d	14.32	43.71 ^d	12.04	—	—	—	—

Note. SD = standard deviation. Unless otherwise stated, results are given as *z*-scores.

^aderived from normative data (Oswald & Fleischmann, 1997); ^bsum of all neuropsychological test results divided by the number of tests; ^c“Memory Index”: sum of Memo Test (delayed) and Rey Osterrieth Figure (delayed) divided by two; ^dIQ-scaled score; WAIS-R; Wechsler Adult Intelligence Scale-Revised.

comparison subjects in both test sessions. Note that in none of the latter tests did the KS patients show *z*-scores lower than $z = -0.84$, indicating performance in a nonpathological range compared to the entire population. Short-term memory and visuo-constructive abilities as measured with the copy of the Rey-Osterrieth Complex Figure were similar to the comparison subjects' results. At both test sessions, reading speed and interference susceptibility measured with the Stroop Test were in

the low average range compared to normative data. Summarizing the neuropsychological performance across tests revealed total *z*-scores below $z = -1.0$, indicating below-average overall performance at both test sessions. The MWT-IQ “Memory Index” difference measure revealed a large discrepancy of over 40 IQ-scaled standard scores between highly deteriorated memory performance and relatively preserved intellectual abilities in our sample. Furthermore, although some patients had

somewhat low MWT-IQ scores, their "Memory Index" was disproportionately lower than would be expected on the basis of their IQ. This pattern is characteristic for KS (e.g., Butters et al., 1973; Kopelman, 1995) and gives additional validation of the clinical diagnoses of our sample (see Table 4).

Changes in neuropsychological performance between the two test sessions

Comparison of Mini-Mental State Examination in T1 and T2 revealed no significant differences, $t = -1.1$, $p = .29$. Pairwise comparisons in neuropsychological test performance between the two sessions are shown in Table 5.

Whereas the majority of the individual test results remained stable between test sessions, we observed significantly higher overall performance in the z -transformed total scores of T1 and T2, $t = -2.13$, $p = .047$. This was mostly due to improvement on three tests: Information, $t = -2.41$, $p = .03$, delayed recall of the Rey-Osterrieth Complex Figure, $t = -2.52$, $p = .02$, and verbal fluency in the FAS Test, $t = -3.21$, $p = .005$. However, these improvements were within the pathological range also at the second test session (cf. Table 4). Most notably, we did not observe any significant drop in performance in any of the tests between the two sessions.

Additionally, we calculated performance changes between T1 and T2 per patient by subtracting individual z -total scores of T2 from z -total scores of T1. With a mean score of $z = -1.37$ ($SD = 0.57$) at T1 and $z = -1.24$ ($SD = 0.57$) at T2, the z -score differences (zdiff) showed an average positive mean of

zdiff = 0.12 ($SD = 0.26$). Arithmetically, we observed improvement between T1 and T2 in 11 patients, whereas 9 patients showed negative change between test sessions. However, the group of patients with negative zdiff scores consisted of only 4 patients with a noticeable deterioration (mean zdiff = -0.22 , $SD = 0.10$), whereas 5 patients in this group did not show major change (mean zdiff = -0.05 , $SD = 0.03$). In contrast, the mean zdiff score of the 11 improved patients indicated substantial positive change between test sessions (mean zdiff = 0.33, $SD = 0.13$). Thus, the majority of patients either improved or retained their cognitive ability level across test sessions. Nevertheless, to compare extreme groups of improvement or deterioration between T1 and T2, we divided the group into three subgroups according to their difference scores and contrasted the top third of patients (zdiff^{high}; $N = 6$) with the bottom third of patients (zdiff^{low}; $N = 6$). The groups did not differ significantly from each other in their z -total score in either session (T1: zdiff^{high}: median = -1.42 , range = -2.75 to -0.81 ; zdiff^{low}: median = -1.42 , range = -2.1 to -0.47 ; $U = 16.0$, $p = .82$; T2: zdiff^{high}: median = -0.96 , range = -2.42 to -0.27 ; zdiff^{low}: median = -1.62 , range = -2.18 to -0.82 ; $U = 12.0$, $p = .39$). This indicates similar levels of general cognitive performance of both groups in either test session, despite the fact that individuals in one group improved and those in the other group deteriorated across sessions (see first two bars per group in Figure 1).

Moreover, the magnitude of positive change observed in the zdiff^{high} group was significantly higher compared to the magnitude of negative change in the zdiff^{low} group (magnitude of change in z -total scores between T1 and T2: zdiff^{high}: median = 0.39, range = 0.32 to 0.54; zdiff^{low}: median = 0.15, range = 0.08 to 0.35; $U = 2.0$, $p = .027$). Therefore, the magnitude of observed improvement between T1 and T2 exceeded the magnitude of deterioration (see third bar per group in Figure 1).

Probably due to the small sample sizes, only a few significant differences in demographic and disease-related parameters were shown between the two groups. These differences were seen in gender distribution, years of education, and number of detoxifications before admittance. In detail, the zdiff^{high} group consisted of 6 male subjects, whereas 3 of the 6 patients in the zdiff^{low} group were female ($\chi^2 = 4.0$, $p = .049$). The zdiff^{high} group, further, had a higher level of education (zdiff^{high}: median 11.5, range = 9.0–13.0 years; zdiff^{low}: median = 9.0, range 9.0; $U = 6.0$, $p = .021$), and fewer documented detoxifications before admittance to the nursing homes (zdiff^{high}: median = 0.5, range = 0–1; zdiff^{low}: median = 2.5, range = 0–6; $U = 6.0$, $p = .046$). Other demographic

TABLE 5

Changes of the patients' neuropsychological performance between test sessions T1 and T2

	Comparisons of performances at T1 and T2	
	<i>t</i> /Wilcoxon <i>z</i> -statistic	significance
Information (WAIS-R)	$t = -2.41^*$	$p = .03$
Stroop (Word Trial)	$t = -0.41$	$p = .69$
Rey-Osterrieth Figure (copy)	$t = -0.24$	$p = .81$
Digit Span forward	$z = -0.49$	$p = .63$
Digit Span reversed	$t = -0.44$	$p = .67$
Memo Test (immediate)	$t = 0.86$	$p = .41$
Memo Test (delayed)	$z = -0.12$	$p = .91$
Rey-Osterrieth Figure (delayed)	$t = -2.52^*$	$p = .02$
Stroop (Interference)	$t = 1.69$	$p = .11$
FAS Test	$t = -3.21^*$	$p = .005$
<i>z</i> -total score	$t = -2.13^*$	$p = .05$

*Significant improvement from T1 to T2; WAIS-R: Wechsler Adult Intelligence Scale-Revised.

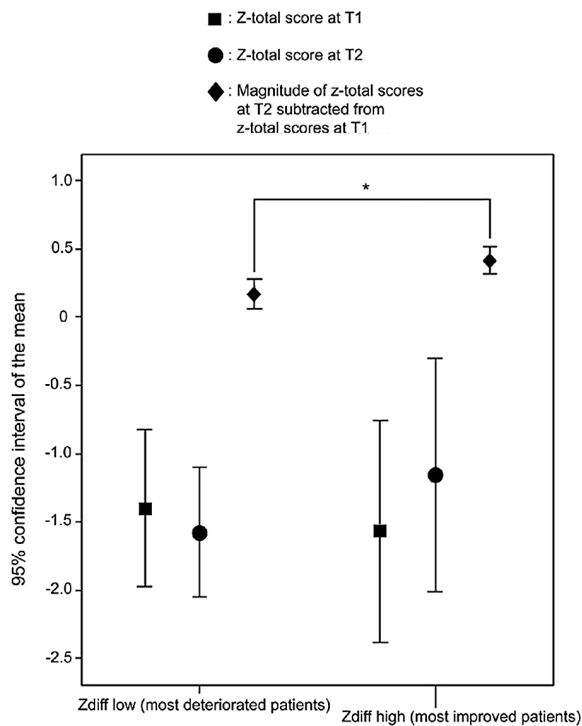


Figure 1. z-total scores at T1 and T2 and magnitude of absolute differences between T1 and T2 in extreme groups of most deteriorated ($zdiff^{low}$) and most improved ($zdiff^{high}$) patients (95% confidence intervals for means); *: the magnitude of change in the $zdiff^{high}$ group was significantly higher than the magnitude of change in the $zdiff^{low}$ group ($U = 2.0, p = .027$).

variables, disease-related parameters, or therapeutic interventions were not statistically different between the two extreme groups.

DISCUSSION

The main result of this study is that cognitive abilities of detoxified chronic-phase alcoholic Korsakoff syndrome inpatients remain stable over two years. In none of the investigated cognitive functions (e.g., memory, attention, executive functions) were significant declines between test sessions observed. Instead, three measures improved significantly after two years. The magnitude of these improvements, though still within the pathological range, exceeded that of the deteriorations. Directly comparing the most improved with the most deteriorated patients, better cognitive outcome tended to occur more frequently in men than in women and was associated with higher premorbid education and fewer detoxifications in the drinking history.

Two characteristics of our investigation have to be considered critically. First, generalization of our

results is limited due to our small sample size. Although the overall estimated IQ was in the normal range, it might still be possible that the patients' premorbid cognitive functioning was already lower before their drinking became excessive. Potentially, this may have led to a higher likelihood of admission to nursing homes, which, in turn, has negatively impacted on cognitive performance. Also, since our comparison group did not originate from the patients' environments (i.e. relatives or friends of the patients), comparisons between patients and comparison subjects may have been somewhat biased against the patients. However, the main conclusions of our study are based on comparing the same individuals at two points in time and do not involve comparisons to healthy individuals. Therefore, we believe that despite limited generalizability due to the small sample size, our results can nevertheless add clarification to the time course of cognitive functions in patients with chronic-phase alcoholic KS.

Secondly, in this dataset it is important to consider the possibility that the observed improvements could be a consequence of retest effects. In the absence of retest data on comparison subjects, we argue that, for a number of reasons, retest effects are unlikely in this study. Most importantly, our patients are densely amnesic. At the second test, no patient remembered having participated in the first test session—at least on an explicit level. Comparing the neuropsychological domains in which we observed changes with previous normative studies, over an average test–retest interval of 11 months, Dikmen, Heaton, Grant, and Temkin (1999) reported small practice effects in visual long-term memory and verbal intelligence measures, and only moderate practice effects for verbal fluency. Accounting for the fact that a shorter test–retest interval was used in Dikmen et al. (1999)—test–retest interval in Chelune, Naugle, Lüders, Sedlak, and Awad (1993) was 6 months—substantial practice effects seem unlikely in our sample. Taken together, given that our population is densely amnesic, the test–retest interval here exceeds those covered by studies of practice effects in normal populations, and improvement was also shown on measures known to be relatively insensitive to practice effects, it is unlikely that we observed stability or improvement in cognitive functions due to retest artefacts.

Our findings are compatible with those of previous longitudinal studies showing that cognitive dysfunctions can be partially reversed after prolonged abstinence in more acute KS patients (Cutting, 1978; Victor et al., 1989) and alcoholics (Brandt, Butters, Ryan, & Bayog, 1983; Mann,

Gunther, Stetter, & Ackermann, 1999; Roseribloom, Pfefferbaum, & Sullivan, 2004). Though the impairment was not reversed in our sample, we did not observe further deterioration on any of the neuropsychological measures, and there was no indication of beginning dementia after two years (cf. MMSE, Table 3). Therefore, our results do not indicate accelerated cognitive decline, even after experience of severe damage to the central nervous system due to alcohol. Instead, the possibility of slight cognitive improvement might remain even at chronic stages of the disease. It has to be noted here that our test–retest interval of two years might not have covered the critical time range during which changes would manifest in overt behavior. Also, retesting performance at older age ranges might be more suited for characterizing the ultimate time course of cognitive functions in KS. Nevertheless, due to the scarcity of longitudinal neuropsychological studies with chronic alcoholic KS patients (but see Mair et al., 1979), we could neither identify an ideal test–retest interval for our investigation nor speculate about the age at which an accelerated onset of dementia-like symptoms might emerge. The follow-up of two years that we chose must, therefore, be regarded a starting point of investigation from which future studies may be designed for a more complete coverage of the time course of cognitive performance in KS.

Neuropsychological measures that improved over the sessions comprised a language and executive functions test (FAS Test), a semantic knowledge test (subtest “Information” from the WAIS–R), and a visual long-term memory test (delayed recall of the Rey–Osterrieth Figure). Though still significantly inferior to the performance of comparison subjects, the patients’ performance at T2 on the former two measures approached the results of healthy subjects, whereas visual long-term memory stayed within the highly deteriorated range. It can be speculated that the common basis of these test measures lies in their recruitment of executive functions controlled by frontal brain regions. The frontal-lobe-associated component of verbal fluency is well documented in patients with frontal brain lesions (Stuss et al., 1998) and in functional neuroimaging studies of healthy individuals (Ravnkilde, Videbech, Rosenberg, Gjedde, & Gade, 2002). Semantic knowledge is part of the generally less affected retrograde memory in KS (Albert, Butters, & Levin, 1979; Kopelman, Stanhope, & Kingsley, 1999). Kopelman (1991) reported that remote memory deficits in KS patients are highly related to frontal-lobe-associated tests of executive functions. He suggested that disturbed remote memory retrieval in KS might result from concomitant

frontal lobe involvement rather than from diencephalic lesions. Similarly, comparing memory deficits of KS patients with those of other amnesic patients, Squire (1982) reported a specific vulnerability in frontal-lobe-associated memory functions only in KS patients. In this regard, Brokate et al. (2003) suggested a restricted vulnerability to alcohol of frontal-lobe-associated functions. In their study, KS patients and alcoholics showed a common impairment only on measures of executive functions, and alcoholics differed from healthy subjects in one of these tests assumed sensitive to frontal lobe damage. In the same vein, Lishman (1990) argued that direct neurotoxic effects of alcohol are most likely to be reflected by frontal lobe changes that are partly reversible with abstinence. In contrast, the thiamine deficiency typically preceding KS may permanently affect diencephalic brain regions and correspond to the long-lasting and severe learning impairment in KS (see also Brun & Andersson, 2001). Taken together, frontal lobe pathology, partially reversible after long-term abstinence, may be reflected in the relative improvement in verbal fluency and retrieval of semantic knowledge in our sample. The observed improvement in visual long-term memory has to be regarded cautiously, since the overall level of performance was highly deficient in the second as well as the first test session.

Similar to previous investigations in other pathologies as well as normal aging (cf. Kramer, Bherer, Colcombe, Dong, & Greenough, 2004), higher education was a beneficial factor for cognitive functions also in our sample. In terms of a cognitive reserve capacity (Satz, 1993), it can be reasoned that higher education may promote a higher redundancy in neural connections, or raises the threshold of neural damage to be exceeded after which disturbances become apparent at the behavioral level. The group that deteriorated the most was composed of more women than the group that improved the most, which consisted of men only. This effect has to be treated cautiously, since the sample sizes are very small. Furthermore, gender and education are confounded since women had less education than did men. Thus, the gender effect might, indeed, be one of education only. Alternatively, it might be that alcohol neurotoxicity as well as thiamine deficiency affects women to a greater degree than it does men (Prendergast, 2004; but see Hommer, 2003). Contrary to the results of Cutting (1978), the female patients in our group did not differ from the men in their drinking history, number of detoxifications, or other disease-related parameters. Assuming a higher vulnerability of female brains to alcohol-induced damage, the female patients included here may

represent a disproportionately more affected group than their male counterparts. Finally, the most improved subgroup had had a smaller number of detoxifications compared to the most deteriorated subgroup. Animal studies reported brain damage following alcohol withdrawals or repeated periods of alcohol supply alternating with abstinence (Crews, Braun, Ali, & Knapp, 2001; Veatch & Gonzalez, 1999). Moreover, Ripley, Borlikova, Lyons, and Stephens (2004) reported positive correlations of alcohol withdrawals and impairment in fear conditioning in rats. Apart from the fact that alcohol withdrawal can kindle seizure activity (e.g., in the amygdala), potentially leading to secondary brain damage (Booth & Blow, 1993), it is associated with general metabolic dysregulation in cortical and limbic brain regions (Clemmesen, Ingvar, Hemmingsen, & Bolwig, 1988). Though seizure activity was not reported in our sample, this variable might be underestimated since the patients' unsupervised attempts to withdraw and potentially undiscovered seizures may not appear in medical records. Regardless of the exact underlying pathology responsible for the deterioration in the group of patients with more previous detoxifications, our results are compatible with a few studies in alcoholic patients reporting lower cognitive performance associated with the number of previous alcohol withdrawals (Duka, Townshend, Collier, & Stephens, 2003; Errico, King, Lovallo, & Parsons, 2002).

To conclude, our study did not reveal accelerated cognitive decline over a time period of two years in detoxified patients with Korsakoff syndrome, a severe neurological condition due to previous excessive alcohol abuse. Although this result has to be treated cautiously since our study sample was small, it casts doubt on the hypothesis that extensive alcoholism inevitably leads to accelerated cognitive decline and the development of dementia. In future studies, it may be worth while studying the course of cognitive functions over a broader age range to determine whether there still may be an antedated onset of cognitive decline in older age. Furthermore, the assessment of larger samples and longer test-retest intervals is necessary to allow generalization of our findings. Also, the slope of cognitive deterioration, once initiated, might be different in healthy individuals compared to patients with alcoholic KS. In the meantime, the slight improvements we observed in some of the neuropsychological test measures encourage rehabilitative efforts even in this population.

Original manuscript received 13 December 2004

Revised manuscript accepted 23 March 2005

First published online day month year

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