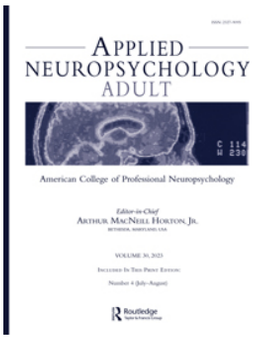

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Altered learning and transfer abilities in Korsakoff's syndrome depending on task complexity

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ABSTRACT

Korsakoff's syndrome (KS) is characterized by episodic memory impairment due to damage to the medial diencephalic structures. Although commonly associated with chronic alcoholism, starvation due to the hunger strike is one of its nonalcoholic causes. Learning the stimulus-response associations and transferring the just-learned associations to novel combinations were previously tested by specific tasks in memory-impaired patients with hippocampal, basal forebrain, and basal ganglia damage. To add to this previous research, we aimed to use the same tasks in a group of patients with hunger strike-related KS presenting a stable isolated amnestic profile. Twelve patients with hunger strike-related KS and matched healthy controls were tested in two tasks varying in task complexity. Each task included two phases: the initial phase is feedback-based learning of (simple *vs.* complex) stimulus-response associations, and the following phase is transfer generalization (in the presence *vs.* absence of feedback). On a task involving simple associations, five patients with KS failed to learn the associations, while the other seven patients showed intact learning and transfer. On the other task involving more complex associations, seven patients showed slower learning and failed at transfer generalization, whereas the other five patients failed even at the acquisition phase. These findings of a task-complexity-related impairment on associative learning and transfer represent a distinct pattern from the spared learning but impaired transfer previously observed on these tasks in patients with medial temporal lobe amnesia.

KEYWORDS

Amnesia; associative learning; Korsakoff's syndrome; task complexity; transfer generalization

Introduction

Wernicke-Korsakoff's syndrome (WKS), once commonly considered the direct consequence of chronic alcoholism, is now well-established as a nutritional nervous system disorder caused by thiamin deficiency. Thiamin is essential for glucose metabolism, which is the brain's principal energy source. Its depletion leads to neuronal dysfunction and loss in the most vulnerable cerebral structures confined to the brainstem and medial diencephalon, which are reflected in turn in the cerebellar and cognitive findings with an amnestic core of the WKS (Victor et al., 1971). Accordingly, thiamin deficiency may be due to decreased thiamin availability as seen in malnutrition and chronic alcoholism, malabsorption, prolonged vomiting, and starvation, accelerated thiamin consumption, such as hypermetabolic conditions, cancer, and intravenous glucose or dextrose loading, and/or impaired thiamin functioning that occurs with certain medications (Isenberg-Grzeda et al., 2012, 2016; Parkin et al., 1991).

Two eponyms of the syndrome correspond to two phases of the disease, where Wernicke's is the initial phase with a confusional state, diplopia due to ocular palsies and cerebellar ataxia (appendicular reaching deficits and wide-based, unsteady gait), and Korsakoff's (KS) is the chronic phase with amnestic state, accompanied by varying degrees of apathy, dysexecutive findings, confabulations, delusions and also by remnant signs of Wernicke's, such as nystagmus and gait ataxia. Very early intervention within a few hours of the onset with adequate thiamin supplementation, it may be completely reversible without progression into KS. Also, later treatment with high doses of thiamin can still lead to substantial recovery, albeit with some major or minor sequelae (Oudman et al., 2021). Treated or not, all WKS patients also tend to recover over the ensuing year in accordance with the mechanisms of reparational neuroplasticity. After ~1 year, this recovery may be complete in patients with milder clinical severity at presentation; otherwise, it stays stable as a lifetime static encephalopathy. It is also established that it is not solely the malnutrition or the prolonged

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hunger per se that causes the disease, but more often than not, it is caused by intravenous or nasogastric tube feeding without thiamin supplements used for refeeding purposes; hence it is inadvertently induced by the treating physician, in other words, it may be an iatrogenic condition (Wallis et al., 1978).

Although it is mainly associated with chronic alcohol use, it also occurs in nonalcoholic patients as well, as stated above. Among nonalcoholic reasons, hunger strike is rare, with a rate of 6.7% (Oudman et al., 2021). The hunger strike is a voluntary fasting leading to starvation, usually practiced as a widespread form of protest, particularly among the political prisoners in a country, such as Turkey, which has an experience of living under prolonged terms of authoritarian rule. There are a few WKS cases due to hunger strikes reported before (Devathasan & Koh, 1982; Frantzen, 1966; Pentland & Mawdsley, 1982), in addition to 52 cases in a Singapore prisoner-of-war camp (De Wardener & Lennox, 1947). The Turkish experience has more widely been reported (Başoğlu et al., 2006; Durmaz et al., 2020; Gürvit et al., 1997; Oge et al., 2000; Sahin et al., 2002; Unlu et al., 2006).

The core feature of KS is an amnestic state. Although frequently accompanied by other signs, as stated above, the amnestic state may be seen in isolation in some patients. In KS, it is not the hippocampus proper but the critical way stations of the neural network for episodic memory, including the mammillary bodies (connected with the hippocampus *via* fornix) and dorsomedial thalamic nucleus (connected with amygdala *via* amygdalo-thalamic tract and interconnected with the entire prefrontal cortex) that are damaged (Victor et al., 1971). Like medial temporal lobe (MTL) amnesia, KS is characterized by profound anterograde amnesia and severe, temporally graded, retrograde amnesia, along with relatively preserved semantic memory, working memory, and implicit memory types, as well as other cognitive functions (Acker et al., 1987; Fama et al., 2012; Kopelman, 1995; Kopelman et al., 2009; Sechi & Serra, 2007).

Associative learning refers to acquiring information about the associations between two separate stimuli, such as objects and events from the environment. Once these associations were learned, responses could be applied to new or altered stimuli or familiar stimuli presented in a new context, indicating that a process described as generalization has occurred. Myers et al. revealed distinct patterns of such learning and transfer in various clinical groups. They showed that individuals with hippocampal atrophy displayed spared associative learning but impaired generalization where they should transfer the learned associations to novel combinations (Myers et al., 2002, 2003), whereas the patients with basal forebrain amnesia demonstrated slower initial learning with spared generalization (Myers et al., 2008). Similarly, patients with idiopathic Parkinson's disease (PD), which entails the disruption of the frontostriatal circuits, tested on their usual dopaminergic medications, showed slower learning but spared generalization (Myers et al., 2003; Shohamy et al., 2006). Such findings from patients with MTL or basal ganglia (BG) damage indicate that these structures support separate and parallel learning systems (Knowlton et al., 1996; Myers et al., 2003). While the cortico-striatal system plays an essential role in the incremental learning of stimulus-response associations (Knowlton et al., 1996; Myers et al., 2003; Packard & Knowlton, 2002; Shohamy et al., 2008; White, 1997), the hippocampal system, on the other hand, is involved in the formation of flexible, episodic, stimulus-stimulus representations and is critical for some forms of more complex learning, such as the ability to generalize when familiar stimuli are presented in novel combinations (Eichenbaum & Bunsey, 1995; Gluck & Myers, 1993; Myers et al., 2002, 2003).

In this study, we worked with a unique group of amnestic patients with nonalcoholic KS to clarify the role of medial diencephalic structures in associative learning and transfer generalization processes, by using two distinct tasks varying in terms of the task complexity: learning simple *vs.* complex associations and subsequently transfer those associations to novel recombinations in the presence *vs.* absence of feedback. Drawing on the evidence for the role of BG and MTL regions in stimulus-response feedback-based learning and transfer generalization, we hypothesized that the KS patients would follow a similar pattern to those previously observed in patients with hippocampal atrophy (Myers et al., 2002, 2003).

Materials and methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established before data analysis, all manipulations, and all measures in the study (see Methods and Participants sections). No part of the study procedures or analyses was pre-registered before the research was conducted.

Participants

The sample size was determined based on previous neuropsychological studies on Korsakoff's patients (Brokate et al., 2003; d'Ydewalle & Van Damme, 2007; Phaf et al., 2000). Twelve KS patients (two females, five from 1996, and seven from 2000 hunger strike) with a mean age of 39.42 ± 6.53 years and mean education of 9.92 ± 2.91 years and 12 healthy control (HC) participants matched on age, sex, and years of education were included the analysis (Table 1). Patients were ex-political prisoners in Turkey who went on hunger strike protesting prison conditions and experienced prolonged hunger while in prison. Our experience with these patients, including their initial diagnoses and follow-ups both while in prison and in our clinic upon their release, were reported before (De Wardener & Lennox, 1947; Gürvit et al., 1997; Pentland & Mawdsley, 1982). All neuropsychological, behavioral, and clinical (e.g., ataxia rating) data reported in this study were collected 10–14 years after their initial diagnosis. None of the patients had any current or past diagnosis of psychiatric disorder and/or additional neurological disease. Healthy participants, having no current or past diagnosis of psychiatric disorder and/or neurological disease, were recruited from the community.

Table 1. Demographical and clinical characteristics of the sample.

	KS ($N = 12$)	HC ($N = 12$)		
Gender (female/male)	2/10	2/10		
	$M \pm SD$ (min–max)	$M \pm SD$ (min–max)	t	p
Age	39.42 ± 6.53 (29–52)	38.67 ± 7.13 (30–50)	0.27	0.791
Education (in years)	9.92 ± 2.91 (5–13)	10.83 ± 3.83 (5–15)	0.66	0.516
BDI	9.75 ± 3.89 (4–16)	4.58 ± 4.85 (0–13)	2.88	**0.009**
AES-C	28.75 ± 7.86 (19–43)	21.17 ± 3.38 (18–27)	3.07	**0.006**
ICARS	22.17 ± 15.09 (0–51)	—	—	—

AES-C: clinician version of the Apathy Evaluation Scale; BDI: Beck Depression Inventory; HC: healthy controls; KS: Korsakoff's syndrome; ICARS: International Cooperative Ataxia Rating Scale; *M*: mean; *SD*: standard deviation. Significant results are shown in bold.

All patients and healthy individuals gave written informed consent and voluntarily participated in the study.

The initial diagnoses and treatment plans of all the participants were managed by the senior author (H.G.), who also conducted follow-up visits in the ensuing years, both in prison and upon their release, in the Department of Neurology, Behavioral Neurology and Movement Disorders Unit of Istanbul Faculty of Medicine, Istanbul, Turkey.

All participants were screened for depression using the Turkish version of the Beck Depression Inventory-II (BDI-II). The cutoff point for BDI-II was 17 (Hisli, 1988). Other neurologic or psychiatric conditions were also screened to eliminate any contribution to memory impairment and cognitive deficit for KS patients. Any patient who had a dementia-like cognitive profile (i.e., functional impairment due to multiple cognitive deficits, such as word-finding and/or navigational difficulties), or a delusional state as part of the KS, a co-morbid neuropsychiatric disorder other than KS, and finally those showing significant recovery in memory as evidenced by the subjective report and by the objective performance on the Turkish version of the California Verbal Learning Test-I (Feyzioğlu, 2020) were excluded, as we wanted to include only stable amnestic KS patients for the clarification of the hypothesis of this study.

The study was approved by the Institutional Review Board of the Istanbul Faculty of Medicine and followed ethical principles and guidelines established by the Declaration of Helsinki for the protection of human subjects.

Scales and neuropsychological tests

All participants were administered three versions of the Apathy Evaluation Scale, a self-rated scale (AES-S), an informant version (AES-I), and a clinician version (AES-C) (Marin et al., 1991), Frontal Systems Behavior Scale (FrSBe) family form (Grace & Malloy, 2001) and the self-report BDI-II (Beck et al., 1996). The FrSBe includes questions to quantify behavioral changes before and after the disease onset to underline the specific contribution of the disease in question to the observed behavioral change. Subjects then underwent a neuropsychological battery, including the California Verbal Learning Test (CVLT) (Delis et al., 1987), WMS-R Digit Span (Wechsler, 1987), Tower of London Test (Shallice, 1982), Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993), Verbal Fluency Tests and Stroop Test (Stroop, 1935) tapping episodic memory, attention, working memory, and executive functions, such as set-shifting, planning, and response inhibition. Ataxia severity was also evaluated by the International Cooperative Ataxia Rating Scale (ICARS) (Trouillas et al., 1997).

Associative learning and transfer generalization tasks

The Concurrent Discrimination and Transfer Task (CDTT) and Acquired Equivalence Task (AET) are two distinct computer-based paradigms that have been developed by Myers et al. (2002, 2003) to assess the acquisition of simple and complex associations, respectively, and transfer generalization as well.

The Concurrent Discrimination and Transfer Task (CDTT) includes two phases, as previously described in Myers et al. (2002). Phase 1 is the acquisition phase in which subjects see pairs of objects and learn through trial and error which member of each pair is the correct choice (Figures 1A–D). Within each pair, either color or shape differs, but not both; thus, one dimension is relevant and one irrelevant. Objects can appear in either left/right ordering but always in the same pairs. On each trial, the subject chooses the left or right object by pressing a labeled key, and the chosen object is raised to reveal a smiley face if correct (e.g., Figures 1B,D) or no smiley face if incorrect. Eight pairs are trained concurrently until a subject reaches a performance criterion of 16 consecutive correct responses or to a maximum of 96 trials. Phase 2 begins without warning to the subject and is similar to Phase 1, except that the irrelevant feature in each object pair is changed (see Figures 1E–H). Thus, if the red object was rewarded in Phase 1, it is also rewarded in Phase 2 (transfer test), regardless of its new shape; likewise, if the frame-shaped object was rewarded in Phase 1, it is also rewarded in Phase 2, regardless of its new color (for methodological details, see Myers et al., 2002). Phase 2 continues until the subject makes 16 consecutive correct responses or a maximum of 48 trials. Performance on both phases is scored as total errors.

The Acquired Equivalence Task (AET) is also a computer-based task consisting of acquisition and transfer phases, as previously described in Myers et al. (2003). For each subject, four drawings of a man, woman, girl, and boy are randomly assigned as antecedent stimuli (Figure 2, A1, A2, B1, and B2). Drawings of fish colored red, blue, green, and yellow are randomly mapped to be consequent stimuli (X1, X2, Y1, Y2). Each antecedent has three apparent, binary-valued features: age (adult *vs.* child), gender (male *vs.* female), and hair color (blond *vs.* brunette); each face shares exactly one feature with the other face. During each acquisition trial, participants see a face presented with two colored fish and press a key to choose the fish paired with that face

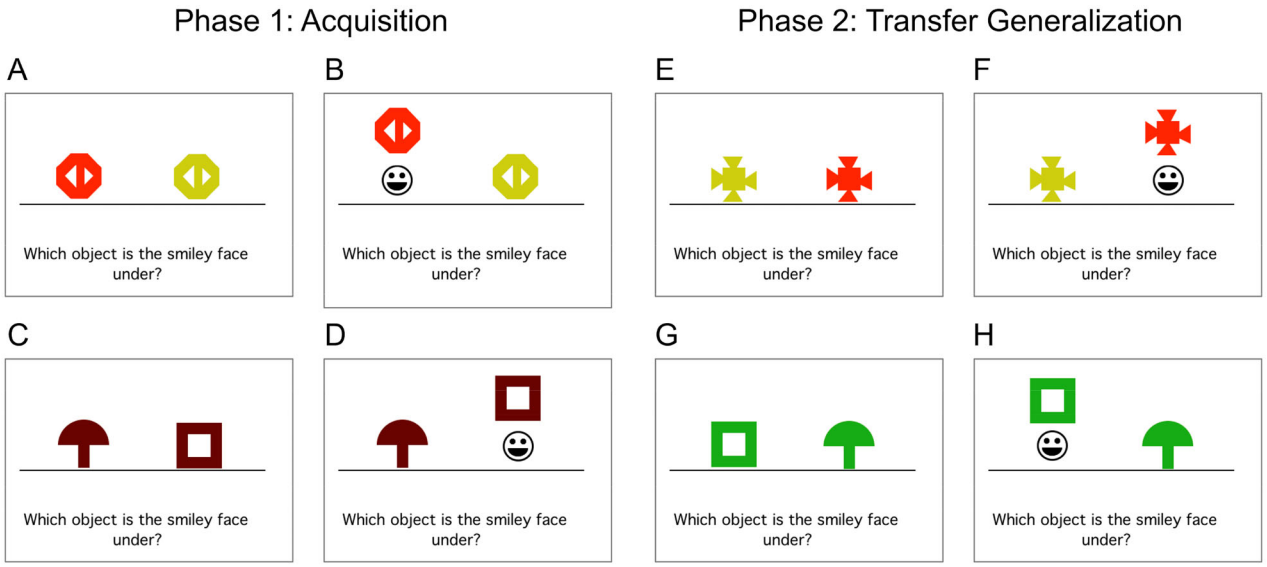

Figure 1. Screen events from sample trials in the Concurrent Discrimination and Transfer Test (CDTT). On each trial in Phase 1 (acquisition), the subject sees a pair of objects presented in either left-right order, with a prompt "Which object is the smiley face under?" (A,C). Each pair differs in color or shape but not both. The subject's chosen object is raised, and if correct, a smiley face is revealed underneath (B,D); otherwise, there is no smiley face. During Phase 2 (transfer generalization), events are similar, except that the irrelevant features are shifted, but the relevant features stay the same (E,G). Thus, if the correct object in Phase 1 was red but not gold (A,B), then the correct object in Phase 2 is still red but not gold (E,F). Similarly, if the correct object in Phase 1 was frame-shaped but not mushroom-shaped (C,D), the same rule applies in Phase 2 (G,H).

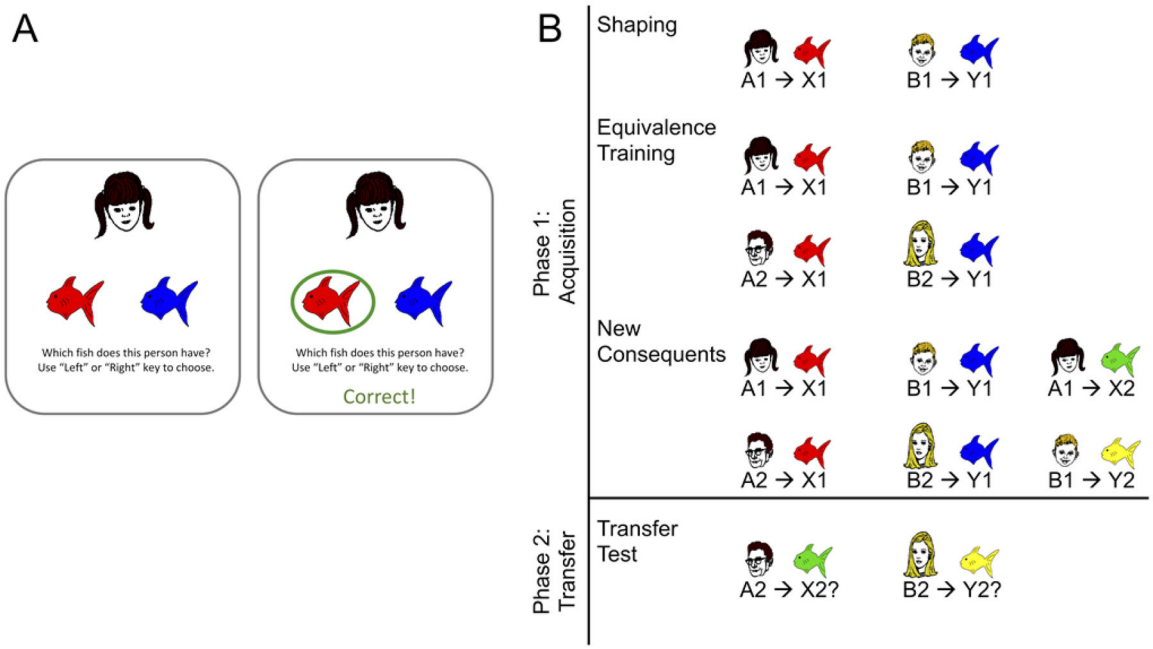

Figure 2. Screen events and stages of the Acquired Equivalence Task (AET). (A) An example of a trial during phase 1. (Left) Stimuli appear. (Right) Participant responds, and corrective feedback is given. (B) Stages of the AET task. In Phase 1 (acquisition), participants learn which faces "have" which fish. The exact mapping of faces to antecedents (A1, A2, B1, B2) and fish to consequents (X1, X2, Y1, Y2) was randomized across participants; one example of mapping is shown here. In Phase 2 (transfer), acquired equivalence is tested by presenting face-fish pairings that were not trained in Phase 1. Acquired equivalence is demonstrated if the subject chooses the fish previously paired with an equivalent face (e.g., A1 was paired with X2, and A1 and A2 are equivalent, so A2 should likewise be paired with X2, even though that pairing was not explicitly trained).

(see Figure 2A for a sample screenshot); the chosen fish is then circled, and corrective feedback is shown. The AET consists of two phases: acquisition and transfer. The acquisition phase consists of three stages, as schematized in Figure 2B. In the first shaping stage, participants see trials containing face A1 or B1 together with fishes X1 and Y1 and learn through trial and error to pair A1 with X1 and B1 with Y1. The second acquisition stage is called the equivalence training, where maintenance trials with the previous pairs from the shaping stage are interspersed with new trials containing new faces (A2 and B2), to be paired with fishes X1 and Y1, respectively. Finally, the third acquisition stage is called the new consequents. The subjects receive maintenance trials on the previously learned pairs, along with training to pair faces A1 and B1 with new fish, X2 and Y2, respectively. Training continues in each acquisition stage

until subjects reach a performance criterion or a maximum number of trials; performance is scored as total errors, summed across acquisition stages. Finally, in the transfer phase, retention of the information gained in the acquisition phase is tested, and generalization of this information is made *via* a transfer test: Faces A2 and B2 paired with X2 and Y2 (Figure 2B). There is no feedback during the transfer phase. Performance in the testing phase is scored as the percentage of errors on both retention and generalization testing.

Statistical analyses

Data were analyzed using SPSS v.24.0 (IBM Corp., Chicago, IL, USA). A two-sample *t*-test was performed to determine group differences for data showing normal distribution on Kolmogorov-Smirnov tests, while a non-parametric Mann–Whitney *U* test was used for data sets without normal distribution or including an outlier. One-way analysis of variance (ANOVA) with *post-hoc* Tamhane tests was performed to compare before and after damage FrSBe scores of the KS cases with the current scores of HCs. Correct scores from the CVLT were analyzed with a two-factorial 2 × 3 mixed-design ANOVA with group (KS and HC) as between-subject factor, and the number of correct recalls across time [(1) immediate recall: trial 5, (2) short, and (3) long-delayed correct recalls of the previously trained words from list A] as within-subject factor.

Then, patients with KS were assigned to subgroups based on their Phase 1 performance on the CDTT and AET. To determine whether subgroups of KS differ from each other and/or the HCs in the memory measures that indicated a significant difference in the initial analysis, one-way ANOVA with *post-hoc* Scheffé's test was performed.

Further, additional group comparisons were carried out to ensure that our patient subgroups regarding hunger strikes (1996 *vs.* 2000) were similar concerning neuropsychological and clinical variables.

The descriptive statistics for the parametric and non-parametric data were expressed as "the mean and standard deviation," and "median, minimum, and maximum values," respectively. The alpha level for the computation of significance was set at $p < 0.05$. Bonferroni correction for multiple comparisons was applied based on the number of variables measured per neuropsychological or behavioral test.

Spearman's correlation was calculated among the ataxia severity (ICARS total score) and Phase 1 data of the CDTT and AET. Statistically significant results surviving Bonferroni correction were reported.

Results

Demographics and behavioral scales

There were no significant differences between the KS patients from the 1996 and 2000 hunger strikes in terms of neuropsychological and clinical measurements, such as memory, attention, executive functions, stimulus-response learning, and ataxia severity (all *p*-values = NS, please see Table S1 provided in the Supplemental Material).

Tables 1 and 2 summarize demographic and clinical information for the KS and HC groups. There were no significant differences between the KS and HC groups in terms of age [$t(22) = 0.27$, p = NS] and years of education [$t(22) = 0.66$, p = NS]. Detailed neuropsychological results of comparisons between KS and HC groups are summarized in Table 3.

As seen in Table 1, none of the subjects showed clinical depression, although the KS group demonstrated significantly higher depression scores than HCs [$t(22) = 2.88$, $p = 0.009$, Cohen's $d = 1.18$]. AES-C scores of the KS group were higher than the healthy subjects ($t = 3.07$, $p = 0.006$, $d = 1.25$) yet did not indicate clinically significant apathy (Andersson et al., 1999; Kant et al., 1998; Marin et al., 1991). KS group had mild ataxia, as the mean score was 22.17 (15.09) out of a maximum score of 100.

One-Way ANOVA conducted on FrSBe data revealed that apathy [$F(2,33) = 12.731$, $p < 0.001$] and executive dysfunction [$F(2,33) = 17.979$, $p < 0.001$] scores differed among groups, but disinhibition did not [$F(2,33) = 0.7$, p = NS]. *Post-hoc* tests showed that apathy and executive dysfunction were significantly higher after brain damage than before damage measurements in KS cases (*Tamhane test*, all *p*-values < 0.001). While after damage apathy (*Tamhane test*, $p = 0.008$) and executive dysfunction scores (*Tamhane test*, $p = 0.001$) were found to be greater than HCs' current scores, there were no significant differences between the before damage scores of KS and current scores of HCs (*Tamhane test*, p = NS) (Table 2).

Memory

Significant group differences were found in the memory measurements of CVLT, with the KS group performing worse on both short and long-delayed recall and response discrimination (all *p*-values < 0.001, see Table 3).

A repeated measure ANOVA revealed a significant group effect [$F(1,22) = 35.96$, $p < 0.001$, $\eta_p^2 = 0.62$] as the KS group performed worse than the HC group and the significant main effect of time [$F(2,44) = 13.6$, $p < 0.001$, $\eta_p^2 = 0.382$] indicating a decay of recollection over time. Pairwise comparison

Table 2. One-way ANOVA results with *post-hoc* Tamhane test conducted on before and after damage scores on FrSBe for KS group and current scores for HCs.

	KS_{BD} $M \pm SD$ (min–max)	KS_{AD} $M \pm SD$ (min–max)	HC $M \pm SD$ (min–max)	ANOVA		Pairwise comparisons[a]		
				F	*p*	BD *vs.* AD	BD *vs.* HC	AD *vs.* HC
FrSBe-A	19.25 ± 2.8 (14–24)	30.17 ± 8.93 (15–46)	19.92 ± 4.27 (14–26)	12.73	**<0.001**	**0.004**	0.959	**0.008**
FrSBe-D	21.58 ± 4.56 (15–29)	22.92 ± 6.36) (15–33)	20.58 ± 3.03 (15–25)	0.7	0.504	—	—	—
FrSBe-ED	27.08 ± 4.54 (21–34)	42.17 ± 10.07 (28–65)	26.58 ± 5.92 (17–35)	17.98	**0.001**	**0.001**	0.994	**0.001**

FrSBe-A: apathy subscale of the FrSBe; FrSBe-D: disinhibition subscale of the FrSBe; FrSBe-ED: executive dysfunction subscale of the FrSBe; HC: healthy controls; KS: Korsakoff's syndrome; AD: after the damage; BD: before the damage; *M*: mean; *SD*: standard deviation.
[a]Results of the *post-hoc* Tamhane test. Significant results are shown in bold.

Table 3. Neuropsychological findings of the sample.

	KS ($N = 12$) $M \pm SD/Mdn$ (min–max)	HC ($N = 12$) $M \pm SD/Mdn$ (min–max)	Test	p
Memory				
CVLT				p^a
Trial 5	10.08 ± 2.23	14.25 ± 1.29	$t = 5.6$	**<0.001**
Learning (trials 1–5)	41.08 ± 8.91	56.92 ± 8.64	$t = 4.42$	**<0.001**
Short-delayed free-recall	7.25 ± 3.11	12.67 ± 2.64	$t = 4.6$	**<0.001**
Long-delayed free-recall	6.75 ± 3.42	12.92 ± 2.19	$t = 5.26$	**<0.001**
Semantic clustering	8.5 (2–21)	13.5 (7–34)	$U = 28.5$	0.010
Total perseverations	9.5 (2–23)	13.5 (7–34)	$U = 68$	0.843
Response discrimination	80.08 ± 6.40	93.83 ± 7.11	$t = 4.98$	**<0.001**
Response tendency	0.25 (–0.4–0.82)	0 (–0.6–0.67)	$U = 57$	0.410
Total target	13 (9–16)	15 (12–16)	$U = 32.5$	0.020
Executive function				
WCST				p^b
Categories	4 (1–9)	5.5 (2–10)	$U = 56.5$	0.378
% Perseverative errors	16.01 (7–28.9)	13.03 (7–24.2)	$U = 52.5$	0.266
Failures to maintain set	2 (0–5)	1 (0–3)	$U = 34$	0.028
TOL				p^c
Total correct	4 (1–7)	5 (3–9)	$U = 48.5$	0.178
Total moves	37.5 (13–50)	30 (6–92)	$U = 65$	0.713
Total time violations	1 (0–6)	0 (0–5)	$U = 36.5$	0.39
Total rule violations (Type I)	0 (0–2)	0 (0–1)	$U = 58$	0.443
Total rule violations (Type II)	0.5 (0–3)	0 (0–2)	$U = 48.5$	0.178
Stroop test				p^d
Interference time (in s)	47.33 ± 24.86	33 ± 10.61	$t = 1.84$	0.08
Verbal fluency				p^e
Semantic (animals)	19.92 ± 4.8	22.67 ± 5.28	$t = 1.34$	0.195
Lexical (letters)	36.25 ± 11.57	46.58 ± 17.33	$t = 1.72$	0.100
Attention and working memory				p^e
Digit span forward	5 (4–7)	5.5 (5–8)	$U = 43.5$	0.101
Digit span backward	4 (2–5)	5 (3–6)	$U = 38.5$	0.052

CVLT: California Verbal Learning Test; DS: digit span; HC: healthy controls; KS: Korsakoff's syndrome; ST: Stroop Test; ToL: Tower of London Test; VF: verbal fluency; WCST: Wisconsin Card Sorting Test; *M*: mean; Mdn: median; *SD*: standard deviation.
Significant results are shown in bold.
[a]Bonferroni corrected alpha level $p < 0.006$ (0.05/9, according to number of measures per domain).
[b]Bonferroni corrected alpha level $p < 0.017$ (0.05/3).
[c]Bonferroni corrected alpha level $p < 0.01$ (0.05/5).
[d]No correction applied. $p < 0.05$.
[e]Bonferroni corrected alpha level $p < 0.025$ (0.05/2).

with Bonferroni adjustment revealed significant differences between trial 5 and short delay recall ($p < 0.001$) and between trial 5 and long delay recall ($p < 0.001$). There was no significant difference between short and long-delay recall ($p =$ NS). Time X Group interaction was not significant [$F(2,44) = 2.02$, $p = 0.145$, $\eta_p^2 = 0.084$], indicating that the short or long delays do not significantly differ between the groups in terms of the number of words recalled from learned items. Separate paired sample *t*-tests revealed no significant difference between any pair in the HC group (all *p*-values > 0.05), whereas, in the KS group, a significant decay was found from trial 5 to both the short [$t(11) = 6.42$, $p < 0.001$, $d = 1.85$] and long [$t(11) = 4.49$, $p = 0.001$, $d = 1.3$] delayed recall.

Executive functions, attention, and working memory

As shown in Table 3, there were no significant group differences on WCST measures, indicating that the KS group showed a similar ability to the HCs on categorization and attentional set-shifting. Likewise, performance in the Tower of London was not significantly different between groups, indicating that the KS group exhibited intact planning and reasoning abilities. There were no significant differences between groups on verbal fluency, Stroop interference, and digit span measurements (all *p*-values = NS).

Acquisition and transfer generalization

CDTT data were analyzed using group (KS *vs.* HC) as the independent variable and the number of acquisition errors (Phase 1) and the number of transfer errors (Phase 2) as dependent variables. AET data were analyzed using the number of total acquisition errors (Phase 1) and the percentage of either retention or transfer errors (Phase 2) as dependent variables.

Following prior studies (Myers et al., 2002; Shohamy et al., 2006), phase 2 (transfer) data from those participants who failed to reach criterion performance in phase 1 of CDTT were excluded from phase 2 analysis. Thereby, one participant from the HC group who could not reach the criterion performance was defined as HC^{c-}, whereas the remaining 11 subjects were defined as HC^{c+}. Similarly, five and seven patients from the KS group were defined as KS^{c-} and KS^{c+}, respectively (see Figure 3). While the KS group made more phase 1 (acquisition) errors than HCs (KS, $M = 22.17$, $SD = 14.81$; HC, $M = 9$, $SD = 6.85$; $t(22) = 2.8$, $p = 0.011$, $d = 1.14$) (Figure 4A), the number of phase 2 (transfer) errors (Figure 4B) were similar between the groups (KS^{c+}, $M = 2$, $SD = 4.43$; HC^{c+}, $M = 1.18$, $SD = 1.25$; $U = 32$, $p = 0.596$). Note that the KS^{c+} patients performed as well as the HCs during phase 1 (KS, $M = 11.43$, $SD = 7.55$; HC, $M = 7.45$, $SD = 4.48$; $t(16) = 1.412$, $p = 0.177$).

The same procedure was applied for defining subgroups regarding acquisition performances on AET. Accordingly, KS^{a-} ($n = 5$) and HC^{a-} ($n = 1$) participants were excluded from further analysis (see Figure 3). Three of the five failed patients were the same persons for both tasks. As seen in Figure 5A, KS cases made more acquisition errors than the HCs (KS, $M = 34.42$, $SD = 18.06$; HC, $M = 10.08$, $SD = 9.37$; $t = 4.143$, $p < 0.001$, $d = 1.69$). To scrutinize this acquisition impairment in KS patients, we further ran a paired-sample t-test to compare the stages of the acquisition phase and found a significant difference between stages 2 and 3 ($t = -3.338$, $p = 0.007$, $d = -0.96$), indicating the number of the acquisition errors in Stage 3 ($M = 19.83$, $SD = 11.96$) is higher than in Stage 2 ($M = 8.67$, $SD = 7.4$). KS patients also made more retention errors (KS^{a+}, $M = 31.75$, $SD = 16.65$; HC^{a+}, $M = 4.04$, $SD = 6$; $U = 1.5$, $p < 0.001$, $d = -0.7$) as well as transfer errors (KS^{a+}, $M = 39.29$, $SD = 25.78$; HC^{a+}, $M = 8.33$, $SD = 17.08$; $U = 11.5$, $p = 0.011$, $d = -0.53$) than the HCs (see Figure 5B). Note that, although the KS^{a+} patients reached the criterion performance in phase 1, they actually made more acquisition errors than the HCs, indicating impaired acquisition ability (KS, $M = 21.79$, $SD = 6.77$; HC, $M = 8.18$, $SD = 6.98$; $t(16) = 3.925$, $p = 0.001$, Cohen's $d = 1.98$).

Ataxia severity is correlated with acquisition ability in KS

The total ataxia score was not correlated with any CDTT measures. Still, it was positively correlated with the number of Stage 3 (New Consequents) errors in AET (Spearman's $\rho = 0.586$, $p = 0.023$, one-tailed), indicating that more severe ataxia is associated with worse acquisition performance (Figure 6). Note that since the patients made significantly different number of errors among the Phase 1 stages of AET, specifically between the Stage 2 (Equivalence Training) and Stage 3 (New Consequents) (please see 3.4. Acquisition and transfer generalization subheading of the Results section), errors in Stages 2 and 3 were included separately in this analysis rather than the total number of acquisition errors, resulting in Bonferroni corrected alpha level of $p < 0.025$ (0.05/2).

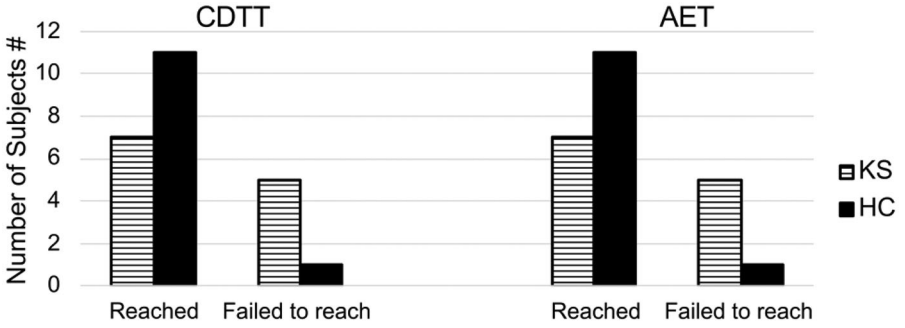

Figure 3. Number in each group reaching acquisition criteria for the two tasks.

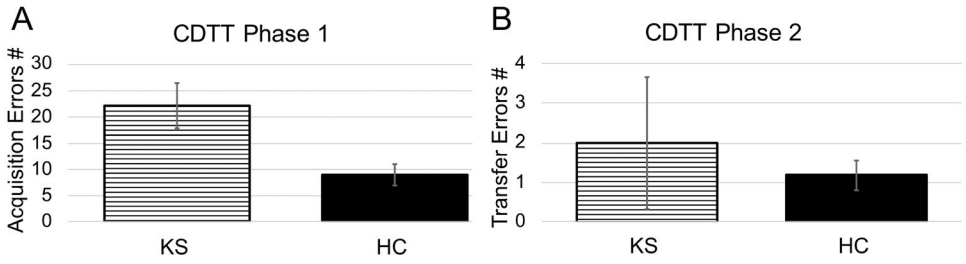

Figure 4. Acquisition and transfer performance on Concurrent Discrimination and Transfer Task (CDTT). (A) Patients with KS ($n = 12$) made more acquisition errors than the HC group ($n = 12$) in Phase 1 ($p = 0.011$). (B) KS^{c+} participants ($n = 7$) performed as well as HC^{c+} participants ($n = 11$) in Phase 2 ($p = $ NS). Error bars denote standard error for each group.

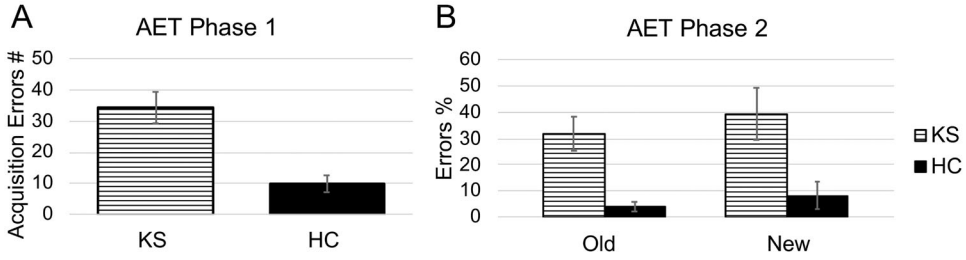

Figure 5. Acquisition, retention, and transfer performance on Acquired Equivalence task (AET). (A) KS cases ($n = 12$) made more acquisition errors than HCs ($n = 12$) ($p < 0.001$) in Phase 1. (B) KS^{a+} participants ($n = 7$) showed both reduced retention of previously-learned pairs ($p < 0.001$) and reduced transfer to new pairs ($p = 0.011$) on Phase 2. Error bars denote standard error for each group.

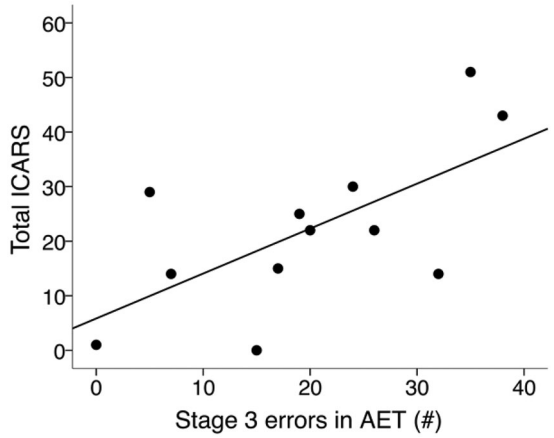

Figure 6. Spearman's correlation between the ICARS total score and the number of errors in stage 3 of the AET. Total ICARS displayed a positive correlation with the impairment in acquiring new stimulus-reward associations (*spearman's* $\rho = 0.586$, $p = 0.023$, one-tailed).

Poor acquisition performance unrelated to verbal episodic memory impairment

To perform one-way ANOVA among subgroups of KS and HC subjects in terms of their acquisition performance, five subjects from the KS group who were able to reach the criterion at both CDTT and AET were defined as KS^+, and seven cases who could not reach the criterion in at least one of these tasks were assigned to KS^- subgroup. Ten HC subjects were defined as HC^+ under the same principles. One-way ANOVA revealed significant differences in various memory measures in the initial analysis between KS and HC, including trial 5, learning, short and long-delayed recall, and response discrimination among subgroups (all *p*-values $\leq$0.001). *Post-hoc* tests revealed that there were no significant differences between KS^+ and KS^- subgroups in terms of their CVLT performance (all *p*-values = NS); however, both KS subgroups demonstrated poor performance on the same measurements compared to HCs (all *p*-values $\leq$0.001; see Table 4).

Discussion

This study aimed to investigate the two phases stimulus-learning paradigms in patients with Korsakoff-type diencephalic amnesia. Patients were carefully chosen KS patients with chronic and clinically stable amnesia for at least 10 years, who also underwent a comprehensive neuropsychological battery. Based on previous findings revealing the role of BG and MTL regions in stimulus-response feedback-based learning and transfer generalization, our main expectation was to find intact acquisition (phase 1) and impaired transfer (phase 2) in KS amnesia, as previously shown in the patients with hippocampal atrophy. Cognitively, our KS patients demonstrated an isolated amnestic profile, displaying a prominent impairment in episodic memory with preserved attention and executive functions, regardless of the hunger strike period (1996 *vs.* 2000). However, contrary to our expectation, the findings indicate a dichotomy between the KS patients in terms of acquiring the simple associations on CDTT. While

Table 4. One way ANOVA and *post-hoc* Scheffé results of subgroups on CVLT measurements.

	KS^- ($n = 7$) 0/7	KS^+ ($n = 5$) 2/3	HC^+ ($n = 10$) 3/7	One-way ANOVA		Pairwise comparisons		
						KS^- *vs.* KS^+	KS^- *vs.* HC^+	KS^+ *vs.* HC^+
Gender (female/male)	*M* ± *SD*			*F*	*p*	*p*	*p*	*p*
Trial 5	10 ± 1.83	10.2 ± 2.95	14.1 ± 1.37	11.68	<0.001	0.985	0.002	0.006
Learning (trials 1–5)	41 ± 6.73	41.2 ± 12.26	59 ± 7.6	11.94	<0.001	0.999	0.002	0.005
S-DR	7.43 ± 3.05	7 ± 3.54	13.1 ± 2.6	10.67	0.001	0.97	0.004	0.005
L-DR	6 ± 3.37	7.8 ± 3.56	13.3 ± 2.16	14.38	<0.001	0.581	<0.001	0.01
Response discrimination	80.86 ± 8.28	79 ± 2.74	96 ± 4.74	20.57	<0.001	0.863	<0.001	<0.001

L-DR: Long-delayed free-recall; S-DR: Short delayed free-recall; KS^+: KS subjects that were able to reach the criterion at both CDTT and AET; KS^-: KS cases that could not reach the criterion in at least one of the CDTT or AET; *M*: mean; *SD*: standard deviation.
Bonferroni corrected alpha level $p < 0.01$ (0.05/5).

almost half of the patients (5/12) failed to reach the criterion, the other half (7/12), after successfully acquiring the simple stimulus-response associations, showed intact transfer to novel combinations. On AET, the same number of KS patients (five) failed to reach the criterion in the acquisition phase of more complex associations. This time, the remaining seven patients who entered the second phase failed both in retention and, consequently, transfer. Furthermore, these impairments in KS patients did not relate to the episodic memory and frontal system measures. In addition to verbal learning impairment, acquisition and transfer performances that differ according to task complexity are discussed under the following subheadings.

Intact acquisition and transfer ability for simple associations

Seven of the 12 KS patients showed acquisition ability in simple associations in the CDTT as good as those of HC participants. These patients, who were available for the second phase, also showed good generalization in the CDTT. This pattern of intact acquisition, and in contrast to our hypothesis, intact generalization is different from previously observed in MTL patients (Myers et al., 2002) by demonstrating spared transfer ability and is different from the PD patients (Shohamy et al., 2006) and basal forebrain-type amnesic patients (Myers et al., 2008) by showing preserved acquisition ability in simple associations.

Due to the nature of the CDTT paradigm, the simple associations that had to be learned at the beginning may have allowed for an implicit transfer generalization without a conscious recollection of them. We suggest that previous rewarding of relevant dimension (shape or color) may facilitate the transfer by allowing the subjects to choose the correct answer without any conscious decision. Likewise, Oudman et al. (2016), manipulating the task with intentional *vs.* incidental conditions, found that patients with KS were able to learn routes automatically rather than effortfully. Furthermore, retrieval of the previously learned material, whether it is learned intentionally or incidentally, could be implicit (Cubelli et al., 2020). However, to understand whether the intact CDTT transfer we observed in our KS patients is indeed implicit, future work is needed in which patients' responses should be checked by querying each choice in transfer trials (e.g., "Why did you choose this one? "Did you see this pair before?).

On the other hand, observed intact transfer ability differentiates our KS patients from the MTL patients that showed impaired transfer in previous studies (Myers et al., 2002). Myers et al. (2003) suggested that mild HA does not impair initial associations but may affect how those associations are learned (see Gluck & Myers, 1993). Similarly, medial diencephalic damage may affect how those associations are learned and then implemented in a new context, allowing the patients, once they learn the initial associations, to transfer them in another way, with implicit processes. Although several studies revealed intact implicit learning in amnestic patients (Channon et al., 2002; Goshen-Gottstein et al., 2000; Graf et al., 1985; Shimamura & Squire, 1984; Squire et al., 1985; Verfaellie et al., 2012) and KS patients (Fama et al., 2006; Hayes et al., 2012; Heyselaar et al., 2017; Oudman et al., 2011, 2013; Phaf et al., 2000), previous research showed evidence that implicit contextual learning is impaired at extended MTL damage including the hippocampus (Chun & Phelps, 1999), but intact when the damage is selective to the hippocampal formation (Manns & Squire, 2001). It was considered that other MTL structures, such as the entorhinal, perirhinal, and parahippocampal cortices, may be more important for implicit contextual processing than the hippocampus proper or diencephalic structures (Kessels & Kopelman, 2012; Watson et al., 2012).

On the other hand, continued feedback during the transfer stage of CDTT might have contributed to the successful transfer ability of our KS patients. If the intact transfer in CDTT arises from feedback, the subjects' responses would be incorrect at the initial exposure of the pairs, then an increasing number of trials would provide transfer generalization by recruiting feedback-learning. However, four of seven KS patients who reached the criterion finished the transfer phase at minimum trials (16) without any incorrect responses, and two made only one error. This favors not learning from feedback but rather a plausible implicit transfer process, as discussed above.

A distinct pattern of spared generalization despite slower acquisition is previously reported on basal forebrain amnesia (Myers et al., 2008). One can wonder whether the underlying mechanism of preserved generalization in both types of amnesia is based on implicit processes.

However, the other five KS patients unexpectedly failed to acquire simple associations in the CDTT. We were unable to interpret this failure with the available evidence, as the failed group was no different than the succeeded group in any measures including the ataxia severity.

Impaired acquisition of complex associations correlated with ataxia severity

Our KS patients showed impairment in the acquisition of complex associations, in contrast to the previous findings observed in MTL patients (Myers et al., 2003). This acquisition impairment in the AET task is partially explainable by the severity of the cerebellar involvement as measured by the ICARS. There was a moderately strong positive correlation between the ICARS scores (ataxia severity) and the Stage 3 scores of the acquisition phase of the AET. Those five who failed the first phase had higher ICARS scores (28) than those seven who passed (18). Nonetheless, the comparison was not significant, probably due to the small sample size. Besides its role in associative learning (Drepper et al., 1999; Timmann et al., 2002), the cerebellum was recently associated with implicit contextual learning, where repeated spatial configurations facilitate the navigation and action in the familiar environment without conscious awareness (Ulasoglu-Yildiz & Gurvit, 2020). Putting the blame on the cerebellum is rather an easy solution to explain the observed finding. As stated in the Introduction, WKS is a two-stage

process. Wernicke's encephalopathy is its acute, and Korsakoff's is chronic stage. The acute stage may completely resolve, or residual findings, specifically gait ataxia with varying severity, may accompany the chronic stage. Thus, Korsakoff's stage may either be a pure amnesia or plus gait ataxia. It has recently become clear that discrete sectors of the cerebellum are components of parallel large-scale neural networks, subserving motor and cognitive-emotional functions (for review, see Habas, 2021). Therefore, the severity of cerebellar involvement as measured by a motor scale can have parallels in some non-motor functions, especially in implicit learning that were not tapped by us.

However, the seven patients were also slow to acquire complex associations with significantly more errors than the HCs despite reaching the criterion. In contrast, on the CDTT, the patients who reached the criterion performed as good as the HCs in phase 1 which consists of simple associations. This indicates an ability modulated by task complexity, which is preserved in acquiring simple associations but deteriorates in the more complex ones.

Impaired transfer ability on complex associations

Seven of the 12 KS patients, who were available for the second phase, showed impairment in generalization in AET. This double impairment with the slower acquisition of complex associations and defaced generalization is probably a unique finding specific to KS amnesia.

Previous studies revealed that the MTL patients (Bódi et al., 2009; Myers et al., 2003), schizophrenia patients (Kéri et al., 2005), and alcoholics (Máttyássy et al., 2012) were impaired in transfer generalization, but not in the retention trials. In contrast, our KS patients displayed poor performance on retention trials in AET. It appears that the KS group "immediately forgot" the previously-trained information on the AET: the lack of feedback not only disrupted generalization but also disrupted retention. Unlike CDTT, a successful transfer is impossible in AET, where the intact transfer requires retention of the previous associations. For example, in the transfer phase, the subject should associate the face with the new consequent (e.g., in the example of Figure 2, brown-haired man–green fish) using the previous knowledge of face–face (e.g., brown-haired man is equivalent with the brown-haired girl) and face–fish (e.g., brown-haired girl–green fish) associations. Hence, the transfer generalization unlikely accomplished by the KS patients, since they are not familiar with the information presented in novel contexts. Thus, our findings indicate that transfer generalization deficit in pure KS is related to impairment in retention, supporting that the limbic-medial diencephalic structures have a crucial role in memory retention and, therefore, in flexible transfer generalization. On the other hand, prefrontal involvement seems responsible for the transfer generalization deficit, where the retention ability is spared in alcoholics (Máttyássy et al., 2012) and patients with schizophrenia (Kéri et al., 2005).

Acquisition and transfer impairments in KS show dependence on task-complexity

Current results indicate a task complexity-related impairment both in acquiring associations and transferring them under novel recombinations. These findings are similar to an earlier study by Oscar-Berman and Zola-Morgan (Oscar-Berman & Zola-Morgan, 1980) which examined visual discrimination learning in KS. The tasks consisted of an easier task (single stimulus pairs presented one at a time) and a more challenging task (six pairs were concurrently present). Both tasks used two conditions: novel and familiar stimuli. The KS group had equally poor performance in the first phase of both tasks, where they had to learn the visual discrimination of novel configurations. In contrast, in the second phase, where they had to discriminate the familiar configurations, they were as good as the controls on the single pairs but significantly worse on the six concurrent pairs (Oscar-Berman & Zola-Morgan, 1980). We suggest that KS patients with the isolated amnestic state can acquire simple associations and subsequently transfer under novel recombinations of familiar stimuli implicitly. On the other hand, they are slower in acquiring the more complex associations and cannot retain them when exposed the novel recombinations, making transfer impossible.

In sum, although Korsakoff's amnesia have been recognized as an episodic memory impairment as seen in MTL patients, our patients showed a distinct pattern in stimulus-response learning and transfer generalization than observed in MTL patients. Previous studies by Myers et al. (2002, 2003) showed that MTL patients acquire stimulus-response associations but are unable to transfer those associations to novel conditions where flexible and explicit strategies are required. However, our findings indicate that unlike MTL patients, pure Korsakoff's patients are likely to acquire simple associations but not the complex ones, which suggest a task complexity dependent associative learning ability in this type of amnesia. Our results also reveal that unlike MTL patients, pure Korsakoff's patients are likely have intact transfer ability, which also depends on task complexity. However, we suggest that they can accomplish transfer trials *via* implicit way, without using any explicit strategy.

The major limitation of our study is the relatively small sample size to be generalizable to adults with KS. Due to the small number of patients, it would have been ideal to include twice as many healthy control participants in the study. On the other hand, studying rarely seen hunger strike type Korsakoff's syndrome, which represents a pure amnestic state, constitutes the strength of our work by mitigating the confounding factors that stem from alcohol consumption and enhancing the reliability of memory measures. A great majority of the studies on KS have been carried out with alcoholic patients. Our findings, however, have a significant potential to elucidate the role of the medial diencephalic structures in two-stage behavioral tasks that recruit different learning and memory strategies by taking into consideration task complexity. Nevertheless, we admit that by the strict inclusion criteria we selected, we cannot claim that our findings are representative of a typical WK

complex, which should include all etiologies, particularly alcohol-related WKS, for such a claim.

In conclusion, the current study showed that KS patients displayed varying acquisition and transfer abilities dependent on task complexity. We argued that (1) our patients with KS with isolated amnestic state might acquire simple associations but not the complex ones, which may be associated with cerebellar dysfunction, and (2) our KS patients, once they learned the simple associations, then they succeed in the transfer generalization of the simpler task presumably implicitly.

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References

Acker, C., Jacobson, R. R., & Lishman, W. A. (1987). Memory and ventricular size in alcoholics. *Psychological Medicine*, *17*(2), 343–348. https://doi.org/10.1017/s0033291700024880

Andersson, S., Krogstad, J. M., & Finset, A. (1999). Apathy and depressed mood in acquired brain damage: Relationship to lesion localization and psychophysiological reactivity. *Psychological Medicine*, *29*(2), 447–456. https://doi.org/10.1017/s0033291798008046

Başoğlu, M., Yetimalar, Y., Gürgör, N., Büyükçatalbaş, S., Kurt, T., Seçil, Y., & Yeniocak, A. (2006). Neurological complications of prolonged hunger strike. *European Journal of Neurology*, *13*(10), 1089–1097. https://doi.org/10.1111/j.1468-1331.2006.01531.x

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Manual for the Beck depression inventory-II. Psychological Corporation.

Bódi, N., Csibri, E., Myers, C. E., Gluck, M. A., & Kéri, S. (2009). Associative learning, acquired equivalence, and flexible generalization of knowledge in mild Alzheimer disease. *Cognitive and Behavioral Neurology*, *22*(2), 89–94. https://doi.org/10.1097/WNN.0b013e318192ccf0

Brokate, B., Hildebrandt, H., Eling, P., Fichtner, H., Runge, K., & Timm, C. (2003). Frontal lobe dysfunctions in Korsakoff's syndrome and chronic alcoholism: continuity or discontinuity? *Neuropsychology*, *17*(3), 420–428. https://doi.org/10.1037/0894-4105.17.3.420

Channon, S., Shanks, D., Johnstone, T., Vakili, K., Chin, J., & Sinclair, E. (2002). Is implicit learning spared in amnesia? Rule abstraction and item familiarity in artificial grammar learning. *Neuropsychologia*, *40*(12), 2185–2197. https://doi.org/10.1016/s0028-3932(02)00037-4

Chun, M. M., & Phelps, E. A. (1999). Memory deficits for implicit contextual information in amnesic subjects with hippocampal damage. *Nature Neuroscience*, *2*(9), 844–847. https://doi.org/10.1038/12222

Cubelli, R., Beschin, N., & Della Sala, S. (2020). Retrograde amnesia: A selective deficit of explicit autobiographical memory. *Cortex*, *133*, 400–405. https://doi.org/10.1016/j.cortex.2020.10.003

d'Ydewalle, G., & Van Damme, I. (2007). Memory and the Korsakoff syndrome: Not remembering what is remembered. *Neuropsychologia*, *45*(5), 905–920. https://doi.org/10.1016/j.neuropsychologia.2006.08.025

De Wardener, H. E., & Lennox, B. (1947). Cerebral beriberi (Wernicke's encephalopathy); review of 52 cases in a Singapore prisoner-of-war hospital. *Lancet*, *1*(6436), 11–17. https://doi.org/10.1016/S0140-6736(47)91272-5

Delis, D. C., Kramer, J. H., Kaplan, E., & Over, B. A. (1987). *California Verbal Learning Test. Research edition manual*. Psychological Corporation.

Devathasan, G., & Koh, C. (1982). Wernicke's encephalopathy in prolonged fasting. *Lancet*, *2*(8307), 1108–1109. https://doi.org/10.1016/s0140-6736(82)90039-3

Drepper, J., Timmann, D., Kolb, F. P., & Diener, H. C. (1999). Non-motor associative learning in patients with isolated degenerative cerebellar disease. *Brain*, *122*(1), 87–97. https://doi.org/10.1093/brain/122.1.87

Durmaz, O., Aktaş, S., & Akkişi Kumsar, N. (2020). From psychosis to Wernicke encephalopathy: A case of hunger strike in prison. *Neurocase*, *26*(4), 248–251. https://doi.org/10.1080/13554794.2020.1786587

Eichenbaum, H., & Bunsey, M. (1995). On the binding of associations in memory: Clues from studies on the role of the hippocampal region in paired-associate learning. *Current Directions in Psychological Science*, *4*(1), 19–23. https://doi.org/10.1111/1467-8721.ep10770954

Fama, R., Pfefferbaum, A., & Sullivan, E. V. (2006). Visuoperceptual learning in alcoholic Korsakoff syndrome. *Alcoholism, Clinical and Experimental Research*, *30*(4), 680–687. https://doi.org/10.1111/j.1530-0277.2006.00085.x

Fama, R., Pitel, A. L., & Sullivan, E. V. (2012). Anterograde episodic memory in Korsakoff syndrome. *Neuropsychology Review*, *22*(2), 93–104. https://doi.org/10.1007/s11065-012-9207-0

Feyzioğlu, A. (2020). California Verbal Learning Test: The normative study of Turkey adult sample. *Haydarpasa Numune Medical Journal*, *60*(4), 383–394. https://doi.org/10.14744/hnhj.2019.78790

Frantzen, E. (1966). Wernicke's encephalopathy. 3 Cases occurring in connection with severe malnutrition. *Acta Neurologica Scandinavica*, *42*(4), 426–441. https://doi.org/10.1111/j.1600-0404.1966.tb01194.x

Gluck, M. A., & Myers, C. E. (1993). Hippocampal mediation of stimulus representation: A computational theory. *Hippocampus*, *3*(4), 491–516. https://doi.org/10.1002/hipo.450030410

Goshen-Gottstein, Y., Moscovitch, M., & Melo, B. (2000). Intact implicit memory for newly formed verbal associations in amnesic patients following single study trials. *Neuropsychology*, *14*(4), 570–578. https://doi.org/10.1037//0894-4105.14.4.570

Grace, J., & Malloy, P. F. (2001). *Frontal systems behavior scale: Professional manual*. Psychological Assessment Resources, Inc.

Graf, P., Shimamura, A. P., & Squire, L. R. (1985). Priming across modalities and priming across category levels: Extending the domain of preserved function in amnesia. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *11*(2), 386–396. https://doi.org/10.1037//0278-7393.11.2.386

Gürvit, H., Gökmen, E., Kinay, D., Şahin, H., Demirci, N., Tuncay, R., Boyaciyan, A., Öge, E., & Gürsoy, G. (1997). 1-27-07 Hunger strike-related Wernicke-Korsakoff's disease. *Journal of the Neurological Sciences*, *150*, S39. https://doi.org/10.1016/S0022-510X(97)85019-8

Habas, C. (2021). Functional connectivity of the cognitive cerebellum. *Frontiers in Systems Neuroscience*, *15*, 642225. https://doi.org/10.3389/fnsys.2021.642225

Hayes, S. M., Fortier, C. B., Levine, A., Milberg, W. P., & McGlinchey, R. (2012). Implicit memory in Korsakoff's syndrome: A review of procedural learning and priming studies. *Neuropsychology Review*, *22*(2), 132–153. https://doi.org/10.1007/s11065-012-9204-3

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). *Wisconsin Card Sorting Test Manual: Revised and expanded*. Psychological assessment resources.

Heyselaar, E., Segaert, K., Walvoort, S. J. W., Kessels, R. P. C., & Hagoort, P. (2017). The role of nondeclarative memory in the skill for language: Evidence from syntactic priming in patients with amnesia. *Neuropsychologia*, *101*, 97–105. https://doi.org/10.1016/j.neuropsychologia.2017.04.033

Hisli, N. (1988). Beck Depresyon Envanteri'nin geçerliği üzerine bir c¸alışma. *Türk Psikoloji Dergisi*, *6*, 118–126.

Isenberg-Grzeda, E., Alici, Y., Hatzoglou, V., Nelson, C., & Breitbart, W. (2016). Nonalcoholic thiamine-related encephalopathy (Wernicke-Korsakoff syndrome) among inpatients with cancer: A series of 18 cases. *Psychosomatics*, *57*(1), 71–81. https://doi.org/10.1016/j.psym.2015.10.001

Isenberg-Grzeda, E., Kutner, H. E., & Nicolson, S. E. (2012). Wernicke-Korsakoff-syndrome: Under-recognized and under-treated. *Psychosomatics*, *53*(6), 507–516. https://doi.org/10.1016/j.psym.2012.04.008

Kant, R., Duffy, J. D., & Pivovarnik, A. (1998). Prevalence of apathy following head injury. *Brain Injury*, *12*(1), 87–92. https://doi.org/10.1080/026990598122908

Kéri, S., Nagy, O., Kelemen, O., Myers, C. E., & Gluck, M. A. (2005). Dissociation between medial temporal lobe and basal ganglia memory systems in schizophrenia. *Schizophrenia Research*, *77*(2–3), 321–328. https://doi.org/10.1016/j.schres.2005.03.024

Kessels, R. P., & Kopelman, M. D. (2012). Context memory in Korsakoff's syndrome. *Neuropsychology Review*, *22*(2), 117–131. https://doi.org/10.1007/s11065-012-9202-5

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science*, *273*(5280), 1399–1402. https://doi.org/10.1126/science.273.5280.1399

Kopelman, M. D. (1995). The Korsakoff syndrome. *The British Journal of Psychiatry: The Journal of Mental Science*, *166*(2), 154–173. https://doi.org/10.1192/bjp.166.2.154

Kopelman, M. D., Thomson, A. D., Guerrini, I., & Marshall, E. J. (2009). The Korsakoff syndrome: Clinical aspects, psychology and treatment. *Alcohol and Alcoholism*, *44*(2), 148–154. https://doi.org/10.1093/alcalc/agn118

Manns, J. R., & Squire, L. R. (2001). Perceptual learning, awareness, and the hippocampus. *Hippocampus*, *11*(6), 776–782. https://doi.org/10.1002/hipo.1093

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Research*, *38*(2), 143–162. https://doi.org/10.1016/0165-1781(91)90040-v

Máttyássy, A., Kéri, S., Myers, C. E., Levy-Gigi, E., Gluck, M. A., & Kelemen, O. (2012). Impaired generalization of associative learning in patients with alcohol dependence after intermediate-term abstinence. *Alcohol and Alcoholism*, *47*(5), 533–537. https://doi.org/10.1093/alcalc/ags050

Myers, C. E., Hopkins, R. O., DeLuca, J., Moore, N. B., Wolansky, L. J., Sumner, J. M., & Gluck, M. A. (2008). Learning and generalization deficits in patients with memory impairments due to anterior communicating artery aneurysm rupture or hypoxic brain injury. *Neuropsychology*, *22*(5), 681–686. https://doi.org/10.1037/0894-4105.22.5.681

Myers, C. E., Kluger, A., Golomb, J., Ferris, S., de Leon, M. J., Schnirman, G., & Gluck, M. A. (2002). Hippocampal atrophy disrupts transfer generalization in nondemented elderly. *Journal of Geriatric Psychiatry and Neurology*, *15*(2), 82–90. https://doi.org/10.1177/089198870201500206

Myers, C. E., Shohamy, D., Gluck, M. A., Grossman, S., Kluger, A., Ferris, S., Golomb, J., Schnirman, G., & Schwartz, R. (2003). Dissociating hippocampal versus basal ganglia contributions to learning and transfer. *Journal of Cognitive Neuroscience*, *15*(2), 185–193. https://doi.org/10.1162/089892903321208123

Oge, A. E., Boyaciyan, A., Gökmen, E., Kinay, D., Sahin, H., Yazici, J., & Gurvit, H. (2000). Neuromuscular consequences of prolonged hunger strike: An electrophysiological study. *Clinical Neurophysiology*, *111*(11), 2064–2070. https://doi.org/10.1016/s1388-2457(00)00458-2

Oscar-Berman, M., & Zola-Morgan, S. M. (1980). Comparative neuropsychology and Korsakoff's syndrome. II–Two-choice visual discrimination learning. *Neuropsychologia*, *18*(4–5), 513–525. https://doi.org/10.1016/0028-3932(80)90153-0

Oudman, E., Nijboer, T. C., Postma, A., Wijnia, J. W., Kerklaan, S., Lindsen, K., & Van der Stigchel, S. (2013). Acquisition of an instrumental activity of daily living in patients with Korsakoff's syndrome: A comparison of trial and error and errorless learning. *Neuropsychological Rehabilitation*, *23*(6), 888–913. https://doi.org/10.1080/09602011.2013.835738

Oudman, E., Van der Stigchel, S., Nijboer, T. C., Wijnia, J. W., Seekles, M. L., & Postma, A. (2016). Route learning in Korsakoff's syndrome: Residual acquisition of spatial memory despite profound amnesia. *Journal of Neuropsychology*, *10*(1), 90–103. https://doi.org/10.1111/jnp.12058

Oudman, E., Van der Stigchel, S., Wester, A. J., Kessels, R. P., & Postma, A. (2011). Intact memory for implicit contextual information in Korsakoff's amnesia. *Neuropsychologia*, *49*(10), 2848–2855. https://doi.org/10.1016/j.neuropsychologia.2011.06.010

Oudman, E., Wijnia, J. W., Oey, M. J., van Dam, M., & Postma, A. (2021). Wernicke-Korsakoff syndrome despite no alcohol abuse: A summary of systematic reports. *Journal of the Neurological Sciences*, *426*, 117482. https://doi.org/10.1016/j.jns.2021.117482

Packard, M. G., & Knowlton, B. J. (2002). Learning and memory functions of the Basal Ganglia. *Annual Review of Neuroscience*, *25*, 563–593. https://doi.org/10.1146/annurev.neuro.25.112701.142937

Parkin, A. J., Blunden, J., Rees, J. E., & Hunkin, N. M. (1991). Wernicke-Korsakoff syndrome of non-alcoholic origin. *Brain and Cognition*, *15*(1), 69–82. https://doi.org/10.1016/0278-2626(91)90016-2

Pentland, B., & Mawdsley, C. (1982). Wernicke's encephalopathy following 'hunger strike'. *Postgraduate Medical Journal*, *58*(681), 427–428. https://doi.org/10.1136/pgmj.58.681.427

Phaf, H. R., Geurts, H., & Eling, P. A. (2000). Word frequency and word stem completion in Korsakoff patients. *Journal of Clinical and Experimental Neuropsychology*, *22*(6), 817–829. https://doi.org/10.1076/jcen.22.6.817.956

Sahin, H. A., Gurvit, I. H., Bilgiç, B., Hanagasi, H. A., & Emre, M. (2002). Therapeutic effects of an acetylcholinesterase inhibitor (donepezil) on memory in Wernicke-Korsakoff's disease. *Clinical Neuropharmacology*, *25*(1), 16–20. https://doi.org/10.1097/00002826-200201000-00003

Sechi, G., & Serra, A. (2007). Wernicke's encephalopathy: New clinical settings and recent advances in diagnosis and management. *The Lancet. Neurology*, *6*(5), 442–455. https://doi.org/10.1016/S1474-4422(07)70104-7

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *298*(1089), 199–209. https://doi.org/10.1098/rstb.1982.0082

Shimamura, A. P., & Squire, L. R. (1984). Paired-associate learning and priming effects in amnesia: A neuropsychological study. *Journal of Experimental Psychology. General*, *113*(4), 556–570. https://doi.org/10.1037//0096-3445.113.4.556

Shohamy, D., Myers, C. E., Geghman, K. D., Sage, J., & Gluck, M. A. (2006). L-dopa impairs learning, but spares generalization, in Parkinson's disease. *Neuropsychologia*, *44*(5), 774–784. https://doi.org/10.1016/j.neuropsychologia.2005.07.013

Shohamy, D., Myers, C. E., Kalanithi, J., & Gluck, M. A. (2008). Basal ganglia and dopamine contributions to probabilistic category learning. *Neuroscience & Biobehavioral Reviews*, *32*(2), 219–236. https://doi.org/10.1016/j.neubiorev.2007.07.008

Squire, L. R., Shimamura, A. P., & Graf, P. (1985). Independence of recognition memory and priming effects: A neuropsychological analysis. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *11*(1), 37–44. https://doi.org/10.1037//0278-7393.11.1.37

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Timmann, D., Drepper, J., Maschke, M., Kolb, F. P., Böring, D., Thilmann, A. F., & Diener, H. C. (2002). Motor deficits cannot explain impaired cognitive associative learning in cerebellar patients. *Neuropsychologia*, *40*(7), 788–800. https://doi.org/10.1016/s0028-3932(01)00181-6

Trouillas, P., Takayanagi, T., Hallett, M., Currier, R. D., Subramony, S. H., Wessel, K., Bryer, A., Diener, H. C., Massaquoi, S., Gomez, C. M., Coutinho, P., Ben Hamida, M., Campanella, G., Filla, A., Schut, L., Timann, D., Honnorat, J., Nighoghossian, N., & Manyam, B. (1997). International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of

Neurology. *Journal of the Neurological Sciences*, *145*(2), 205–211. https://doi.org/10.1016/s0022-510x(96)00231-6

Ulasoglu-Yildiz, C., & Gurvit, H. (2020). Implicit contextual learning in spinocerebellar ataxia. *Neuropsychology*, *34*(5), 511–523. https://doi.org/10.1037/neu0000614

Unlu, E., Cakir, B., & Asil, T. (2006). MRI findings of Wernicke encephalopathy revisited due to hunger strike. *European Journal of Radiology*, *57*(1), 43–53. https://doi.org/10.1016/j.ejrad.2005.07.002

Verfaelllie, M., LaRocque, K. F., & Keane, M. M. (2012). Intact implicit verbal relational memory in medial temporal lobe amnesia. *Neuropsychologia*, *50*(8), 2100–2106. https://doi.org/10.1016/j.neuropsychologia.2012.05.011

Victor, M., Adams, R. D., & Collins, G. H. (1971). The Wernicke-Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations. *Contemporary Neurology Series*, *7*, 1–206.

Wallis, W. E., Willoughby, E., & Baker, P. (1978). Coma in the Wernicke-Korsakoff syndrome. *Lancet*, *2*(8086), 400–401. https://doi.org/10.1016/s0140-6736(78)91867-6

Watson, H. C., Wilding, E. L., & Graham, K. S. (2012). A role for perirhinal cortex in memory for novel object-context associations. *The Journal of Neuroscience*, *32*(13), 4473–4481. https://doi.org/10.1523/JNEUROSCI.5751-11.2012

Wechsler, D. (1987). *WMS-R: Wechsler Memory Scale–Revised: Manual*. Psychological Corp.

White, N. M. (1997). Mnemonic functions of the basal ganglia. *Current Opinion in Neurobiology*, *7*(2), 164–169. https://doi.org/10.1016/s0959-4388(97)80004-9