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Implicit Memory in Korsakoff's Syndrome: A Review of Procedural Learning and Priming Studies

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Abstract

Korsakoff's syndrome (KS) is characterized by dense anterograde amnesia resulting from damage to the diencephalon region, typically resulting from chronic alcohol abuse and thiamine deficiency. This review assesses the integrity of the implicit memory system in KS, focusing on studies of procedural learning and priming. KS patients are impaired on several measures of procedural memory, most likely due to impairment in cognitive functions associated with alcohol-related neural damage outside of the diencephalon. The pattern of performance on tasks of implicit priming suggests reliance on a residual, non-flexible memory operating more or less in an automatic fashion. Our review concludes that whether measures of implicit memory reveal intact or impaired performance in individuals with KS depends heavily on specific task parameters and demands, including timing between stimuli, the specific nature of the stimuli used in a task, and the integrity of supportive cognitive functions necessary for performance.

Keywords

Procedural memory; Implicit memory; Priming; Amnesia; Korsakoff's syndrome; Wernicke's encephalopathy

Introduction

The examination of patients with Korsakoff's syndrome (KS) has contributed significantly to our knowledge of memory and the identification and delineation of multiple memory systems. Although landmark studies of amnesic patients with bilateral medial temporal lobe (MTL) damage such as HM provided a canonical reference for empirical papers examining dissociations in memory (Milner et al. 1968; Scoville and Milner 1957), several landmark studies elucidating impaired and preserved memory systems, as well as processes, have utilized KS patients (Cohen and Squire 1980; Graf et al. 1984; Warrington and Weiskrantz 1968). Many studies of KS have focused on explicit memory, including episodic memory, the most striking deficit in the clinical presentation of KS (Fama et al. 2012), as well as retrieval of contextual information (Kessels and Kopelman 2012) and remote memories (Race and Verfaellie 2012). Although there is a general impression that implicit memory is intact in KS, there is much evidence of impairment depending on the particular task used (McGlinchey-Berroth et al. 1995), stimulus types within the same task (Verfaellie et al. 1991), or the format of test list (Cermak et al. 1991).

An examination of the various procedural and priming paradigms implemented with KS patients and their results may clarify the implicit memory profile in KS. Here we briefly describe KS, followed by a review of results of studies of KS within the domains of procedural memory and priming. Although the current review is focused on implicit memory, some discussion of explicit memory is included, particularly when results shed light on the interpretation of implicit memory data. To assure that the findings we reviewed were representative of KS, studies met one of the following criteria for inclusion in this review: 1) a minimum of two-thirds of a mixed-etiology amnesic group must have been designated as KS (Cermak et al. 1992); 2) data from KS patients were reported separately from other patient groups (Cohen and Squire 1980); 3) statistical tests reporting no difference in performance between KS and non-KS amnesic patients (Cermak et al. 1997).

Korsakoff's syndrome is associated with a severe memory disorder with hallmark symptoms typically described within the domain of episodic memory, including anterograde and retrograde amnesia, as well as confabulation. The anterograde amnesia is stable in KS, often requiring prolonged hospitalization and placement in long-term care facilities (Kopelman et al. 2009). The retrograde amnesia is temporally graded and can span up to 30 years in KS (Kopelman 1989). Confabulation, another common symptom in KS sometimes described as 'honest lying,' has various definitions, but they all share the notion that patients make false statements or behave in ways that reflect false memories without deliberate intentions to deceive (Johnson et al. 2000; Van Damme and d'Ydewalle 2010).

The amnesia associated with KS is a result of damage to the diencephalon, primarily the mammillary bodies, mammillothalamic tract, and anterior thalamus (for review of brain changes associated with KS, see Kril and Harper 2012; Jung et al. 2012). In addition to lesions to the diencephalon, imaging studies with KS have demonstrated cortical atrophy (Shimamura et al. 1988; Sullivan et al. 2000) and reductions in white matter volume (Shimamura et al. 1988; Sullivan, Deshmukh et al. 2000). Evidence also suggests extensive alcohol-related brain changes in chronic alcoholics who do not develop KS. For example, reduction in white matter integrity has been found in chronic alcoholics (demonstrated with

diffusion tensor imaging; Pfefferbaum et al. 2006; Pfefferbaum et al. 1996; Schulte et al. 2005), with much of thiswork implicating the frontal lobes and underlying white matter tracts (e.g., corpus callosum). Additionally,Fortier et al. (2011) demonstrated alcohol-associated reductions in cortical thickness in a group of abstinent alcoholics, with the most severe reductions in frontal and temporal brain regions. In a parallel investigation examining white matter tracts,McGlinchey et al. (2011) found reduced white matter integrity in a number of subcortical white matter structures and pathways (i.e., corpus collosum, internal capsule, corona radiata, thalamus, cingulum, longitudinal fasiculus, superior fronto-occipital fasiculous, and the uncinate fasciculus) in a group of abstinent alcoholics compared to non-alcoholic controls. Changes were also noted in the microstructural properties of subcortical white matter, including the caudate and pallidum. Lastly, reduced tissue integrity in cingulum, frontal and occipital regions was correlated with measures of alcohol abuse and severity, implying a negative relationship between white matter integrity and alcohol abuse. Interestingly, alcoholics have also demonstrated dendritic shrinkage (Harper and Corbett 1990) that has been shown to be reversible in experimental models (McMullen et al. 1984). The reversible nature may account for some of the functional improvements seen by KS patients and alcoholics when they have abstained from alcohol (Pfefferbaum et al. 1995; Shear et al. 1994; Sullivan et al. 2000).

Korsakoff's Syndrome and Procedural Memory

A number of paradigms have been used to examine the integrity of procedural memory processing in individuals with KS (see Table 1). Procedural memory falls under the rubric of the nondeclarative memory system (Squire 2004) and refers to the acquisition of skills and habits that occur without conscious awareness and over the course of practice. In the following section, we review the literature regarding procedural memory processes in KS. In anticipation, there is no clear dichotomy as to whether procedural memory is preserved or impaired in KS. The widespread nature of the neuropathology associated with chronic alcohol abuse in KS does not allow one to make a clear prediction without considering specific task requirements and the underlying essential neural circuitry for those specific tasks. Performance of KS on tasks of classical eyeblink conditioning makes this point explicitly.

Eyeblink Classical Conditioning

Eyeblink Classical Conditioning (EBCC) is based on the principles of associative learning, a form of learning that results in a relatively permanent change in behavior as the result of a temporal conjunction of two events (Lashley 1916). Variations of two primary tasks are typically used to investigate EBCC (see Fig. 1a). The most basic is the single-cue delay paradigm in which a neutral conditioned stimulus (CS; e.g., auditory tone) is presented followed by an unconditioned stimulus (US; e.g., airpuff) that elicits an eyeblink unconditioned response (UR). In delay conditioning, the CS and US terminate simultaneously. Over the course of repeated pairings of the CS and US, an adaptive eyeblink response begins to occur prior to the onset of the US; this is the learned conditioned response (CR). Because delay conditioning is dependent only on cerebellar function and can occur without awareness of the CS-US relationship (e.g., Thompson 1986), it has often been considered a purely procedural memory task (Squire 1994). Another primary EBCC task is the single-cue trace paradigm that introduces a temporal gap (silent period) between the CS and the US (see Fig. 1a). The trace conditioning paradigm is considered a more complex and demanding associative task because there is temporal separation between the CS and US, which requires the formation of an abstract link or a conjoined representation between the two stimuli in order for learning to occur. Trace conditioning is acquired over the course of practice and involves an essential contribution from the hippocampal system (Moyer et al. 1990), leading some to consider it an explicit memory task (Squire 1994). Nevertheless, we

review both delay and trace EBCC tasks that have been used to investigate the integrity of learning and memory systems in individuals with chronic alcoholic histories both with and without KS.

Eyeblink Classical Conditioning in KS and Chronic Alcoholism

Weiskrantz and Warrington (1979) were the first to use a delay EBCC task to investigate associative learning in amnesia. One of the patients reported was a 50 year-old male KS patient (A.S.; a MTL amnesic was also reported). Acquisition of CRs was observed after roughly 50 trials (and percentage of CRs increased thereafter), and was retained over delays of 10 min and 24 h. However, because this study did not include normal control participants, it was not possible to determine the normalcy of the KS patient's acquisition rate.

McGlinchey-Berroth et al. (1995) also examined delay EBCC in KS, comparing the performance of four male KS patients, ten recovered chronic alcoholic participants (ALC), and ten non-alcoholic control participants. The findings indicated that KS patients were unable to acquire CRs; they showed no evidence of an increase in CRs during paired CS-US conditioning trials relative to an established pre-learning baseline. In contrast, non-alcoholic control participants (no history of alcohol abuse or dependence) showed robust learning (see Fig. 1b). Somewhat surprisingly, the ALC group was also impaired, albeit to a lesser extent than KS patients, relative to the normal control group. Thus, although recovered chronic alcoholics showed statistical evidence of acquisition, their performance was markedly impaired relative to non-alcoholic controls (see also McGlinchey-Berroth et al. 2002).

The fact that learning in the ALC group was depressed in a manner similar to the KS patients suggested that the impairment in delay EBCC may have been related to years of alcohol abuse and not to KS or amnesia, per se. Furthermore, the finding of eliminated delay EBCC in KS patients stands in sharp contrast to a parallel study in our laboratory that found intact delay EBCC in patients with severe amnesia due to bilateral temporal lobe damage (Gabrieli et al. 1995); others have also documented successful acquisition of CRs in MTL amnesic patients using delay paradigms (Daum et al. 1989; Daum et al. 1991). Intact delay EBCC has also been reported in a case study of bilateral thalamic lesion (Daum and Ackermann 1994). Therefore, the impairment observed in delay EBCC in KS patients (as well as recovered alcoholics) may be attributable to cerebellar degeneration caused by excessive alcohol consumption over an extensive time period, rather than memory impairments associated with damage to the diencephalon or medial temporal lobe memory system. Although neuropathological or neuroimaging data are not available for confirmation, it is possible that the discrepancy observed in performance on delay EBCC in KS is attributable to differences in cerebellar damage. That is, the single KS patient that demonstrated acquisition of CRs reported by Weiskrantz and Warrington (1979) may have had less cerebellar damage than the KS patients reported by McGlinchey-Berroth et al. (1995).

We also examined the performance of KS patients in the more complex trace conditioning task (see Fig. 1a; McGlinchey et al. 2005). KS patients, as well as ALC with no prior EBCC training, were significantly impaired in the acquisition of trace CRs compared to ALC with prior eyeblink training, as well as trained and untrained healthy control participants (see Fig. 1c). KS patients performed similarly to an ALC group who was naïve to eyeblink conditioning and had never participated in a prior EBCC study. Once again, given that learning in the untrained ALC group was depressed to a similar extent to the KS group, the impairment in classical conditioning was thought to be related to a common factor between these groups - years of alcohol abuse, rather than factor(s) specific to the amnesic impairment in KS. As many of the participants in this trace conditioning study had received prior training in the delay conditioning paradigm (McGlinchey-Berroth et al. 1995), a

regression analysis was conducted to determine if acquisition in the delay task was predictive of performance in the trace task. Indeed, performance in delay conditioning was highly predictive of performance in trace conditioning; those participants who showed learning in the delay task also showed learning in the trace task, and those who did not learn in delay also did not learn in trace. There was some evidence of this in KS as well: two of the six KS patients showed clear evidence of learning (although only one achieved learning within a normal range).

In conclusion, the KS patients were significantly impaired on both delay and trace eyeblink conditioning as a group. However, there is a great deal of heterogeneity in these patients that suggests that learning is possible in both. As such, it must be concluded that procedural memory as assessed with EBCC is impaired and, indeed, often eliminated in KS. However, the impairment may more likely be due to alcohol-related structural damage to the cerebellum as opposed to KS-related damage to the diencephalon (McGlinchey et al. 2005).

Motor Skill Learning

Cermak et al. (1973) were the first to conduct a systematic examination of motor learning in KS. They reasoned that KS patients' ability to acquire a motor skill task would depend on the amount of verbal mediation that was required for the task, as it had been demonstrated that KS patients were severely impaired in the retention of verbal compared to non-verbal materials. Toward this end, they tested nine KS patients and nine control participants on a finger maze (verbally mediated) and pursuit rotor (non-verbally mediated) task. For the pursuit rotor task, participants had to learn to maintain contact between a stylus and a small metallic disc on a turntable. There were eight trials per day, four with each hand, for 5 days. For the finger maze, the participant extended the index finger of the preferred hand through a block cloth (that blocked the view of the maze) and was instructed to find the correct pathway beginning at the bottom of the maze to the top. In one version of the task, there were four choice points (left or right), and in a second version there were six choice points. Training on the task continued to a criterion of two consecutive errorless trials or until 60 trials (20 per day) had elapsed. Consistent with their predictions, the KS patients showed normal acquisition of the pursuit rotor task but were impaired on the finger maze task. Cermak and colleagues concluded that this pattern of performance was consistent with their overall hypothesis that "failures in verbal encoding processes underlie the Korsakoff patient's amnesic syndrome" (page 261). Later investigations confirmed that KS patients display a normal rate of learning on pursuit rotor tasks (see Fig. 2; Brooks and Baddeley 1976; Heindel et al. 1988; McEntee et al. 1987) supporting Cermak's initial claim of intact procedural memory in KS on non-verbally mediated tasks.

More recently, Van Tilborg and colleagues investigated whether the observed impairment in explicit contextual processing in KS (e.g., Postma et al. 2008) extends into the realm of implicit motor learning (Van Tilborg et al. 2011). Two implicit motor learning tasks were used, a standard serial reaction time task (see also Nissen et al. 1989) and a pattern learning task which was based on the serial reaction time task but additionally required the manipulation of a hand-held stylus (Van Tilborg and Hulstijn 2010). The serial reaction time task required participants to press one of four buttons that corresponded to boxes displayed on a computer screen. The target was indicated by an asterisk, and participants pressed the corresponding key as quickly as possible. For the pattern learning task, participants viewed four circles and were instructed to move the cursor along a paper (fixed to a digitizer) toward the red target. Stimulus presentation for both tasks comprised 6 blocks of 100 trials each. In block one, stimuli were presented in pseudorandom order, but in blocks two through five they were presented in a fixed ten-trial sequence, followed by one more pseudo-randomized block. Although KS patients performed more slowly than controls in the serial reaction time task, they did show normal implicit acquisition, as revealed by an increase in

reaction time from the final block of the fixed trial sequences to the final pseudo-random block. Also, the error rate between groups did not differ. Similarly for the pattern learning task, both groups showed implicit learning based on timing measures. However, a measure of accuracy, the directional error rate, revealed impairment in the KS patients. Specifically, there was a significant increase in errors in the final pseudo-randomized block in the control group but not in the KS group, which was interpreted as superior learning in the controls. It was concluded that KS affects motor skill learning if the task has a strong spatial response component.

Cognitive Skill Learning

One task that has been used to assess cognitive skill learning is the mirror reading test. In a typical task, participants are asked to read novel and repeated mirror image words (or word triads). Testing usually entails multiple blocks of trials within a session and multiple sessions across longer delays (e.g., days). Reductions in reading time are the primary indicator that procedural learning has occurred. We are aware of three studies using mirror reading in KS, which together report data from 13 patients (Beaunieux et al. 1998; Cohen and Squire 1980; Martone et al. 1984). In a seminal paper examining a dissociation in implicit and explicit memory, Cohen and Squire (1980) asked participants to read mirror images of novel (nonrepeated) and repeated word triads across sessions on three consecutive days, as well as a fourth session 13 weeks later. The group of KS patients evinced similar reductions in reading time of novel mirror image word triads across the three daily sessions as the group of ALC (see Fig. 3). The KS patients also demonstrated retention of mirror reading 13 weeks later. KS patients also demonstrated reductions in reading time for repeated words across blocks and sessions; however, the magnitude of facilitation was smaller in KS relative to ALC. Thus, KS patients were able to acquire the cognitive skill of mirror reading, but were not able to benefit from stimulus repetition, which was attributed to impairments in explicit memory. A subsequent study replicated the finding of intact cognitive skill acquisition of mirror reading word triads (again, measuring performance across three days), as well as the attenuated effect of reduced reading time for repeated words in KS relative to controls (Martone et al. 1984). In the same study, they also demonstrated that the KS patients were severely impaired on measures of explicit memory (recognition memory). A more recent case study (Beaunieux et al. 1998) again demonstrated intact acquisition of mirror reading, although there was some indication of impairment in retention in the second session, which was delayed only 1.5 h (as opposed to the 24 h delays in the previous studies). Overall, the findings across the three studies of mirror reading are quite consistent, indicating intact cognitive skill learning in KS.

Another task used to assess cognitive skill learning is the Tower of Hanoi (or Tower of London) puzzle (see Fig. 4a). The tower consists of three vertical pegs of the same length arranged on a base. On the first peg, disks of decreasing diameter are stacked (number of disks depends on the task version). The goal of the puzzle is to move the disks from the first peg to another peg. The rules are that only one disk can be moved at a time, each move must involve moving the upper disk from one peg and putting it on another peg, and no disk can be place on top of a smaller disk. Although Tower of Hanoi was developed by mathematicians and computer scientists to demonstrate recursive reasoning and is often employed by neuropsychologists as a measure of executive functions, Anzai and Simon (1979) showed that when this test was repeated it recruited cognitive procedural memory because participants were unable to describe the strategies that they used to solve the task. As participants become more proficient in the task they are able to use more efficient strategies based on prior learning (e.g., the most effective approach involves using problem solving abilities to compute moves on a move-by-move basis without having to remember previous moves of puzzle configurations). Although there are some inconsistencies, MTL

amnesic patients are generally impaired in learning the Tower of Hanoi task (for review, see Xu and Corkin 2001), most likely due to deficits in explicit memory that appear necessary for successful task completion using recursive strategy. Patients with frontal, basal ganglia, and striatal lesions also show deficits, but impairments are more likely due to deficits in planning and problem solving skills (Xu and Corkin 2001).

Not surprisingly given the combined explicit memory and executive functions demands of this complex problem solving task, KS patients are impaired in the standard administration (5 disc version) of the Tower of Hanoi (Butters et al. 1985). However, Butters and colleagues hypothesized that their impairment was not in the acquisition of the procedural skills per se, but rather in deficits of initiation and planning secondary to executive dysfunction. They noted that despite their overall impairment, KS patients demonstrated improved performance across administration of the test, suggesting some preservation of procedural skills. Butters and colleagues called into question the validity of the Tower of Hanoi task as a test for cognitive procedural memory in KS, emphasizing the difficulty of isolating the cognitive procedural memory piece, as the test involves the use of multiple cognitive processes in addition to procedural abilities (e.g., identification, sequencing, and retention of moves).

More recently, the standard test administration of the tower task has been manipulated by reducing the number of trials per session in an attempt to prohibit normal control participants from recruiting explicit memory for successful learning (Beaunieux et al. 1998). This necessarily restricted the study to the early phase of the learning, but reduced the occurrence of the verbalization of strategies by the healthy participants. In Beaunieux et al., a group of healthy participants was compared to a single KS patient. The KS patient did not differ from the control group in either time or moves under these conditions. The findings suggest that cognitive procedural memory can be preserved in a KS patient using an adapted version of the Tower of Hanoi that limits reliance on explicit memory.

Similarly, Joyce and Robbins (1991) examined a large group of KS patients and matched alcoholic and nonalcoholic control participants on a modified computer version of the Tower of Hanoi. Although KS patients were able to solve as many problems as controls, they were less accurate according to two measures: minimum move solutions and excess moves (see Fig. 4b). The alcoholic control group was only less efficient according to the excess moves measure at the most difficult level of the problem. By also assessing targeted neuropsychological performance differences between the groups, the authors concluded that the KS deficit in the Tower of London task was not due to impairments in visuospatial skill or memory but, more likely, to planning ability. Thus similar to the studies by Butters et al. and Beaunieux et al., KS deficits on this computerized Tower of Hanoi task appear to be related to other necessary cognitive abilities (e.g., executive functions such as planning) underlying task performance rather than to procedural memory deficits, per se.

Charness et al. (1988) examined the ability of a KS patient to learn to mentally square two-digit numbers. This was a single case report of a 64-year old male with 12 years of education who had been employed as a salesman prior to becoming disabled due to chronic alcoholism and subsequent development of KS. The study took place over the course of seven sessions in which G.P. was systematically exposed to training on a seven-step algorithm for mentally squaring two-digit numbers (see Table 2). Remarkably, G.P. acquired this skill at a rate comparable to a group of 16 healthy adults, despite his complete inability to describe the steps of the algorithm and his insistence throughout the learning sessions that he had never previously encountered the technique. G.P. did not show improvement on specific problems, whereas the control did perform better on old versus new problems. He also failed to show an advantage for specific practiced items compared to unpracticed items.

The authors concluded that G.P.'s learning was attributable to change in the overall compilation of the seven steps, as opposed to improvement within the steps themselves (a dissociation that was observed in two amnesic patients due to an anterior communicating artery aneurysm (Milberg et al. 1988)).

Korsakoff's Syndrome and Priming

Priming, another category of implicit or nondeclarative memory, refers to indirect measures of memory in which the subject is typically not asked to intentionally retrieve the contents of a specific prior learning event. Rather, memory is indicated by a change in performance in response to a previous experience with the same or a related stimulus. For instance, one might identify a picture of a basketball more quickly after previously seeing that same picture (perceptual priming). Alternatively, one might identify the word "basketball" more quickly after seeing the word "sports" (semantic priming). In these examples, fluency (facilitated processing) is indicated by reductions in response latency for saying the word or making a word/nonword classification (Whittlesea and Leboe 2003). Below we provide brief descriptions of different priming paradigms implemented in studies of KS, as well as a description of the results from studies with KS patients (Table 3).

Lexical Decision

To clarify contributions of semantic information and influence of specific episodes of learning (and retention intervals) on implicit memory,Verfaellie et al. (1991) presented real words and pseudowords to KS patients and ALC. Target stimuli were repeated at various lags ranging from 6.5 s (lag 0: no intervening items) to 104 s (lag 15: 15 intervening items). Participants made word/nonword judgments and verbal response latencies to these judgments were recorded. The results indicated that KS patients showed equivalent priming for real words at all lags except lag 0, indicating that repetition priming was intact in KS even at longer intervals. In contrast, KS patients showed no evidence of priming for pseudowords. ALC demonstrated repetition priming for pseudowords, albeit at only the shorter delays (lags of 0 and 1). In a follow-up experiment (Experiment 2), the procedures were replicated although stimuli consisted of high and low frequency words, half of which were transformed into pseudowords as in Experiment 1. The results from Experiment 2 were consistent with Experiment 1, as no difference in repetition priming of real words was observed for KS and ALC. In contrast, KS patients failed to show priming effects for pseudowords, whereas ALC exhibited reductions in response time for pseudowords (with these effects occurring at the shorter lags). In Experiment 2, both groups showed faster response latencies for high relative to low frequency words and greater repetition priming effects for low relative to high frequency words (although responses for high frequency words were still faster than low frequency at the second presentation). Findings of repetition priming for real words at longer lags, as well as the observation of the frequency attenuation effect (smaller priming effects for high frequency words), provide evidence that KS patients are able to retain information from a single learning episode. Using a continuous recognition paradigm, the authors subsequently demonstrated that explicit memory was severely impaired in KS patients at all lags except lag 0. Thus, the influence of "episodic" memory on an implicit memory task was unlikely due to explicit retrieval processes.

Lexical decision tasks have also been used to examine the impact of semantic relations on priming (Verfaellie et al. 1990). In Experiment 3 reported byVerfaellie et al. (1990), related, unrelated, and neutral word pairs were presented to participants (as well as nonwords). The stimulus presentation rate used in this study was fast, as shorter delays in presentation rate are considered to increase reliance on automatic processes as opposed to strategic or controlled processes that may impact priming. Thus, the prime was presented for 150 ms, followed by 100 ms of a blank screen, and then the target was presented for 2 s, with the

subject making a lexical decision in response to the target. KS patients exhibited similar associative word priming as ALC (see Fig. 5a). That is, both groups responded faster to related prime-target pairs than unrelated and neutral pairs. In fact, KS patients showed some evidence of greater facilitation than ALC, but this difference was not statistically significant. The primary conclusion drawn from this experiment was that the organization of semantic memory is intact in KS, at least when interrogated with a task that does not require controlled processing (i.e., a semantic task such as category fluency being on the opposite end of the spectrum in terms of requiring controlled processes relative to the automatic processes associated with the lexical decision task in the current experiment).

Additional work using lexical decision tasks have been used to further examine the integrity of semantic memory in KS, as well as the influence of semantic information in priming. Glass and Butters (1985) reported two experiments in which category primes were used to examine the impact on lexical decision of category exemplars. In their first experiment, they used primes that had no pre-existing relationship to typical semantic categories. Thus, in Experiment 1 (referred to as the control task) the non-semantic category prime was a string of x's, while neutral category prime was a string of o's. Participants were informed that 75 % of the time that the x's appear, the item that follows will be from a particular category (body parts). Neutral primes consisted of the presentation of a series of o's, followed by presentation of target item (word/nonword). Thus, there were three prime conditions: expected (xxx-hand), unexpected (xxx-robin), and neutral (ooo-roof), with participants making a lexical decision about item presented after the cue. Experiment 2 (experimental task) replicated Experiment 1, although this time the xxx prime was replaced with the name of a real category (e.g., furniture), and participants were told that 75 % of the time that they saw the word "furniture," the item that follows would be from a particular category (body parts). Unknown to the participants, sometimes the item that followed the category cue was in fact related to the category (e.g., chair). Thus, there were three conditions: expected-unrelated (furniture-hand), unexpected-related (furniture-chair), and neutral (ooo-roof). The results revealed KS patients were able to use the 'xxx' priming cues normally and effectively in the control task (Experiment 1), as faster responses were observed for the expected relative to the neutral condition. Furthermore, there was no group difference in response latencies for KS, ALC, and NCs. In Experiment 2, when real category names were used as primes, the KS patients were the only group that did not show response facilitation for the expected relative to the neutral condition (see Fig. 5b). This group difference was hypothesized to reflect KS patients' inability to inhibit semantic associations of the category prime (BIRD) to facilitate responses to probes of a different category (BODY PARTS).

The discrepancy in findings of intact (Verfaellie et al. 1990) and impaired (Glass and Butters 1985) semantic priming in lexical decision tasks warrants a brief discussion. This discrepancy is likely due to differences in reliance on automatic versus controlled processes alluded to previously. By decreasing the delay duration between prime and target,Verfaellie et al. (1990) intentionally designed their task to rely more heavily on automatic processes and reduce the likelihood of control processes contributing to task performance. Conversely, the paradigm used by Glass and Butters (1985), which uses a semantic category to cue the likelihood of an exemplar from a different category, was implemented for the opposite reason: to specifically examine control processes. Therefore, Glass & Butters used a longer delay between target and prime (750 ms) to examine control processes in priming, in this case, inhibiting the automatic generation of high dominance category exemplars.

The dearth of studies using lexical decision tasks in KS provides little insight to the consistency of the effects reported above. Nevertheless, the studies using lexical decision in KS demonstrate that: 1) Repetition priming for real words is intact in KS at temporal delays that fall within the domain of long term memory. Furthermore, KS patients show similar

word frequency effects in repetition priming as controls for real words; 2) KS patients demonstrate impaired repetition priming in the context of lexical decision when nonwords are used; 3) Semantic priming is intact in KS when short delays between prime and target (increasing reliance on automatic processing) are used; 4) KS patients exhibit impairments in semantic priming when the task is more likely to rely on control processes (i.e., inhibition of semantic associates as in Glass and Butters 1985).

Word Identification

Cermak and colleagues reported a series of experiments examining the impact of prior representations (semantic memory) on word identification in KS. In their first report Cermak et al. (1985), participants read words in the study phase. Next, participants completed the word identification task, in which the item was presented for 35 ms and then increased in 10 ms durations until subject correctly identified the word. Finally, participants completed an old/new recognition test. KS patients attended two sessions in which test order was varied to manipulate study-test delay between tasks: study, identification, recognition and study, recognition, identification. The KS group demonstrated intact priming (shorter presentation duration needed to identify studied relative to new words) for words during both immediate and delayed testing, with no difference in priming observed between the two sessions. Furthermore, priming effects for real words were of equivalent magnitude for those seen in the ALC group. Recognition memory was intact in KS patients for the immediate condition but impaired for the delay, with KS recognition memory performance decaying more rapidly than ALC across delay. In Experiment 2, the primary goal was to ascertain whether priming was intact for stimuli in which pre-existing representations do not exist (i.e., pseudowords). The design was the same as Experiment 1, although pseudowords (instead of real words) were used and there was only one task order: study, identification, and recognition. The results indicated that KS patients were impaired on identification of pseudowords relative to ALC. That is, whereas ALC demonstrated substantial reductions in presentation duration needed to identify pseudowords, KS patients showed minimal priming. The authors concluded that for priming to occur in KS, “the item of information must represent a previously learned bit of information” (pg. 621), such as words. In contrast, KS patients will not show response facilitation for items involving novel information, such as pseudowords, which are not represented in semantic memory. Thus, a primary process associated with word identification priming is the activation of old information (semantic memory).

In a follow-up series of studies,Cermak et al. (1991) attempted to more directly support their previous conclusions by examining word identification of real words, pseudowords, and pseudohomonyms. Noting that pseudowords differ from real words because they lack representation in semantic memory, as well as have an unfamiliar orthography and phonology, they reasoned that pseudohomonyms, such as “phaire” have phonological representations that may indirectly access semantic meaning, despite a lack of existing orthographic representation. Thus, support for the notion of semantic activation supporting word identification priming would be provided if pseudohomonyms elicited priming in KS patients (as pseudohomonyms should provide indirect access to semantic meaning).

In Experiment 1, real words, pseudowords, and pseudohomonyms were presented to participants in separate lists, with the participants asked to say each item aloud (Cermak et al. 1991). Priming was assessed by presenting items at minimal presentation duration and asking the subject to identify the item, again by verbal report. Presentation duration was increased at 10 ms intervals until the subject was able to correctly identify the item. The identification phase was followed by a test of explicit memory (old/new recognition). The results indicated that similar levels of priming occurred in KS and ALC for real words and pseudohomonyms. KS exhibited some priming for pseudowords, but substantially less than ALC. These data were further supported by re-analysis (that controlled for baseline

differences in overall ability to identify stimuli) of previous data reported (Cermak et al. 1985), which also indicated minimal, but statistically significant levels of priming for pseudowords in KS. Importantly, the pattern of results observed in the current study, intact priming for pseudohomonyms but impaired priming for pseudowords in KS, led the authors to conclude word identification priming was supported by semantic activation. If familiar orthography was supporting priming, then no difference should have been seen between pseudowords and pseudohomonyms. Recognition memory was severely impaired in KS in all conditions and demonstrated a similar pattern as that observed in the identification task, in that recognition was worse for pseudowords relative to real words (with pseudohomonyms falling between the two, but not different from either).

Experiment 2 reported byCermak et al. (1991) used a similar design as Experiment 1, although a mixed list design was used. Each list contained 2 of the 3 experimental conditions (e.g., real words and pseudowords). When real words and pseudohomonyms were presented in the same list, KS patients exhibited priming of equal magnitude for both conditions, while ALC controls did not exhibit priming to real words. When pseudohomonyms and pseudowords were presented in the same list, priming effects were larger in ALC than KS, regardless of stimulus type. Priming was greater for pseudowords relative to pseudohomonyms. Furthermore, in KS patients, significant priming was observed for pseudowords, but not for pseudohomonyms (in contrast to Experiment 1). When real words and pseudowords were presented in the same list, KS and ALC exhibited equivalent priming for real words, whereas ALC showed greater priming for pseudowords than KS (and ALC showed greater priming for pseudowords relative to words). As in Experiment 1, recognition memory was severely impaired in KS relative to ALC for all test lists.

To summarize, KS patients exhibited similar levels of priming in word identification tasks when real words were used as stimuli. In contrast, priming was impaired in KS when pseudowords, which do not have prior representations in semantic memory, were used. Priming results using pseudohomonyms, believed to provide indirect access to semantic meaning, were less consistent. In KS, priming for pseudohomonyms was intact when lists were not mixed across stimulus types, suggesting word identification priming may be mediated by activation of items stored in semantic memory. However, priming for pseudohomonyms, when mixed with other stimulus types, was impaired in KS.Cermak et al. (1991) suggested that when pseudohomonyms are mixed with pseudowords, “familiar auditory word form may have been concealed by unfamiliar orthography of all stimuli on the list. Consequently, pseudohomonyms may have lost their semantic saliency and simply looked like pseudowords.” Recognition memory for all stimulus types, regardless of list format, was impaired, with the exception of Experiment 1 reported byCermak et al. (1985) when recognition immediately followed study.

Picture Identification

In a seminal study of perceptual priming, fragmented line drawings of animals and objects (and words) were presented over 5 trials that varied from the most fragmented version to complete rendering (see Fig. 6a; Warrington and Weiskrantz 1968). Testing was repeated across three consecutive days, and learning was assessed by comparing performance across days one, two, and three. Although group results were reported for amnesic patients of mixed etiology, five of the six amnesic patients were KS, suggesting the results are representative of KS. Control participants had peripheral nerve lesions but no known cerebral disease. Although performance was impaired relative to controls, KS patients exhibited evidence of learning and retention of both fragmented pictures and words over delays of 24 and 48 h (see Fig. 6b). This was one of the first studies demonstrating retention of newly learned materials in amnesia (albeit impaired relative to controls). To examine whether these expertise would generalize, participants were tested with a novel set of

stimuli. However, there was no evidence of any transfer effects, even within stimulus type. Anecdotally, the authors reported that the patients exhibited striking impairment on traditional recall and recognition test of words used in the word-fragment task, although no data were reported.

Subsequently, the relationship between perceptual priming and episodic memory was directly assessed in KS (Cermak et al. 1993). During the study phase, participants were presented "noisy" line drawings and made button presses to clarify the picture (each button press increased the signal to noise ratio). Participants were instructed to provide a "hypothesis" for their answer as early as possible. If correct, the picture was fully "clarified" and presented for seven seconds to study. If incorrect, participants continued to press a button for further clarification of image. At test, priming was assessed by repeating the same study procedures with identical stimuli, similar stimuli with the same name, or new stimuli. At the end of each trial, the complete version of the stimulus was presented, and participants judged whether the stimulus was identical, similar, or different to items previously presented (episodic memory task). In addition to KS, there were two control groups, one tested in the same manner as KS, and another with the test occurring after a 1-week delay. The results indicated that during the study phase, there were no group differences in number of button presses to identify the object, suggesting visuo-perceptual abilities were equivalent among groups during encoding. At test, KS patients and the ALC delay group were impaired relative to ALC in the object identification task. KS patients exhibited priming for identical pictures relative to new, but not for the same-name condition (similar picture, same name). In contrast, both ALC groups required the fewest key presses for the identical condition, followed by similar, and then different pictures. Similarly, recognition memory was impaired (although unexpectedly above chance levels) in KS relative to both the ALC immediate and 1-week delay groups. Examination of the recognition errors revealed that KS patients frequently classified same-name stimuli as different, whereas the ALC immediate group was more likely to classify same name stimuli as identical. The results led the authors to conclude that in healthy adults, a specific perceptual record based on the study episode, as well as a generic version (priming of semantic information), exists, as priming of semantic information may have lead to attribution of same-name items as identical rather than different. In contrast, KS may rely primarily on the specific perceptual trace encoded during study, as KS patients tended to classify the same name stimuli as new (rather than classifying same name stimuli as identical based on semantic priming influences).

Additional work has revealed differences in priming effects in KS patients based on the study paradigm. In the most comprehensive study of picture identification in amnesia to date, Verfaellie and colleagues presented a series of experiments in which complete and fragmented pictures were presented to both KS and non-KS amnesics (Verfaellie et al. 1996). Experiment 1 examined repetition priming using complete pictures, with priming indicated by reductions in latency of picture naming. KS patients exhibited reduced response latency to previously presented pictures, and no difference in the magnitude of priming relative to ALC was observed. Intact priming was also observed in non-KS amnesics. Experiment 2 used a fragmented pictures procedure similar to those previously described. The results indicated that KS showed evidence of priming, identifying old pictures at a more fragmented level relative to new pictures; however, in this case, priming was reduced relative to ALC. Non-KS amnesics exhibited reduced priming with fragmented pictures. The authors noted the possibility that in addition to perceptual processes underlying subsequent facilitation of picture identification, conceptual processes may also contribute to picture priming. That is, naming the picture during study may activate semantic representations, in addition to the perceptual representation, and therefore naming the item may facilitate performance. Alternatively, repeated presentation of more complete versions of the stimulus may allow for contributions of explicit memory to task performance. Thus, the impairment

in priming could be attributed to deficits in explicit memory in patients. To examine this issue, in Experiment 3 complete line drawings were presented during the initial study phase. At test, fragmented line drawings were presented. As in Experiment 2, KS patients required more complete versions of line drawings for identification. KS did show enhanced identification for old relative to new pictures; however, magnitude of priming in KS was impaired relative to ALC. Unlike KS, non-KS amnesics showed no differences in priming relative to their control group. In Experiment 4, participants completed an old/new recognition memory task, and both amnesic groups were equally impaired. Thus, the difference in priming in Experiment 3 was not attributable to differences in explicit memory performance. The authors conclude that in KS, there may be some impairment in perceptual processes that mediate picture completion. The difference in performance in non-KS amnesics across Experiments 2 and 3 was not attributed to fluency associated with picture names themselves supporting object identification, because picture names were available in both experiments. Rather, normal individuals rely on explicit memory for the name-picture link to further facilitate picture identification.

More recent work has supported the suggestion that deficits in picture fragment completion may be related to impaired visuoperceptual processing in KS (Fama et al. 2006). Using a standard fragmented pictures paradigm, KS patients were tested at delays of 1 h and 1 day. In this case, the authors use number of errors per trial (with trial representing the list of stimuli presented at a particular fragmentation level) for the dependent variable learning. For instance, in Trial 1, the most fragmented version of 20 pictures was presented. If a subject correctly identified 4 pictures, they would have an error score of 16 (20–4) on Trial 1. The results indicated that KS patients made more errors identifying fragmented pictures than both normal and alcoholic controls during the initial presentation, suggesting impairment in visuoperceptual ability for a picture fragment completion task. At the one hour test delay, KS exhibited a reduced number of errors relative to the initial study session, and no group differences in number of errors were observed when results were adjusted for initial visuospatial deficits. KS showed retention of learning over the 1 day delay, although KS patients made more errors than healthy adults at the longer delay. Performance of ALC fell between KS and healthy adults, but was not different from either group. Importantly, the authors were also able to examine transfer of learning because participants completed an additional study-test (1 h delay) session prior to the 1 day delay testing. Consistent with an initial report by Warrington and Weiskrantz (1968), transfer of learning (improved identification of a novel set of fragmented pictures) was not evident in KS (or 6 young control participants). Explicit memory was also examined, and as expected, KS were impaired relative to healthy adults and ALC on free recall of drawings at 1 h and 1 day delay.

To summarize, presence or absence of picture identification priming effects in KS is impacted by the particular paradigm used. Standard repetition priming paradigms using complete pictures at study and test indicate that priming in KS is intact and of a similar magnitude as controls. In contrast, KS patients exhibit impairments in picture identification priming relative to controls when a picture fragmentation approach is implemented at test (regardless of whether initial study was with complete or fragmented pictures). Non-KS amnesics do not show this same impairment in picture fragment completion, leading to the suggestion that impaired visuoperceptual abilities in KS may account for the observed impairment in picture identification priming. Recent work has suggested impairment in fragmented picture identification priming is eliminated (at least at shorter delays) if baseline differences in visuoperception are accounted for during the analysis. These priming effects occur in the face of striking impairments in explicit memory processes. KS patients can exhibit learning based on a single episode and retain this information over substantial delays, although learning appears to be stimulus specific. That is, data from picture

identification paradigms suggest that learning does not transfer to novel stimuli, even within the same stimulus type (Fama et al. 2006; Warrington and Weiskrantz 1968).

Word Stem Completion

Word stem completion is a task commonly used to examine dissociations in explicit and implicit memory. A primary attraction of the paradigm is that study and test stimuli can be exactly the same, with the distinction made between implicit and explicit memory based on whether participants are instructed to intentionally retrieve items from the study list. For implicit memory, priming is assessed by comparing proportion of stems completed with studied words to baseline (in which no "study" targets were presented prior to the stem completion task). In a seminal paper, a dissociation between implicit (stem completion) and explicit (cued recall) was demonstrated with a group of amnesics, including KS patients (see Fig. 7a; Graf et al. 1984). A subsequent study replicated the dissociation using word pairs in which the context was either the same or different at retrieval (e.g., study: winter—butter, and at test: winter—but ___ (same) or highway—but___ (different)) (Cermak et al. 1988), and further demonstrated that amnesics were unable to benefit from context (see Fig. 7b). Interestingly, both studies found that KS patients completed a higher portion of stems in the implicit memory condition relative to controls.

Cermak and colleagues subsequently published a series of experiments using a word stem completion task in association with the process dissociation procedure (Jacoby 1991) to elucidate the role of automatic and controlled processed in word stem completion. In their first paper (Cermak et al. 1992), a list of words was sequentially presented, and the participants generated a sentence for each word. In the Inclusion test condition, participants were asked to complete each stem with the first word that came to mind. In the exclusion condition, participants were asked to complete the stem with words NOT on the initial study list. Test lists contained both target (studied) and filler (new) stems. The results showed that KS completed stems more frequently with primed targets relative to ALC, regardless of test instructions. Furthermore, whereas ALC were able to reduce the proportion of stem completions with primed targets in the exclusion relative to the inclusion condition, consistent with task instructions, KS patients were not. The authors suggested that KS participants rely more heavily on automatic memory processes (fluency), rather than conscious recollection during word stem completion (KS patients were also severely impaired on an explicit recognition task administered after the stem completion task). However, KS patients were able to show some reduction in the proportion of primes generated in the exclusion condition, suggesting potential sparing of conscious recollection in KS.

To further investigate this issue, in Experiment 2 (Cermak et al. 1992) the study list was presented to participants five times (generating a sentence for each word at every exposure) in an attempt to increase conscious recollection in KS. As in Experiment 1, KS generated a larger proportion of studied targets relative to Controls in the word stem completion task. In contrast to Experiment 1, priming was equivalent in both groups during Inclusion (repetition enhanced priming of controls compared to Experiment 1). KS did exhibit a reduction in generation of studied words in the Exclusion relative to the Inclusion condition. However, priming effects were evident in the Exclusion condition and were much larger than those seen in ALC, consistent with the notion that amnesics were relying on response fluency and unable to oppose this fluency with controlled recollection of studied items. Recognition memory remained impaired in KS, despite 5 presentations during study.

In a related study, Cermak and colleagues again applied aspects of the process dissociation procedure, with an additional test condition ("direct" retrieval; see Richardson-Klavehn et al. 1994), in which participants were explicitly asked to complete word stems with items

from the study list (Cermak et al. 1997). The authors also included a levels-of-processing encoding manipulation, in which participants used a graphemic analysis (counting the number of "closed" letters in the word, e.g., A, B, D, P) for half of the words and semantic analysis (generate a semantic associate) for the other half. As in the previous report, KS used more studied words to complete stems in the inclusion and exclusion conditions. No group differences in proportion of studied items generated during stem completion in the direct condition. In addition, KS patients showed greater priming for semantic relative to graphemic analysis, even when instructed not to use studied items for stem completion (exclusion condition). A more recent study (Experiment 1; d'Ydewalle and Van Damme 2007) replicating this approach with a larger group of KS patients found a roughly similar pattern of results (see Fig. 7c). It is worth noting that d'Ydewalle and Van Damme (2007) report three additional experiments examining stem completion in KS, but the remaining Experiments focus on intentional retrieval of studied items during stem completion, and do not include an indirect or inclusion condition in which participants can complete the stems with the first word that comes to mind.

Taken together, these results demonstrate that performance of KS patients in word stem completion tasks is not restricted to perceptual processing, but is also significantly impacted by semantic processing during encoding. Furthermore, the available evidence supports the notion that KS patients rely solely on unconscious retention, in contrast to control participants who show evidence of both conscious and unconscious processes during word stem completion. That is, during the exclusion conditions, control participants are able to recollect (controlled retrieval) items presented at study and choose an alternative solution to the stem. In contrast, KS patients respond primarily on the basis of automatic retrieval, and due to recollection deficits, they are not able to identify that the source of familiarity is due to previous exposure during study. Finally, it is important to note that non-KS amnesics demonstrate a similar pattern of performance as that seen in KS. Indeed,Cermak et al. (1997) tested groups of KS and non-KS amnesics, but ultimately collapsed their analyses across groups because there was no difference in the pattern of performance between the two groups.

Conclusions

Our review of procedural learning and priming in KS presents a complicated pattern of results that undoubtedly reflects the complexity of the syndrome itself. Further complicating matters is the lack of "process pure" behavioral tasks (Dew and Cabeza 2011). A pattern that emerges for KS is that patients may exhibit intact implicit memory performance to the extent that the task minimizes contamination by other cognitive processes. For instance, KS patients show evidence of procedural learning on tower tasks, but obvious impairment when standard administration methods are implemented, which is attributable to impaired executive functions (planning) observed in KS. Moreover, pursuit rotor performance is relatively intact in KS, whereas finger maze performance is impaired, presumably due to additional verbal mediation strategies associated with performance on the finger maze. Similarly, performance is impaired on a simple serial reaction time task (SRTT), but impaired on a more complex version that requires additional spatial processing (PLT). For priming tasks, there are similar discrepancies in performance, again likely attributable to the fact that even the most basic tasks require multiple cognitive operations. For instance, KS patients exhibit intact performance when repetition priming procedures are used with intact pictures. In contrast, KS patients exhibit impairment when picture fragments are used at test, and in this case the deficit is attributed to impairments in visuoperceptual processing rather than priming per se. On semantic priming tasks, KS patients exhibit intact performance when the task design increases reliance on automatic processing, but impaired performance when task design allows for an influence of controlled processing.

It is worth noting that this pattern of impaired performance in KS on implicit memory tasks that may require some additional cognitive processing does not hold for all measures of implicit memory. For instance, KS patients exhibit frank impairments on delay EBCC, a task renowned for its successful implementation in both animals and humans and considered one of the most basic indicators of implicit memory. In contrast, performance on word identification tasks, which probed the integrity of semantic memory in KS have shown remarkably consistent priming for real words, suggesting that there is not a simple pattern of performance of KS patients on implicit memory tasks based on the complexity of the behavioral task.

Much of the idiosyncratic behavioral and cognitive deficits observed in the literature are likely due to the widespread pathology associated with years of chronic alcohol abuse and possible focal damage due to head injury from falls that are common in this group. For example, deficits in classical conditioning are most likely attributable to alcohol-related cerebellar damage, whereas some of the deficits observed with priming studies may be attributable to impairments in controlled versus automatic processing associated with frontal lobe pathology. Because of the profound amnesia associated with KS, any reliance on intentional episodic memory processes is likely to contribute to performance deficits, even for tasks that probe procedural (e.g., Tower of Hanoi) or implicit (e.g., word stem completion) memory. In addition to the more striking deficits in episodic memory, KS is accompanied by impairment in other cognitive domains (executive functions, visuospatial, and visuoperceptual abilities) that can have a significant impact on both procedural memory and priming.

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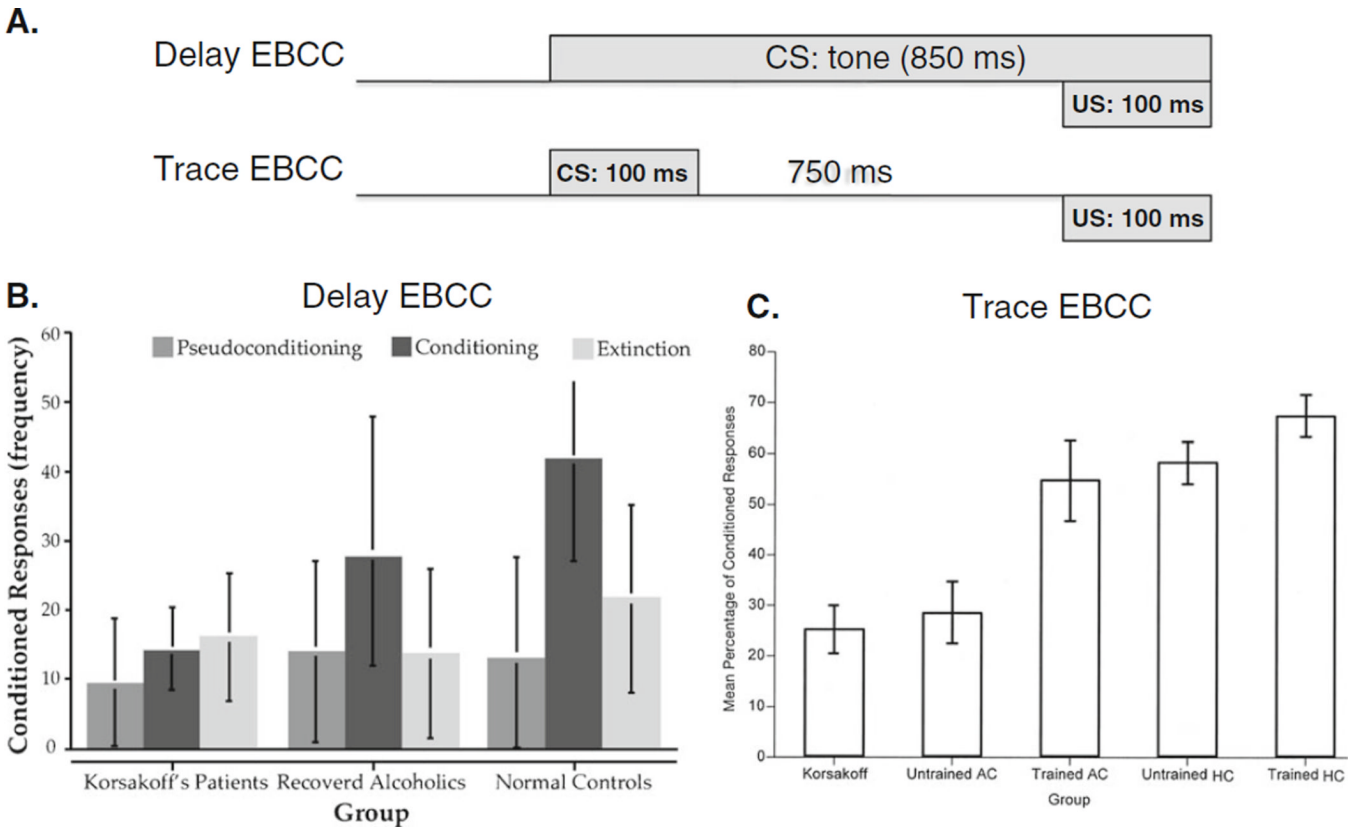

Fig. 1.

a. Example of temporal characteristics of delay and trace eyeblink classical conditioning (EBCC) paradigms. *CS*: conditioned stimulus (e.g., auditory tone), *US*: unconditioned stimulus (e.g., airpuff). **b.** Mean number of conditioned responses during pseudoconditioning, conditioning, and extinction in KS patients, recovered alcoholics and control participants in a delay EBCC paradigm. From "Impaired delay eyeblink conditioning in amnesic Korsakoff's patients and recovered alcoholics," by McGlinchey et al., 1995, Alcoholism: clinical and experimental research, 19, Fig. 1, p. 1129. Copyright 1995 by the research society on alcoholism. Adapted with permission. **c.** Mean percentage of conditioned responses acquired by each group. Korsakoff's patients and untrained AC participants acquired fewer conditioned responses than did all other groups. *AC*=abstinent alcoholic; *HC*=healthy control. *Error bars* represent standard error of the mean. From "Trace eyeblink conditioning in abstinent alcoholic individuals: effects of complex task demands and prior conditioning," by McGlinchey et al. 2005, Neuropsychology 19, Fig. 1, p. 164. Adapted with permission

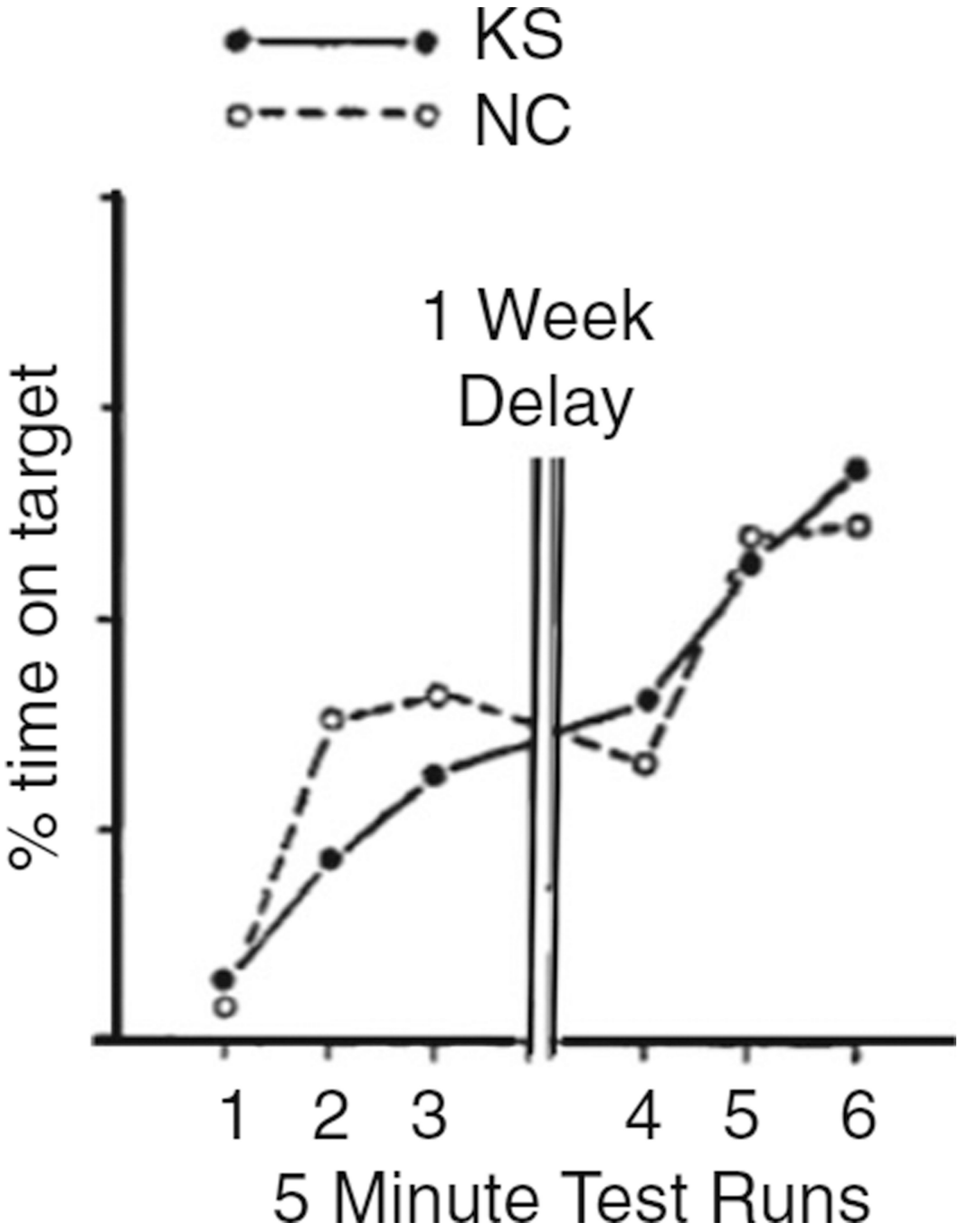

Fig. 2.

KS patients demonstrate normal performance on pursuit rotor, as time on target increases over the testing sessions with gains retained over a 1 week delay. NC=normal control participants. From “What can amnesic patients learn?” by Brooks and Baddeley 1976, Neuropsychologia 14, Fig. 7, p 119. Adapted with permission

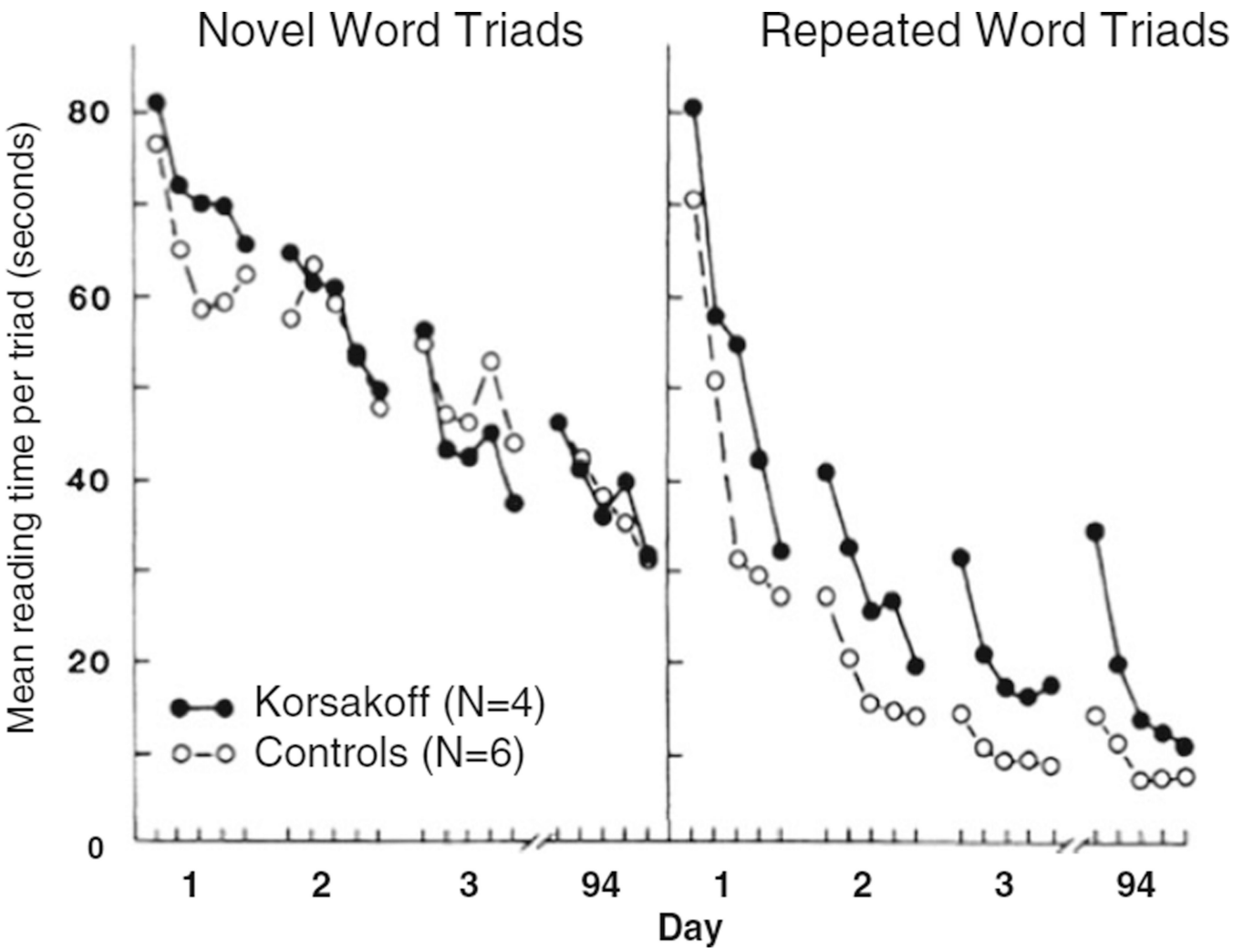

Fig. 3.

Performance of KS patients and controls on mirror reading of novel and repeated word triads across three daily sessions and retention three months later. From “Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that,” by Cohen and Squire 1980, Science, 210, Fig. 2, p. 208. Adapted with permission

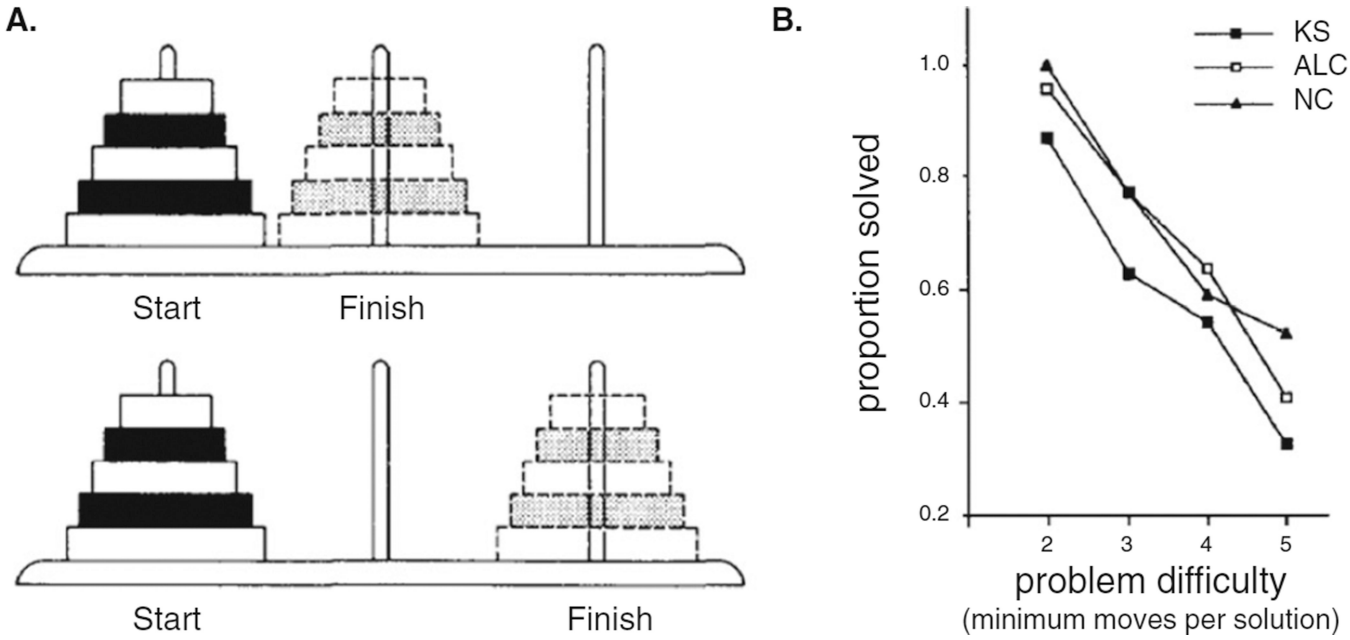

Fig. 4.

a Illustration of the Tower of Hanoi puzzle showing starting position of 5 layers (*blocks*) on peg 1 (*solid lines*) and two possible solutions (*dotted lines*), with either peg 2 (*top*) or peg 3 (*bottom*) as the end (i.e. goal) peg. From "Memory disorders associated with huntington's disease: verbal recall, verbal recognition and procedural memory," by Butters et al. 1985, Neuropsychologia 23, Fig. 4, p. 738. **b.** Proportion of moves solved (group means) in the minimum amount of moves during the tower of London task at each level of difficulty. From "Frontal-lobe function in Korsakoff and non-Korsakoff alcoholics— planning and spatial working memory," by Joyce and Robbins 1991, *Neuropsychologia* **29**, Fig. 3, p. 717. Adapted with permission

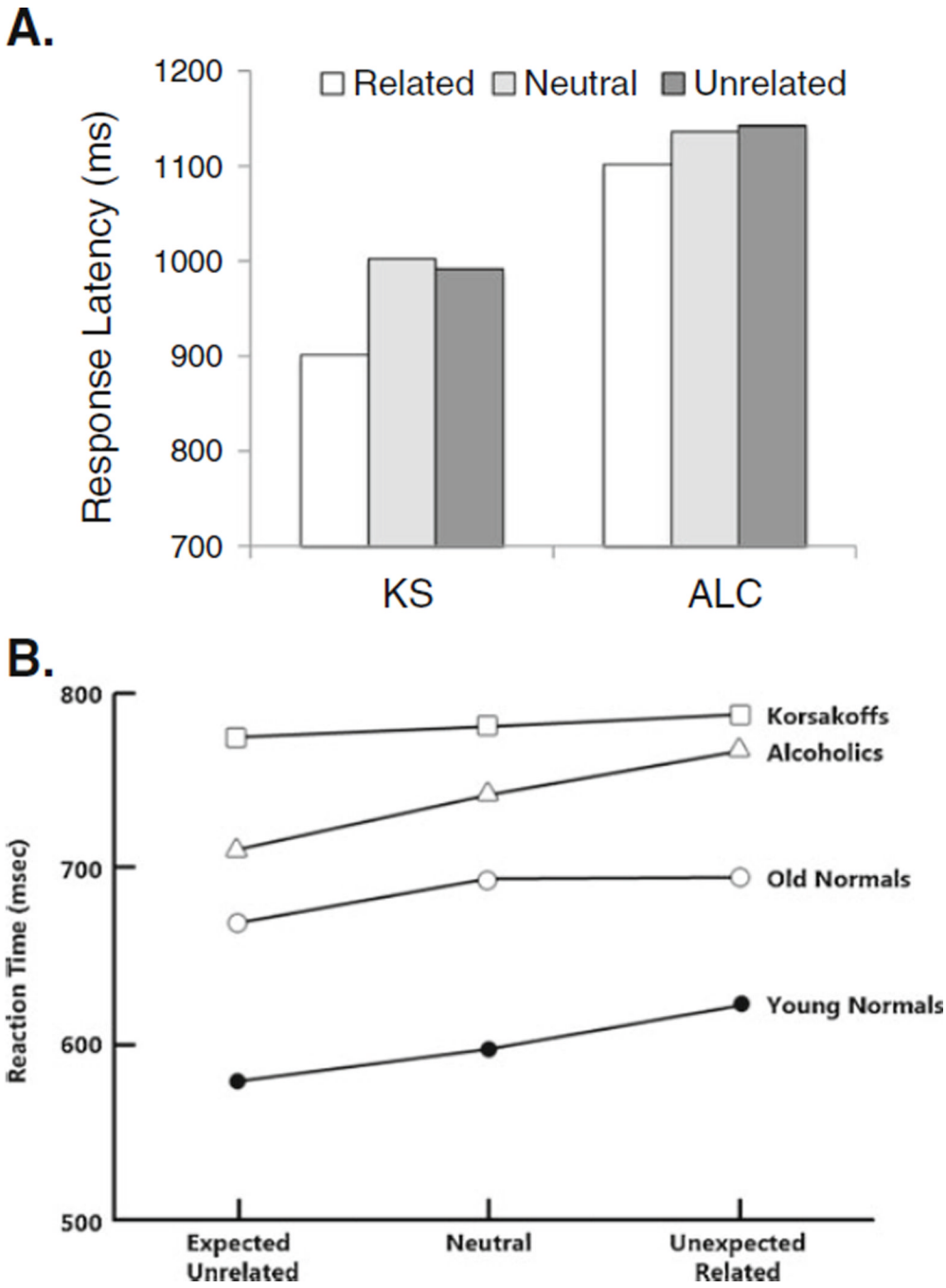

Fig. 5.

a. Response latencies in KS patients and alcoholic controls (ALC) during a lexical decision task for semantically related, unrelated, or neutral word pairs. KS patients exhibited intact semantic priming for related words. From "Strategic and automatic priming of semantic memory in alcoholic Korsakoff patients," by Verfaellie et al. 1990, *Brain and Cognition*, *13*, p. 188. Figure created from data presented in Table 6 of Verfaellie et al. 1990. **b.** Response latencies in KS patients and controls groups for a priming task that required the inhibition of semantic associates. KS patients were the only group that failed to show response facilitation for the expected trial condition. From "The effect of associations and

expectations on lexical decision making in normals, alcoholics, and alcoholic Korsakoff patients," by Glass and Butters 1985, *Brain & Cognition*, 4, p. 472. Adapted with permission

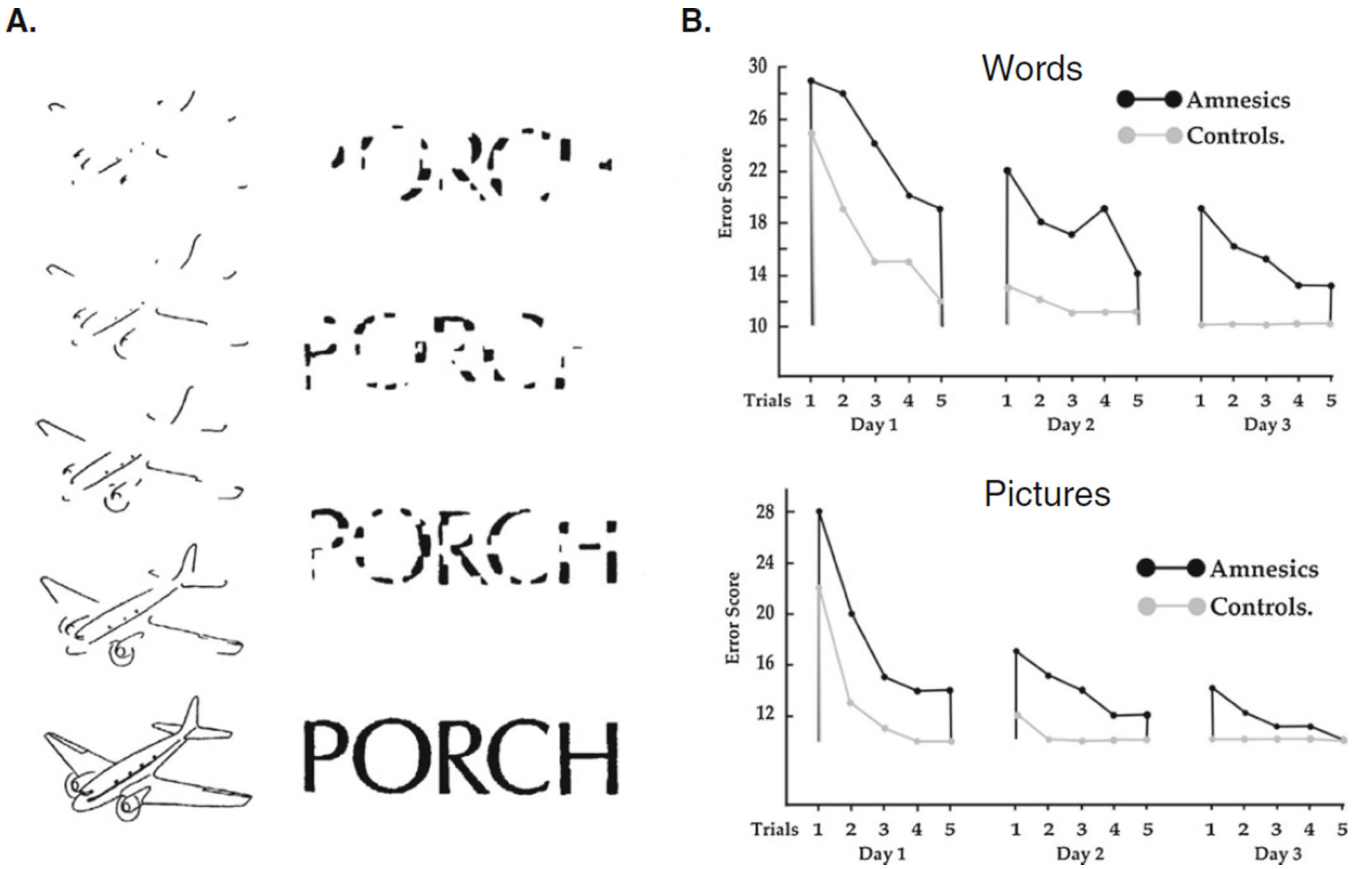

Fig. 6.

a. Examples of various fragmentation levels of objects (e.g., Gollin 1960) and words commonly employed in priming paradigms. **b.** The mean number of errors for each trial by block and day for amnesics (5 KS patients and 1 MTL amnesia) and controls in a word identification task and picture identification task. From “New method of testing long-term retention with special reference to amnesic patients,” by Warrington and Weiskrantz 1968, Nature, 217, Fig. 1, p. 972. 1968 nature publishing group. Adapted with permission

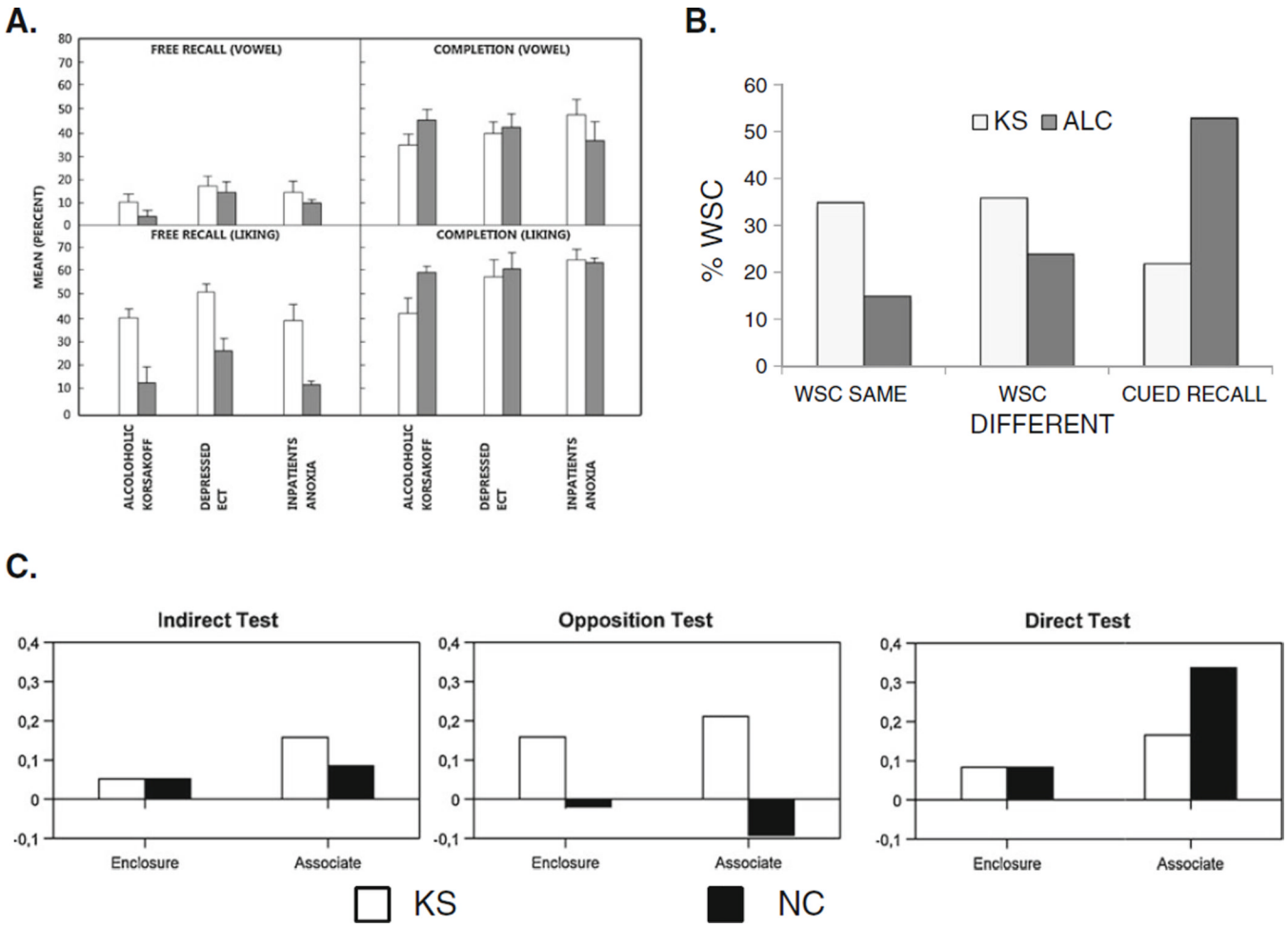

Fig. 7.

a. Free recall and word stem completion performance (WSC) in KS patients and ALC. From "The information that amnesic patients do not forget," by Graf et al. 1984, Journal of Experimental Psychology: Learning, Memory, & Cognition, 10, Fig. 1, p. 169. **b.** WSC performance in KS and ALC when study context (word paired with target) is the same or different. From "Deficits in the implicit retention of new associations by alcoholic Korsakoff patients," by Cermak et al. 1988, Brain & Cognition, 7, 312–23. Figure created from data presented in Table 1, p. 316. **c.** Proportion of correct word stem completions in KS and normal controls (NC) as a function of encoding task and test format. From "Memory and the Korsakoff syndrome: not remembering what is remembered," by d'Ydewalle, G. and I. Van Damme 2007, Neuropsychologia, 45, Fig. 1, p. 909. Adapted with permission

Table 1

Summary of procedural memory studies with Korsakoff's syndrome patients

Task	Authors	Year	KS (# females)	KS age (years)	ALC (n)	NC (n)	Brief summary of study results
Delay EBCC	Weiskrantz and Warrington	1979	1	50	0	0	KS subject A.S. acquires conditioning, retained at intervals of 10 min and 24 h. Eyeblink monitored off-line w/ video. No control group to compare acquisition and extinction of CR.
Delay EBCC	McGlinchey et al.	1995	4	65 (5.5)	10	10	KS: no evidence of acquisition or extinction of conditioned response relative to pseudoconditioning. KS impaired relative to normal controls. No difference w/ ALC, although ALC were able to acquire conditioning and show extinction.
Trace EBCC	McGlinchey et al.	2005	6	62 (3.61)	12	12	KS patients were significantly impaired as compared to nonalcoholic controls. Learning in the untrained abstinent alcoholic group was depressed to a similar extent to the KS group.
Pursuit rotor	Brooks and Baddeley	1976	3	35.4 (17–49)	0	5	There were no differences between either group of amnesics (MTL or KS) and their respective controls. Learning curves were presented for KS separately and display a normal rate of learning.
Pursuit rotor	Cermak et al.	1973	9	53	9	9	All three groups showed equivalent improvement (KS=ALC=NC).
Pursuit rotor	Heindel et al.	1988	2	59.5 (6.5)	0	10	There were no differences between the group of amnesics (KS, MTL, PCA) and the controls.
Pursuit rotor	McEntee et al.	1987	8	57.9	0	0	There was a significant increase in mean time on target across the three test days indicating the KS patients were capable of learning the task over time.
Maze task	Cermak et al.	1973	9	53	9	9	KS patients show normal acquisition on a non-verbal motor task (pursuit rotor), but when there is some verbal mediation required, they do significantly worse than matched controls.
Maze task	Nissen et al.	1989	7 (1)	60.4 (38–73)	8	7	KS impaired relative to ALC and NC on both versions of maze that was administered. KS patients were able to show some improvement, but only in the first third of trials administered.
Bimanual motor skill	Swinnen et al.	2005	11 (1)	50 (5.1)	0	11	KS patients exhibit impaired acquisition and retention. There was an absence of retention for the nonaugmented conditions for KS patients, but during the feedback condition, KS performance levels were close to those obtained on the second practice day, indicative of some learning.
Serial reaction time	Nissen and Bullemer	1987	6 (1)	65.2 (58–72)	0	8	KS were slower than controls, but the pattern of response times were the same in both groups. KS patients responded less accurately than controls, especially in the first block of each condition.
Serial reaction time	Nissen et al.	1989	7 (1)	60.4 (38–73)	8	7	KS group was significantly slower than ALC and NC, but no group differences in accuracy. All three groups showed significant effects of session and a similar pattern of performance.
Serial reaction time	Van Tilborg et al.	2011	20 (4)	52.90 (7.8)	0	14	KS patients showed significantly slower reaction times than controls, but both groups showed implicit learning of the fixed sequence. The percentage of errors was not significantly different between the two groups.
Pattern learning task	Van Tilborg et al.	2011	20 (4)	52.9 (7.8)	0	14	Learning was significantly worse in KS patients, attributed to spatial nature of task.

Task	Authors	Year	KS (# females)	KS age (years)	ALC (n)	NC (n)	Brief summary of study results
Mirror reading	Beaunieux et al.	1998	1	47	1	10	KS patient learned in both sessions, but retained less than controls.
Mirror reading	Cohen and Squire	1980	4	51	6		KS show similar rate of skill acquisition as controls. KS also demonstrated retention of skill learning 13 weeks later. KS show reduced learning of repeated words relative to controls.
Mirror reading	Martone et al.	1984	8	57.9 (9.5)	0	10	KS show similar rate of skill acquisition as controls as evidenced by similar reductions in reading time of novel mirror image word triads across 3 daily sessions, but reduced facilitation in reading time for repeated words.
Visual hyperacuity	Fahle and Daum	2002	4	63.8 (5.9)		6	KS patients can improve visual hyperacuity with training and improvements are sustainable for at least 1 week.
Tower of Hanoi	Butters et al.	1985	5	53 (9.2)	0	12	KS patients were impaired relative to NC, although there was some evidence of learning.
Tower of Hanoi	Beaunieux et al.	1998	1	47	1	10	KS patient did not differ from NC in the 3 or 4-disc version of the Tower task.
Tower of London	Joyce et al.	1991	23 (8)	55.5 (28–73)	22	22	The KS group was less efficient than the controls both in terms of minimum move solutions and time to completion.

ALC=abstinent alcoholic control participants; *EBCC*=eyeblink classical conditioning; *KS*=number of Korsakoff's syndrome patients (number of females in group); *MTL*=medial temporal lobe; *NC*=normal control participants; *n*=number of participants; *KS* age=age of KS patients in years (sd or range)

Table 2

Order of primary tasks done by KS patient G.P. over 7 consecutive days

Day	Tasks
1	Naming digits from 0 to 9, and three- or four-digit square answers (NAME)
	Multiplying single digits in the range 2×2 to 9×9 (MULT)
	Doing subcomponents of the squaring procedure in isolation (COMP)
	Forward digit span via a staircase procedure, followed by 30 trials of span+1 digits, with every third trial repeated (SPANHEBB)
	Ten trials of a video game (VIDEO)
2	MULT, squaring a subset of numbers between 1 and 99 (SQR), SPAN-HEBB,VIDEO
3	MULT, SQR, SPAN-HEBB, VIDEO
4	MULT, SQR, SPAN-HEBB, VIDEO
5	MULT, SQR, SPAN-HEBB, VIDEO
6	MULT, SQR, SPAN-HEBB, VIDEO
7	(AM) MULT, SQR (all numbers between 1 and 99), SPAN-HEBB, VIDEO
7	(PM) NAME, MULT, COMP, SPAN-HEBB, VIDEO

Table 3

Summary of priming studies with Korsakoff's syndrome patients

Task	Authors	Year	KS (# females)	KS age (years)	ALC (n)	NC (n)	Results (brief verbal description)
Lexical decision	Glass and Butters	1985	8	59.3	12	12	KS patients were able to use the 'xxx' priming cues normally and effectively in the control task (Exp 1), as faster responses were observed for the expected relative to the neutral condition. Furthermore, there was no group difference in response latencies for KS, ALC, and NCs. In Exp 2, when real category names were used as primes, the KS patients were the only group that did not show response facilitation for expected relative to the neutral condition. This group difference was hypothesized to reflect KS patients' inability to inhibit semantic associations of the category prime (BIRD) to facilitate responses to probes of a different category (BODY PARTS).
Lexical decision (Exp 1)	Verfaellie et al.	1991	7	63 (56–68)	8	0	KS showed equivalent repetition priming for real words at all lags except lag 0 (no intervening items), indicating that priming was intact in KS even at longer intervals (lag 15). KS showed no evidence of repetition priming for pseudowords. In contrast ALC demonstrated repetition priming for pseudowords, albeit at only the shorter delays (lags of 0 and 1).
Lexical decision (Exp 2)	Verfaellie et al.	1991	7	61 (53–67)	8	0	For real words, there was no between group differences for KS and ALC, and responses were faster for high than low frequency words. The repetition priming effect was larger for low relative to high frequency words. For pseudowords, KS patients failed to show priming effects, whereas ALC exhibited reductions in response time, with these effects occurring at the shorter lags (1 and 3).
Lexical decision (Exp 3)	Verfaellie et al.	1990	7	60.7 (53–67)	7	0	KS exhibited similar associative word priming as ALC; that is, both groups responded faster to related prime-target pairs than unrelated and neutral pairs. In fact, KS showed some evidence of greater facilitation than ALC, but this difference was not statistically significant. Organization of semantic memory intact in KS.
Lexical decision	Smith and Oscar-Berman	1990	8	63.5 (7.3)	8	0	The repetition-related decrease in RT for pseudowords was observed in control participants but not in KS patients. KS did show benefits of repetition in terms of accuracy, as performance was more accurate with repeated stimuli (words and nonwords).
Word identification (Exp 1)	Cermak et al.	1991	6	60	6	0	Similar levels of priming observed in KS and ALC for real words and pseudohomonyms. KS exhibited some priming for pseudowords (5 %), but substantially less than ALC (29 %; supported by re-analysis of previous data reported by Cermak et al. 1985).
Word identification (Exp 2)	Cermak et al.	1985	6	57	6	0	ALC showed substantial priming for pseudowords, KS patients showed no priming. Note that in 1991 paper, Cermak et. al. reanalyze these data and soften their interpretation to note that some priming occurs in KS, but still impaired relative to ALC.
Word identification (Exp 2)	Cermak et al.	1991	7	66	7	0	Real words-pseudohomonyms: KS exhibited priming of equal magnitude for both conditions, while ALC controls did not exhibit priming to real words. Pseudohomonyms-pseudowords: priming larger in ALC than KS, and KS exhibited significant priming to pseudowords but not pseudohomonyms (in contrast to Exp. 1). Real words-pseudowords:

Task	Authors	Year	KS (# females)	KS age (years)	ALC (n)	NC (n)	Results (brief verbal description)
							equivalent priming in KS and ALC for real words, while ALC showed greater priming for pseudowords than KS (and ALC showed greater priming for pseudowords relative to words).
Word identification (Exp 1)	Cermak et al.	1985	6	57.8	12	0	KS demonstrated intact perceptual priming (identification) for words during both immediate and delayed testing, with no difference in priming observed between the two sessions.
Word identification (Exp 1)	Komatsu et al.	2003	8	53.6 (38–63)	8	0	KS patients level and pattern of performance matched ALC on the perceptual priming task. KS patients exhibited enhanced priming when study-test font matched, but still exhibited priming when study-test font mismatched.
Word identification (Exp 2)	Komatsu et al.	2003	8 (1)	58.8 (54–68)	8	0	Results replicated those reported in Exp. 1 (see above).
Word identification-(Exp 1)	Verfaellie et al.	1990	7	62.1 (56–68)	8	0	The baseline threshold for word identification was higher for KS patients than ALC. No difference in magnitude of word-associate priming in KS. Both groups exhibited priming for high and medium associate words relative to unrelated words. Priming of semantic memory in KS not limited to previous presentation of a word.
Word identification (Exp 2)	Verfaellie et al.	1990	7	63 (53–68)	7	0	KS exhibited similar categorical priming as ALC; that is, both groups showed faster responses to the category prime when responding to high and low dominance category targets than unrelated targets. Both KS and ALC made more errors when responding to targets unrelated to the category. Knowledge of categories preserved in KS.
Word identification	Brunfaut and d'Ydewalle	1996	8 (2)	50 (9)	8	0	KS patients took longer to identify the words, but no difference in pattern of performance relative to ALC.
Picture identification	Warrington and Weiskrantz	1968	5	NR	0	5	KS patients exhibited evidence of learning and retention of both fragmented pictures and words over delays of 24 and 48 h, although performance was impaired relative to controls. Testing with a new set of stimuli did not provide evidence of any transfer effects.
Picture identification	Cermak et al.	1993	9	65	12/10	0	No group differences in object identification during the study phase. At test, KS and ALC delay group were impaired relative to ALC. KS exhibited priming for identical pictures relative to new, but not for the similar condition (similar picture, same name). In contrast, both ALC groups required the fewest key presses for the identical condition, followed by similar, and then different pictures.
Picture identification (Exp 1)	Verfaellie et al.	1996	7	66.4	7	0	KS exhibit reduced response latency to previously presented pictures, and no difference in magnitude in priming relative to ALC. Non-KS amnesics also exhibited intact priming. Striking deficit in recognition memory observed in both KS and non-KS amnesics relative to respective control groups.
Picture identification (Exp 2)	Verfaellie et al.	1996	8	65.4	8	0	KS patients required more complete versions of line drawings for identification. KS showed enhanced identification of old pictures relative to new, but priming was reduced relative to ALC. Non-KS amnesics showed the same pattern relative to their controls.
Picture identification (Exp 3)	Verfaellie et al.	1996	8	65.4	8	0	As in Exp 2, KS patients required more complete versions of line drawings for identification. KS showed enhanced identification for old relative to new pictures; however, magnitude of priming in KS was

Task	Authors	Year	KS (# females)	KS age (years)	ALC (n)	NC (n)	Results (brief verbal description)
							impaired relative to ALC. Unlike KS, non-KS amnesics showed no differences in priming relative to their control group.
Picture identification	Fama et al.	2006	4	65 (7.5)	9	21	Visuoperceptual ability: KS make more errors identifying fragmented pictures than NC and ALC during the initial resentation. Visuoperceptual learning: no group difference at 1 h, but at 1 day delay, KS make more errors than normal controls. Incidental learning: reduced number of errors when procedure is repeated at 1 h delay (i.e., test vs. retest) in KS and learning retained over 20+ hour delay. Transfer of learning not observed.
Figure generation from 5 dot configuration	Verfaellie et al.	1992	9	64 (53–76)	18	18	Priming was evident in KS patients, as they incorporated target figures in their final drawing more frequently in the copy relative to the no-copy condition. However, priming in KS was much weaker compared to both ALC and NC.
Spatial configurations	Oudman et al.	2011	18 (6)	53.3 (7.1)	0	22	Slower response times in KS relative to NC, but KS demonstrated similar priming curves as NCs.
Word fragment completion	Jenkins et al.	1998	9	58 (1.1)	0	NR	KS patients show reliable priming in word fragment completion; however, levels of processing effect was lower in KS relative to NC.
Word fragment completion	Kinoshita & Wayland	1993	12 (4)	67.7	0	9	KS patients failed to show enhanced performance when typography (handwritten, typed) matched versus mismatched between study and test, whereas NC show facilitation in the match condition.
Word Stem completion (Exp 1)	Graf et al.	1984	7 (3)	51.7 (38–72)	14	0	KS patients showed intact (and even better performance) on stem completion relative to ALC, and better performance under semantic relative to graphemic encoding conditions. Significant impairment in KS during free recall.
Word Stem completion (Exp 2)	Graf et al.	1984	7 (3)	51.7 (38–72)	6	0	KS patients demonstrated intact stem completion performance, as their pattern of performance was not different from controls. Again, recall was severely impaired in KS.
Word Stem completion	Shimamura et al.	1987	7	53.9	6	8	KS demonstrated intact priming relative to control groups, with KS tendency to complete word stems to form previously presented words by 30 % to 40 % above baseline (5–11 %).
Word Stem completion (Exp 1)	Cermak et al.	1988	8	60 (54–66)	8	0	KS completed more stems than ALC, and neither group showed an effect of context (same vs. different).
Word Stem completion (Exp 2)	Cermak et al.	1988	8	60 (54–66)	8	0	Again, KS completed more stems than ALC, and neither group showed an effect of context (same vs. different).
Word Stem completion (Exp 1)	Cermak et al.	1992	6	62	8	0	KS (plus 3 non-KS amnesics) completed stems more frequently with primed targets relative to ALC, regardless of instructions. ALC were able to reduce the proportion of stem completions with primed targets in the Exclusion relative to the Inclusion condition, whereas KS patients were not.
Word stem completion (Exp 2)	Cermak et al.	1992	7	NR	8	0	As in Exp 1, KS (plus 3 non-KS amnesics) generated a larger proportion of studied targets relative to Controls in the word stem completion task. In contrast to Exp 1, priming was equivalent both groups during Inclusion. KS did exhibit a reduction in generation of studied words in the Exclusion relative to the Inclusion condition; however, priming effects were evident in the Exclusion condition, and were much larger

Task	Authors	Year	KS (# females)	KS age (years)	ALC (n)	NC (n)	Results (brief verbal description)
							than those seen in ALC. Recognition memory remained impaired in KS, despite 5 presentations during study.
Word stem completion	Brunfaut and d'Ydewalle	1996	8 (2)	50 (9)	8	0	No difference was observed between KS and ALC on word stem completion.
Word stem completion	Cermak et al.	1997	7	65	7	6	Note: KS and non-KS amnesic participants (n=6) were combined for the analysis because no effects of encoding or test manipulations (or their interactions) were significant. KS used more studied words to complete stems in the Indirect and Opposition conditions, with no difference observed in the Direct condition. KS patients showed greater priming for semantic relative to graphemic analysis, even when instructed not to use studied items for stem completion.
Word stem completion (Exp 1)	d'Ydewalle & Van Damme	2007	24 (1)	53 (41–63)	0	26	KS patients showed greater priming during semantic relative to perceptual encoding conditions for the indirect and direct test conditions, but not under opposition test conditions. Under indirect test conditions, the encoding levels of processing effect was larger for KS than NC. KS show significant priming during opposition test (whereas NCs did not), indicative of failure of KS patients to inhibit items presented during test.

ALC=abstinent alcoholic control participants; *KS*=number of Korsakoff's syndrome patients (number of females in group); *MTL*=medial temporal lobe; *NC*=normal control participants; *n*=number of participants; *KS* age=age of KS patients in years (sd or range)