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REVIEW

Remote Memory Function and Dysfunction in Korsakoff's Syndrome

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Abstract Korsakoff's syndrome (KS) is a pervasive disorder of memory characterized by both anterograde and retrograde amnesia. Although retrograde memory impairment in KS has been less frequently studied, the status of remote memory in KS has been tested across a number of different tasks that measure knowledge of public information (e.g., famous faces/news events), general semantic information (e.g., vocabulary words), personal semantic information (e.g., facts about oneself), and autobiographical events (e.g., events from one's personal past). In each of these domains, Korsakoff patients demonstrate remote memory impairments that can extend back many years or decades. In addition, a majority of studies report that the extensive remote memory impairment in KS is temporally graded, with relative preservation of memories from childhood and early adulthood. The current paper reviews published experimental studies of remote memory in KS, with particular attention paid to (a) the selectivity of the deficit with respect to the age of the memory and (b) the relationship of memory impairment to underlying neuropathology. We discuss the significance of the reported pattern and extent of remote memory impairment with respect to theories about the nature of the underlying cognitive deficits in KS.

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Introduction

Korsakoff's syndrome (KS) manifests as a severe and persistent impairment in memory. While the hallmark of KS is the striking inability to encode and retrieve information encountered after the onset of illness (Cermak et al. 1971; Corkin et al. 1985; Squire 1982; Verfaellie 2003), patients with KS also demonstrate pervasive deficits in remote memory, or memory for information acquired premorbidly. Observations of remote memory impairment in KS have been noted since the earliest clinical descriptions of the disease, with S.S. Korsakoff himself noting in his clinical description that "not only memory of recent events is lost, but also that of the long past" (Kopelman 1995). More recently, remote memory impairments in KS have been studied experimentally using more objective formal testing procedures. These tests have revealed that remote memory impairment in KS can extend back many years or decades and can occur for a range of declarative information, including public and personal facts as well as autobiographical events. In contrast to documented deficits in remote declarative memory in KS, there is little information concerning the status of remote memory for procedural information. Table 1 presents a summary of prior studies investigating the status of remote memory in KS.

While the pervasive nature of remote declarative memory impairment in KS has been well documented, debate continues about the pattern and extent of this memory impairment and its significance. A topic of particular interest in the literature has been the presence of a temporal gradient of remote memory impairment in KS, in which

Table 1 Experimental studies investigating the status of remote memory in Korsakoff's Syndrome

Authors	Date	Memory Domain	Test	Temporal Gradient
Sanders & Warrington	1971	Semantic	Famous Events	No
Sanders & Warrington	1971	Semantic	Famous Faces	No
Seltzer & Benson	1974	Semantic	Famous Events	Yes
Marslen-Wilson & Teuber	1975	Semantic	Famous Faces	Yes
Albert, Butters & Levin	1979	Semantic	Famous Faces	Yes
Albert, Butters & Levin	1979	Semantic	Famous Events/People	Yes
Mair, Warrington & Weiskrantz	1979	Semantic	Famous Faces	No
Mair, Warrington & Weiskrantz	1979	Semantic	Famous Events	No
Meudell, Northen, Snowden & Leary	1980	Semantic	Famous Voices	Yes
Albert, Butters & Brandt	1981	Semantic	Famous Faces	Yes
Albert, Butters & Brandt	1981	Semantic	Famous Events/People	Yes
Cohen & Squire	1981	Semantic	Famous Faces	Yes
Cohen & Squire	1981	Semantic	Famous Events	Yes
Cohen & Squire	1981	Semantic	Famous T.V. Programs	No
Zola-Morgan, Cohen & Squire	1983	Autobiographical	Crovitz	Yes
Butters	1984	Semantic	Famous Faces	Yes
Butters	1984	Semantic	Famous Scientists	Yes
Butters	1984	Autobiographical	Autobiographical	Yes
Shimamura & Squire	1986	Semantic	Famous Faces	Yes
Shimamura & Squire	1986	Semantic	Famous Events	Yes
Shimamura & Squire	1986	Semantic	Famous T.V. Programs	-
Kopelman	1989	Autobiographical	Autobiographical Incidents (AMI)	Yes
Kopelman	1989	Semantic	Personal Semantic Memory (AMI)	Yes
Kopelman	1989	Semantic	Famous Names	Yes
Kopelman	1989	Semantic	Famous Events	Yes
Parkin, Montaldi, Leng & Hunking	1990	Semantic	Famous Faces	Yes
Verfaellie, Reiss & Roth	1995	Semantic	Vocabulary	Yes
Kopelman, Stanhope & Kinglsey	1999	Autobiographical	Autobiographical Incidents (AMI)	Yes
Kopelman, Stanhope & Kinglsey	1999	Semantic	Personal Semantic Memory (AMI)	Yes
Kopelman, Stanhope & Kinglsey	1999	Semantic	Famous Events	Yes
Fama, Marsh & Sullivan	2004	Semantic	Famous People	Yes
Kopelman, Bright, Fulker, Hinton, et al.	2009	Semantic	Vocabulary	Yes
Kopelman, Bright, Fulker, Hinton, et al.	2009	Autobiographical	Autobiographical Incidents (AMI)	Yes
Kopelman, Bright, Fulker, Hinton, et al.	2009	Semantic	Personal Semantic Memory (AMI)	Yes
Kopelman, Bright, Fulker, Hinton, et al.	2009	Semantic	Famous Events	Yes

memory for the distant past (e.g., childhood) is relatively spared compared with memory for the more recent past (e.g., the years immediately preceding the onset of illness). While some studies have found evidence for a steep temporal gradient of memory impairment is KS, others have observed more uniform remote memory impairment across all past time periods.

The aim of this paper is to review prior experimental studies of remote declarative memory in KS, paying particular attention to the selectivity of the deficit with respect to the age of the memory. Prior studies in KS have tested remote memory for autobiographical information (personal semantic information and events from one's personal past) as well as memory for nonpersonal information (public information such as famous faces/news events and general semantic information such as vocabulary words). We separately review experiments that can be considered measures of semantic memory (memory for public information, general semantic information, and personal semantic information) and experiments that can be considered measures of autobiographical memory (memory for personal events). We consider a range of factors that may influence the pattern and extent of remote memory impairment in KS, including the nature of the declarative information being tested, the

type of testing procedures used to assess remote memory, and underlying neuropathology. The ways in which these factors influence remote memory performance provide a window into the underlying cognitive deficits in KS and inform competing theories about the nature of remote memory impairment in KS.

Patterns of Remote Memory Impairment

Remote Semantic Memory

Remote Memory for Public Information

The first controlled experimental studies of remote memory in KS investigated the status of remote memory for public information. In contrast to tests of remote memory for personal autobiographical information, tests that cover publicly available knowledge have the advantage of assessing information that is widely accessible and more easily verifiable (Squire and Cohen 1982). In the first study of this sort, Sanders and Warrington (1971) tested five amnesic patients (including three KS patients) on their ability to recognize famous faces and public news events from different past time periods (1930s through 1960s) (Sanders and Warrington 1971). Patients demonstrated severe remote memory impairments in comparison to controls for all time periods tested, regardless of whether tested by recall or recognition (Fig. 1). In addition, patients' memory impairment was equally severe across all decades tested, without any evidence for sparing of older memories. This study confirmed the clinical observation that remote memory is severely impaired in KS and additionally suggested that the magnitude of this remote memory impairment in KS may be uniform across past time periods. The presence of such temporally extensive, ungraded remote memory impairment was taken to support interference retrieval theories of amnesia which attribute memory difficulties to an inability to retrieve information from long-term memory (E.K. Warrington and Weiskrantz 1973).

Two subsequent studies investigating remote memory for public information identified similarly profound remote memory deficits in KS, but in contrast to the report by Sanders and Warrington, these studies found that the magnitude of the impairment varied according to the age of the memory. Seltzer and Benson (1974) tested patients on a multiple-choice questionnaire about famous public events from the 1920s–1970s and found that memory impairments were more severe for recent events (events from the 1960s and 1970s) than for distant events (events from the 1920s and 1930s) (Seltzer and Benson 1974). Similarly, Marslen-Wilson and Teuber (1975) tested subjects on a picture identification test of famous public figures and found that KS patients had greater difficulty remembering public figures from the more recent compared with the more distant past (Fig. 2) (Marslen-Wilson and Teuber 1975). Thus, while initial experimental studies found convergent evidence for profound remote memory impairment in KS, the pattern of this remote memory impairment and presence of a temporal gradient varied from study to study.

What sources of variability could have yielded these mixed results across studies? One proposal was that the temporal gradients of memory impairment emerged as a byproduct of variable item difficulty over the time periods tested (Sanders and Warrington 1971). In particular, superior performance on earlier compared with later test decades could occur if earlier test decades contained relatively easier items that patients had been exposed to many times (i.e.,

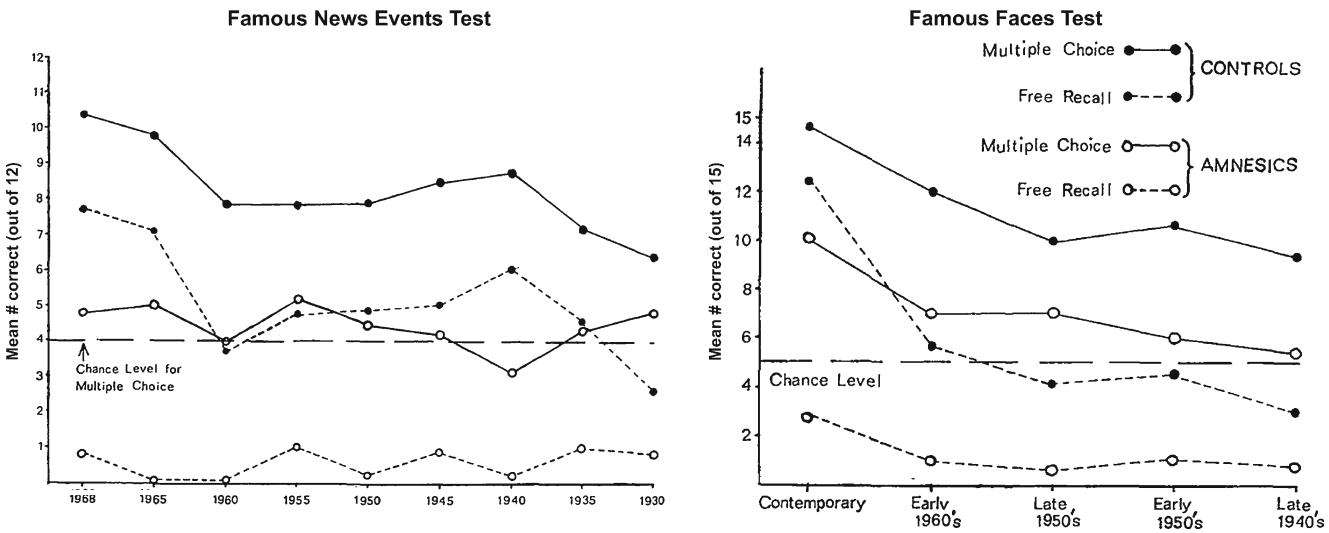

Fig. 1 Severe, ungraded remote memory impairment for famous news events (left) and famous faces (right) in the study by Sanders and Warrington (1971)

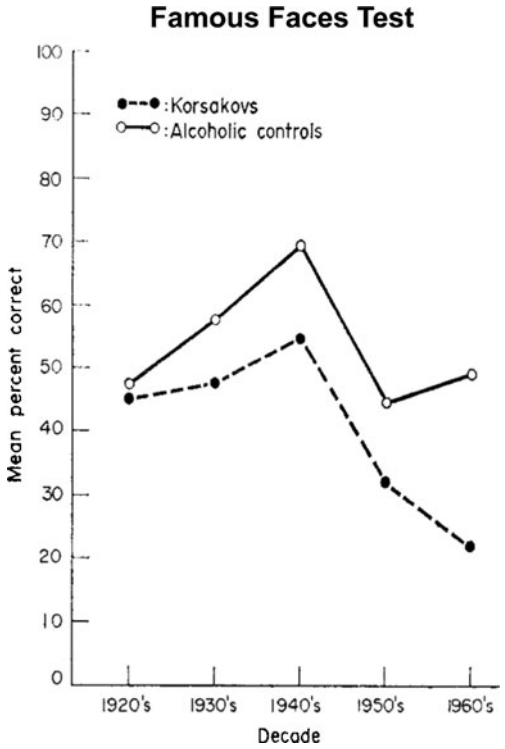

Fig. 2 Graded remote memory impairment for famous faces (unprompted) in the study by Marslen-Wilson and Teuber (1975)

over-learned items). To address this issue, Albert et al. (1979, 1981) tested patients on remote memory test batteries of famous faces, famous names, and public events that controlled for item difficulty across time periods (items from each test decade were standardized such that they were remembered by 80 % of normal controls) (Albert et al. 1981, 1979). When tested on these standardized batteries, Korsakoff patients continued to demonstrate a steep temporal gradient of remote memory impairment, with superior performance for more remote than more recent memories, and the presence of the temporal gradient did not depend on the method of testing (recall or recognition) or the difficulty of the test items (e.g., patients' performance was better for "hard" faces from the distant past compared with "easy" faces from the recent past) (Butters and Albert 1982).

The finding that patients had more difficulty remembering items from more recent than remote time periods, even when items in all test decades were equally remembered by controls, argues against the proposal that temporal gradients of memory impairment in KS simply reflect variable item difficulty or stimulus overlearning in more remote time periods. However, to explore this possibility further, Albert et al. (1979) tested patients and controls on their ability to identify photographs of famous people that were taken when the famous person was younger, before they had been in the news for several decades, compared to when the famous person was older, after decades of exposure had occurred. While controls were more accurate at identifying photographs of personalities when they were older compared to when they were younger, patients demonstrated the opposite pattern of performance. Together, these results suggest that temporal gradients of remote memory impairment in KS are not an artifact related to item difficulty or stimulus overlearning.

Given these results, the question remains as to why a temporal gradient of memory impairment was not present in the original Sanders and Warrington (1971) study. One possibility is that the mixed etiology of the amnesic patients in that study (including Korsakoff and non-Korsakoff amnesics) is not representative of KS in general. However, a similar pattern of temporally extensive, ungraded memory impairment was found when analysis was subsequently restricted to a single KS patient from the amnesic group (Mair et al. 1979). An alternative, more tenable, possibility is that any impact of memory age on memory performance could not be detected because of the low level of patients' performance across all time periods (i.e., floor effects). Indeed, the patients in Sanders and Warrington's study performed near chance across all time periods tested. Further support for this hypothesis comes from the fact that subsequent studies have consistently identified graded patterns of remote memory impairment in KS when subject performance is not at chance (Cohen and Squire 1981; Fama et al. 2004; Kopelman 1989; Kopelman et al. 2009, 1999; Meudell et al. 1980; Parkin et al. 1990; Shimamura and Squire 1986). The following sections describe the details of those studies.

Kopelman (1989) tested Korsakoff patients and controls on their knowledge of famous news events and the names of famous personalities from the past. In the famous news event test, subjects were shown 50 pictures of famous news events across five past decades and were instructed to identify the news event. In the famous names test, subjects were shown a standardized list of famous names that were known by different age groups of healthy subjects as well as the names of non-famous people and had to recognize whether or not a given name was considered famous. Korsakoff patients demonstrated impairment across all time periods tested, with relative sparing of early memories (e.g., Fig. 3a). This result has been replicated in more recent studies by Kopelman et al. (1999, 2009).

Meudell et al. (1980) tested remote memory in KS by having patients and controls attempt to identify the voices of people who had become famous from the 1930s through the 1970s. Impairments in KS extended across all time periods and were proportionally greater for recent compared with remote decades, regardless of testing format (recall, cued recall, recognition). Similarly, Cohen and Squire (1981) and Shimamura and Squire (1986) tested patients' memory for famous television programs, past public events, and famous

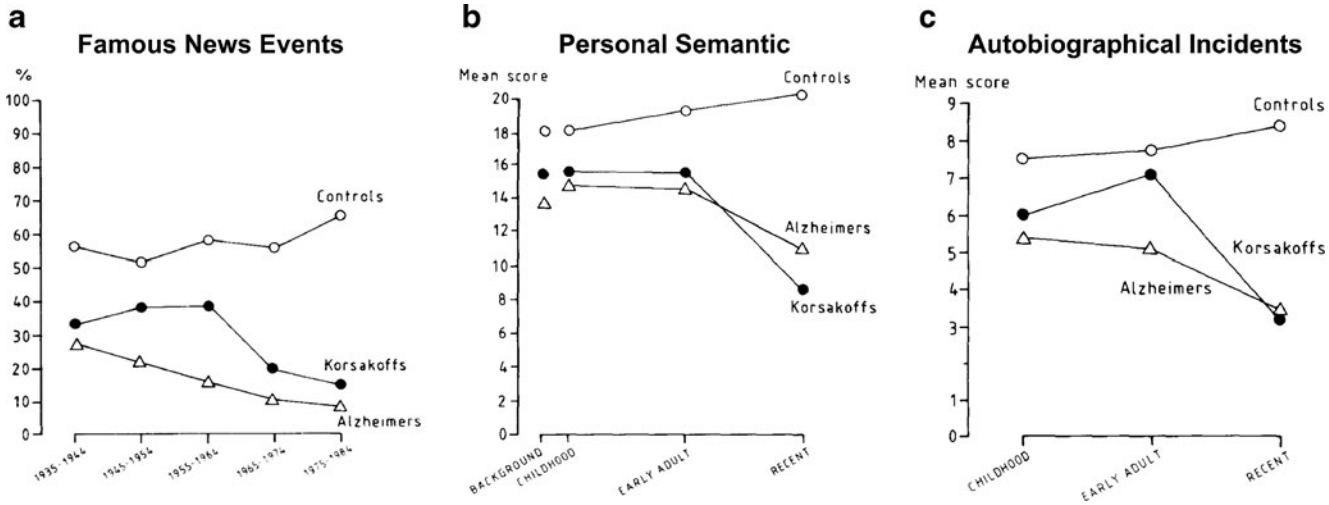

Fig. 3 Graded remote memory impairment for (**a**) famous news events, (**b**) personal semantic information, and (**c**) autobiographical incidents in the study by Kopelman (1989)

faces, and found severe and temporally extensive impairments that included the most remote time periods sampled in each test. Additionally, a temporal gradient of memory impairment was present in the public event and famous faces tests. Although a temporal gradient was not present in the famous television programs test, this pattern could reflect the fact that all of the television programs in this study were specifically selected such that they were broadcast for only a single season (thus more remote stimuli would not have benefitted from continued rehearsal). The authors also note that the television programs test was confounded by a floor effect that could have masked the presence of a temporal gradient of memory impairment. Parkin et al. (1990) also tested subjects on a famous faces test and observed an extensive, temporally-graded pattern memory impairment in KS. Finally, further evidence for temporal gradients of remote memory impairment in KS were identified by Fama et al. (2004) using remote memory tests involving recall, recognition and sequencing of presidential candidates and candidate election years.

Remote Memory for General Semantic Information

While patients' impaired memory for public information suggests that KS is characterized by remote memory impairment in the semantic domain, it has been suggested that tests of memory for public information entail an autobiographical component and are not simply dependent on retrieval from a general semantic knowledge system (Kopelman et al. 1999; MacKinnon and Squire 1989; Westmacott and Moscovitch 2003). For example, Westmacott and Moscovitch (2003) found that autobiographical significance contributes to memory for public information. Specifically, the names of famous people that are associated with autobiographical recollection are recalled and recognized better than names of famous people that are not associated with autobiographical recollection, even when the two types of names are equated in terms of familiarity and number of semantic facts known about the names (Westmacott and Moscovitch 2003). Thus, it is difficult to determine whether disrupted performance on memory tests for public information reflect isolated deficits in semantic memory.

To investigate the status of remote memory in KS for more purely semantic information, Verfaellie and colleagues tested patients' ability to retrieve general knowledge not tied to a singular event (vocabulary words) that was acquired prior to the onset of KS (Verfaellie et al. 1995). Specifically, 82 vocabulary words were selected such that their date of entry into the English language could be precisely linked to one of seven different five-year time intervals from 1955–1990. For example, the word "tupperware" appeared in the English language in the period from 1955–1960 whereas the word "futon" appeared in the English language in the period from 1980–1985. Patients' knowledge of the meaning of the vocabulary words was assessed both by recall and recognition. In the recall task, participants were asked to define each word. In the recognition task, each of the words was presented, followed by the target definition and three plausible, but unrelated, distracter definitions. For example, the word "Frisbee" was followed by the following definitions: (a) A small sample of a product given away for free in order to encourage people to buy the full-priced product at a later date; (b) A hair style; (c) A small plastic disk that may be thrown through the air for recreation; (d) A refrigerator that maintains temperatures below zero degrees centigrade to freeze perishable goods.

On both recall and recognition versions of the vocabulary test, Korsakoff patients were impaired across the 25-year

sampling period and demonstrated a temporal gradient of memory impairment, with reduced knowledge about words acquired during more recent than more remote time periods (Fig. 4). Importantly, patients' and controls' memory for baseline words (i.e., memory for words which had entered the English language prior to 1920 and presumably were acquired during the course of normal linguistic development in childhood) did not differ. These results indicate that memory for premorbid general semantic information is severely impaired in KS, just as memory for premorbid public information is impaired in KS, and is characterized by a steep temporal gradient of memory impairment.

Remote Memory for Personal Semantic Information

Personal semantic memory refers to factual knowledge about one's own past. The status of remote memory for personal semantic information in KS has been investigated in several prior studies (Kopelman 1989; Kopelman et al. 1999, 2009) that have used the personal semantic schedule of the Autobiographical Memory Interview (AMI). The personal semantic schedule of the AMI is a semi-structured interview in which subjects answer questions which probe their knowledge of facts about their personal past (e.g., names of schools attended and names of teachers; prior home addresses; when and where married; first job) as well as personal semantic memory for general background information (e.g., the location where a parent was born). The schedule is divided into four sections: background (family) information, childhood, young adulthood, and recent. The veracity of subjects' responses was checked in four different ways: (1) extensive medical records and clinical histories were carefully examined; (2) current caretakers were interviewed to obtain information about recent facts; (3) next-of-kin were interviewed to obtain additional information, particularly about earlier life periods; (4) inaccuracies were sometimes indicated by inconsistencies in the patients' replies to items within the questionnaire.

Across studies, Korsakoff patients consistently demonstrated remote memory impairments across all periods tested (background, childhood, early adult, recent) (Fig. 3b). In addition, patients demonstrated relative sparing of early memories compared to more recent memories (significant group x time-period interaction) in each study. Together, these results provide evidence for a temporal gradient of memory impairment in the personal semantic domain. Furthermore, this temporally extensive, graded pattern of impairment mirrored the pattern of impairment observed in tests of public and general semantic information, highlighting the pervasive nature of remote semantic memory impairment in KS.

Remote Autobiographical Memory

In contrast to the robust literature investigating the status of remote semantic memory in KS, relatively few studies have investigated patients' ability to remember events from their personal past (autobiographical memory). Of those studies that have tested remote autobiographical memory in KS, severe and temporally graded impairments have been consistently reported, as described below.

Zola-Morgan et al. (1983) investigated remote autobiographical memory in KS using a 'Crovitz' cueing procedure in which patients were presented with ten words (e.g., flag, bird, window) were asked to recall and date specific episodes from their past involving the words (Crovitz and Schiffman 1974; Zola-Morgan et al. 1983). If patients were unable to recall an episode in response to a stimulus word, the experimenter provided cues to aid the subject in generating a personal episode (e.g., "When you baby-sat was there a time that the child got sick or something unusual happened?"). Results from this test revealed that while

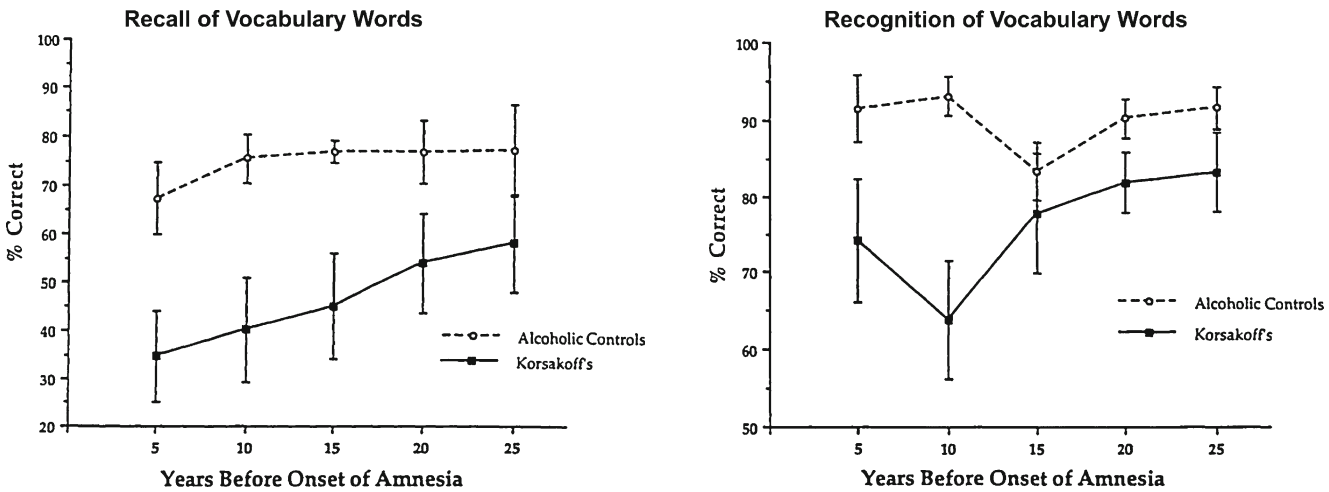

Fig. 4 Graded remote memory impairment for vocabulary words in the study by Verfaellie et al. (1995)

Korsakoff patients were able to retrieve episodes when cued as well as controls, they recalled episodes almost entirely from the distant past (e.g., childhood and early adulthood). This pattern of performance stood in contrast to that of control subjects who retrieved memories from both the recent and distant past. These results suggested that the temporal gradient of remote memory impairment in KS previously identified for semantic information extends to the autobiographical domain.

However, it has been argued that the presence of a temporal gradient in tests that require subjects to retrieve and date autobiographical memories in response to cue words may reflect a bias to report memories from particular time periods rather than the capacity to do so (Kopelman et al. 1989). To avoid this problem, Kopelman et al. (1989, 1999, 2009) tested patients on the autobiographical incidents schedule of the Autobiographical Memory Interview (AMI) which probes memory for events within specific, pre-determined time periods across the lifespan. Specifically, subjects were cued to provide autobiographical events from three specific time periods (childhood, young adult, recent). For the childhood time period, memory cues included "pre-school", "primary school", and "secondary school." For the early adult period, cues included "first job", "a wedding", and "meeting someone when aged 20–30." For the recent time period, cues included "a visit or relative", "recent institution" and "a journey." Subjects were given a score based on the richness of the event description and its specificity in time and place. When tested in this format, patients continued to demonstrate remote memory impairments across all time periods, with a particularly severe impairment for autobiographical memories from the recent time period (Fig. 3c).

While these studies suggest that KS is characterized by extensive, temporally graded remote memory impairment in the autobiographical domain, additional insight into the pattern of remote autobiographical memory impairment and the nature of underlying impairments in KS could be gained by studies that use more sensitive measures to evaluate the richness and detailed nature of patients' extended autobiographical narratives (Levine et al. 2002). The use of such an approach may additionally serve to clarify the contribution of medial temporal lobe damage to remote memory impairment in KS (Sullivan and Marsh 2003).

Summary

Formal testing has consistently demonstrated severe remote memory impairment for both semantic and autobiographical information in KS, including memory for public facts and events, general semantic information, personal semantic information, and personal life events. Remote memory impairment in KS is temporally extensive and can extend back decades. In addition, converging experimental evidence indicates that the magnitude of premorbid memory impairment in KS is graded across time, with greater impairment for recent compared to remote time periods. The presence of a temporal gradient of remote memory impairment in KS does not appear to be an artifact related to the method of testing or stimulus overlearning, as it is present when testing takes the format of recall and recognition as well as when item difficulty is equated across events from the recent and distant past.

Theories of Remote Memory Impairment in KS

The patterns of remote memory impairment observed in experimental studies of KS inform competing theories about the nature of the underlying cognitive impairments in KS. A two-factor model was first proposed to account for the extensive, temporally graded pattern of remote memory impairment in KS (Albert et al. 1979; Butters and Albert 1982; Squire and Cohen 1982). According to this model, the presence of memory impairment across all remote time periods in KS is due to deficits in memory retrieval associated with the onset of KS that uniformly impair access to memories regardless of their age, whereas the temporal gradient of remote memory impairment in KS is due to a superimposed progressive anterograde amnesia during the period of alcoholism prior to the onset of KS diagnosis.

The first factor of this two-factor model is based on faulty retrieval theories of amnesia in which memory difficulties are thought to result from an inability to access information in long-term memory rather than an inability to store information in long-term memory (E. K. Warrington and Weiskrantz 1978). According to faulty retrieval theory, memory performance should improve under conditions of retrieval support. Congruent with this proposal, Korsakoff patients demonstrate marked improvements in remote memory performance when tested by recognition or cued recall (e.g., Kopelman 1989; Kopelman et al. 1999; Verfaellie et al. 1995; Parkin et al. 1990). For example, Verfaellie and colleagues found that Korsakoff patients benefitted twice as much from recognition testing in comparison to controls when tested on remote memory for vocabulary words (Verfaellie et al. 1995). Similarly, Parkin and colleagues found that contextual cueing during the famous faces test (e.g. presenting Elvis Presley on stage with a guitar vs. without any contextual information) improved recognition performance in KS to a greater extent than it did for controls (Parkin et al. 1990) (Fig. 5).

The improvement in patient performance with retrieval support suggests that deficits in controlled search and retrieval play an important role in the remote memory impairment in KS. However, the magnitude of the improvement with retrieval support in KS has not always been greater

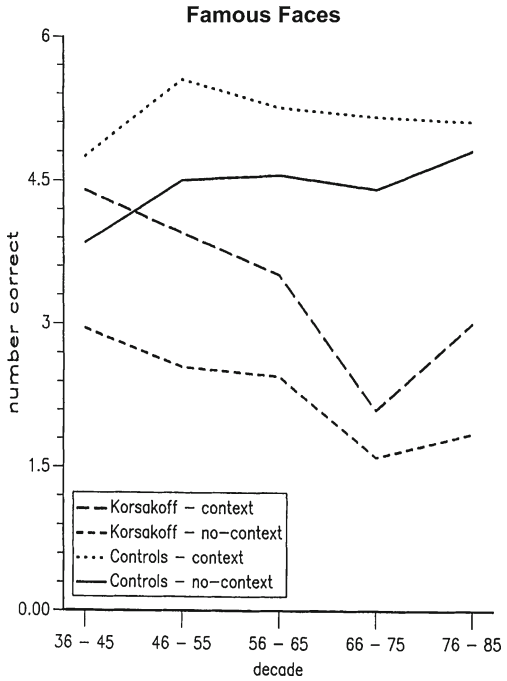

Fig. 5 Effect of contextual cueing on the famous faces test of remote memory in the study by Parkin et al. (1990)

than equivalent improvements in healthy controls (Albert et al. 1979; Kopelman et al. 2009; Meudell et al. 1980). These results suggest that remote memory impairment may reflect "higher-order" deficits related to memory retrieval (e.g., post-retrieval processing) that may not always be overcome by simple recognition or cueing methods (Greene et al. 1995; Kopelman et al. 2009). For example, after mnemonic information has been retrieved during memory search, the veracity and relevance of this information must be verified. Recognition and cueing methods are unlikely to improve deficits in higher-order memory verification/monitoring processes, which may also relate to memory distortions that present as confabulations in KS. Confabulation refers to the propensity to confuse true memories with untrue memories and, while not always present in KS, confabulation has recently received attention as one of the clinical features of KS (Borsutzky et al. 2008; Kessels et al. 2008; Van Damme and d'Ydewalle 2010). Confabulation has been linked to deficits in the controlled aspects of memory retrieval, such as post-retrieval monitoring and verification (Gilboa and Verfaellie 2010; Kan et al. 2010). The occurrence of confabulation in KS suggests that deficits in memory monitoring and verification, in addition to deficits in memory retrieval, may contribute to remote memory impairments in KS.

While faulty retrieval is largely accepted as an important component of the remote memory deficit in KS, there has been mixed support for the second factor of the two-factor model that attributes the graded pattern of memory impairment in KS to encoding deficits during the alcoholic premorbid period. Support for this factor initially came from reports of verbal and non-verbal learning deficits in long-term alcoholics as well as reports that the magnitude of anterograde memory impairment in KS positively correlates with the magnitude of remote memory impairment (specifically in the most recent decades of the premorbid period) (Butters and Albert 1982; Shimamura and Squire 1986). However, there is no significant correlation between the temporal extent of remote memory impairment in KS and the duration of alcoholism, and measures of anterograde memory impairment in KS do not consistently correlate with measures of remote memory impairment (Fama et al. 2004; Kopelman 1989; Kopelman et al. 1999; Parkin 1991). Furthermore, graded impairments in remote memory have been observed in amnesic populations in which the onset of amnesia is acute rather than progressive (e.g., temporal lobe amnesia due to anoxia or herpes encephalitis) (Squire and Cohen 1982).

The most convincing evidence to date that argues against contributions of deficient encoding to retrograde amnesia in KS comes from the case study of patient P.Z. (Butters 1984; Butters and Cermak 1986). Patient P.Z. was a college professor who had written his autobiography in the several years just prior to developing KS. When his remote memory was tested, P.Z. demonstrated a severe and temporally graded impairment. Importantly, this impairment was present even when P.Z. was tested on recent premorbid information drawn from his autobiography (e.g., information that had been encoded adequately). The presence of such severe, temporally graded memory impairment for self-generated autobiographical information in P.Z. argues against deficient encoding as the root cause of temporally graded remote memory impairment in KS.

Butters and Cermak (1986) offered an alternative explanation for the temporally graded pattern of remote memory impairment in KS. They proposed that memory for different periods of time tap qualitatively different knowledge systems, with recent memory primarily tapping autobiographical information (e.g., information anchored in a spatial and temporal context) and remote memory primarily tapping semantic information (e.g., information that has lost its contextual qualities through continued rehearsing and retelling). By this view, temporal gradients of memory impairment are due to the difference in the nature of declarative information in recent and remote time periods and the fact that autobiographical information is more vulnerable to the effects of brain damage in KS. However, this view relies on the assumption that premorbid semantic memory is largely intact in KS, which was contradicted by subsequent reports of impaired memory for vocabulary words in KS (Kopelman et al. 2009; Verfaellie et al. 1995).

An alternative, but related, hypothesis argues that the differential vulnerability of recent compared with remote memories in KS may be due to the fact that recent memories are less frequently rehearsed and less well established than remote memories, regardless of their declarative content (Kopelman 2002; Verfaellie et al. 1995). If recent memories are more fragile in comparison to remote memories that have been strengthened through continued rehearsal, recent memories may be more susceptible to retrieval failures. In this way, retrieval deficits could account for both the temporally extensive and temporally graded patterns of remote memory impairment in KS, by impairing access to remote memories across all time periods but impairing access to recent memories to a greater degree than remote memories.

Summary

Theories of remote memory impairment in KS must account for both the extensive range and temporally graded pattern of the impairment. Faulty retrieval processes that impair access to memories across all remote time periods have been proposed to account for the extensive nature of remote memory impairments in KS. This proposal has been supported by demonstrations of improved performance in KS under conditions of retrieval support (e.g., recognition testing or cued retrieval). Specifically, Korsakoff patients can demonstrate a disproportionate benefit from retrieval support during remote memory testing in comparison to controls. In some cases, this disproportionate benefit from retrieval support in KS may be due to the fact that control performance is at ceiling. Importantly, however, this disproportionate benefit from retrieval support occurs in KS even when control performance is off of ceiling. Faulty retrieval may also account for the temporally graded patterns of remote memory impairment in KS, under the assumption that more recent memories are differentially susceptible to retrieval failures due to the fact that they have been less frequently rehearsed and are less well established than remote memories.

While faulty retrieval provides a parsimonious explanation for the pattern and extent of remote memory impairment in KS, we cannot exclude the possibility that impoverished encoding during the period of premorbid alcoholism also makes subtle contributions to the pattern of remote memory impairment in KS. However, impoverished encoding is unlikely to account for the full extent of the temporal gradient in KS given that gradients of memory impairment often begin long before the onset of illness. The fact that retrieval support benefits memory across all time periods further supports the notion that faulty retrieval underlies to the pattern and extent of remote memory impairment in KS.

Neural Basis of Remote Memory Impairment in KS

The neuropathological profile of KS has been well documented by postmortem pathology and in vivo MRI. Structural neuropathology in KS occurs most notably in the diencephalon (e.g., anterior and dorsomedial nuclei of the thalamus and the mamillary bodies) and is accompanied by atrophy in neocortical areas (particularly frontal and parietal cortex) and the hippocampus (Jernigan et al. 1991; Shimamura et al. 1988; Sullivan and Pfefferbaum 2009; Visser et al. 1999). Neural dysfunction in KS has also been identified in both diencephalic and neocortical regions (e.g., frontal, parietal and cingulate cortex) using quantitative measurements of cerebral metabolism (Eustache et al. 2000; Heiss et al. 1992; Paller et al. 1997). While the neuropathological characteristics of KS have been the topic of much research, the majority of studies have investigated the link between anterograde amnesia and neuropathology in the limbic system while the relationship between neuropathology and remote memory impairment in KS has received significantly less attention. Although little is known about the relative contribution of specific loci of neural damage to remote memory impairment in KS, research to date has emphasized the relevance of neocortical damage, particularly in the frontal lobes. The following section reviews available evidence from prior experimental studies that have investigated the neural substrates of remote memory impairment in KS.

In order to investigate whether structural damage within the frontal, thalamic and medial temporal regions implicated in KS specifically relates to impairments in remote memory, rather than symptoms of KS unrelated to memory impairment, Kopelman and colleagues (Kopelman et al. 2003) tested whether the size of these critical brain regions correlates with measures of remote memory performance. Structural MRI was used to quantify the size of these brain regions in 15 patients with diencephalic lesions (including 13 KS patients) and the relationship was examined between these values and remote memory performance (as measured by the news events test, autobiographical incidents schedule of the AMI, and personal semantic schedule of the AMI). When taken together, measurements of these critical brain regions accounted for 60 % of the variance in autobiographical memory scores, 60 % of the variance in personal semantic scores, and 48 % of the variance of news events scores. In addition, significant correlations were found between remote memory performance and the size of each of the individual brain regions examined.

While these results suggest that remote memory impairments in KS may reflect neural damage across multiple brain regions, they do not address whether the severity of remote memory impairment in KS is differentially related to particular loci of neural damage. It has been suggested that cortical pathology, in particular, critically leads to the

remote memory impairments observed in KS (Kopelman 1991; Verfaellie et al. 1995; Kopelman et al. 1999; Kopelman 1989). According to this view, damage to diencephalic structures may produce a relatively brief memory impairment of 3 years or less, but widespread cortical pathology in the temporal or frontal lobes is required for the pattern of extensive, temporally graded memory impairment observed in KS (Kopelman 1993). Comparisons across neuropsychological populations lend support to this hypothesis.

In one such study, Kopelman et al. (1999) compared the remote memory performance of KS patients to that of patient groups with more focal lesions in the diencephalon, frontal lobes, and medial and lateral temporal lobes. Each of the groups performed remote memory tests of public information (news events), personal semantic information, and autobiographical information. Across each of the tests, the Korsakoff patients demonstrated severe remote memory impairments in comparison to controls with relative sparing of early memories, as expected. In contrast, the performance of patients with focal diencephalic lesions closely matched the performance of controls and was significantly better than that of Korsakoff patients across all three tests. This difference in performance between the Korsakoff and the focal diencephalic group argues against diencephalic damage as the primary source of remote memory impairment in KS and instead points to concomitant cortical damage. Indeed, the patients with temporal lesions in this study demonstrated a similar severity of remote memory deficit as the KS group across all three tasks, and the severity of the deficit in the patients with frontal lesions was closely matched that of the Korsakoff group on the news event and autobiographical memory tests. Interestingly, frontal patients were less impaired than the Korsakoff group on the personal semantic memory test, which the authors suggested may reflect reduced demands on more strategic aspects of retrieval given the highly rehearsed and familiar nature of personal semantic information. Together, these results emphasize the contribution of frontal and temporal pathology to the remote memory impairment in KS, and suggest that the combination of cortico-diencephalic damage may affect remote memory performance to a greater degree than either cortical or diencephalic damage in isolation.

Additional support for the notion that cortical abnormalities play a critical role in Korsakoff patients' remote memory impairment comes from a more recent study that examined the relationship between regional brain volumes and memory performance in KS (Fama et al. 2004). In this study, impairments in memory for premorbid public information in KS correlated with the volume of prefrontal as well as posterior paritel-occiptal white matter. These results highlight the important contribution of cortical regions to remote memory, and further suggest that disrupted cortical connectivity may contribute to remote memory impairments in KS.

The importance of cortical processing for remote memory function has also been suggested by neuroimaging studies that have demonstrated increased recruitment of cortical regions during performance of remote memory tasks in healthy controls. In one such study, Conway and colleagues (Conway et al. 1999) identified increased activity in left frontal, inferior temporal and occipito-parietal regions during verbal cueing of autobiographical memories using positron emission tomography (PET). Left frontal activation was proposed to reflect control processes that modulate the construction of autobiographical memories in posterior neocortical networks. Similarly, Ryan et al. (2001) identified activity in neocortical regions (including the dorsolateral prefrontal cortex, anterior medial frontal cortex and anterior parietal lobe) during retrieval of recent and remote autobiographical memory using fMRI (Ryan et al. 2001).

Further evidence highlighting the contribution of frontal dysfunction to remote memory impairment in KS comes from the finding that remote memory performance in KS correlates with behavioral performance on tests of frontal lobe function. In one such demonstration, Kopelman (Kopelman 1991) found that impaired retrieval of remote autobiographical and semantic memories in KS correlates with several measures of frontal function (e.g., scores on FAS Verbal Fluency). Similarly, Verfaellie et al. (1995) found that a composite score of three frontal tests significantly correlated with the recall of premorbidly acquired vocabulary. In addition, this measure of frontal function also correlated with the benefit obtained from recognition (versus recall) testing in KS, indicating that patients with more severe frontal dysfunction performed more poorly when recalling remote semantic memories but showed greater improvement with recognition testing. The association of remote memory performance with metrics of frontal lobe function support the hypothesis that frontally-mediated deficits in memory retrieval play an important role in the remote memory impairment in KS. Indeed, damage to the frontal cortex has also been linked to confabulation in KS (Benson et al. 1996).

Summary

Although few studies have investigated the neural substrates of remote memory impairment in KS, a handful of neuroimaging studies have found significant correlations between the remote memory performance and the extent of structural damage, particularly in neocortical regions. Emphasis has been placed on the contribution of frontal lobe damage in KS, a point that has been further emphasized by significant behavioral correlations between remote memory performance and tests of frontal function. This emphasis on frontal dysfunction in KS is congruent with faulty retrieval theories of remote memory impairment that propose that deficits in frontally-

mediated retrieval processes make a critical contribution to remote memory impairment in KS. While damage to medial temporal and diencephalic structures may produce relatively brief memory impairment in KS, widespread cortical pathology, particularly in the frontal lobes, may be required to generate temporally extended remote memory impairment.

Conclusion

The experimental studies reviewed herein provide a window into the nature of the remote memory impairment in KS. Several points of convergence across studies are of note: (1) Korsakoff patients demonstrate striking remote memory deficits for both semantic and autobiographical information that can extend back years or decades; (2) remote memory impairment in KS is temporally graded, with relative sparing of early memories; (3) the magnitude of remote memory impairment in KS correlates with the magnitude of neuropathology, particularly in the neocortex, as well as the magnitude of impairment on behavioral measures of frontal function. The pattern and extent of remote memory impairment in KS has been proposed to result from faulty retrieval processes that prevent access to premorbidly acquired information, particularly recent premorbid information that is more susceptible to retrieval failures. Observations of frontal dysfunction are in line with this hypothesis.

Although there is still much to learn about the nature of neural damage and neural dysfunction that leads to remote memory impairment in KS, future research could provide additional insight into these questions by adopting a multimodal imaging approach that takes advantage of the spatial resolution of fMRI, the temporal resolution of magnetoecenpahalography (MEG) and electroencephalography (EEG), and the structural specificity of DTI. Future research should also focus on clarifying the precise nature of the faulty retrieval processes contributing to remote memory impairments in KS. While it is known that KS patients benefit from cueing in experimental settings, a better understanding of the retrieval processes that are impaired in KS would inform the types of retrieval support and compensatory strategies that might be most beneficial to KS patients in daily life. Clinicians and caregivers should be informed of the benefits that retrieval support might provide to patients with KS and more research should be done to determine the impact of different types of retrieval support on memory rehabilitation. Although such strategies are unlikely to ameliorate the full extent of remote memory impairment in KS, full advantage should be taken of every opportunity to potentially enhance patients' quality of life.

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Conflict of Interest None

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