gible here) plus the rate of loss of variation due to hitchhiking. Evolutionary divergence could be estimated under the same conditions as $t = [1/(k_1 + k_2)] \times \ln D_e/(D_e - D)$, where t is the number of generations since the last common ancestor and D_e is the proportion of differences expected at equilibrium. It is still quite possible that an objectively ascertainable subset of substitutions may be a proper subject for this sort of analysis.

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Forms of Memory Failure

Abstract. *Memory may fail in a variety of ways. Patients with Korsakoff's syndrome demonstrate global memory deficits similar to those seen in patients with early progressive dementia. Korsakoff's patients, however, may recall rules and principles for organizing information and can gain access to their previously acquired knowledge (semantic memory), whereas recent memory may be grossly impaired. In contrast, dementia patients may have little access to previously acquired knowledge and therefore have great difficulty in organizing and encoding ongoing events. These contrasting forms of memory failure have implications for understanding the structure and mechanisms of memory and learning, particularly the relationship between episodic and semantic memory, as well as the development of therapeutic strategies for cognitive impairments.*

Psychobiological determinants of memory failures remain poorly understood and are complex, variable in their form, and rarely complete. A variety of theoretical explanations have been proposed to account for memory failures in amnestic syndromes including disruptions in consolidation of memories (*1, 2*), acquisition and encoding processes (*3, 4*), retrieval processes (*1–5*), or unlinking some event from its processing context (dissociation of memory and awareness) (*6–9*). These explanations of memory failures are all concerned with episodic memory—memory for an event that has occurred at a particular time and place, and in a unique context. In contrast, semantic memory—the representation of structured and organized information, or knowledge in memory, which serves as a basis for appreciating, interpreting, and encoding ongoing experience—may be a separate, distinct memory system (*10, 11*); access to that type of memory is a necessary condition for forming new memories. This study was designed to contrast and relate aspects of episodic and semantic memory by comparing the determinants of comparably memory-impaired patients with Korsakoff's disease (KD) and those in an early stage of a progressive degenerative dementia (PD), probably of an Alzheimer's type (a diagnosis confirmable only on the basis of neuropathological findings).

The most common amnestic syndrome is KD; although these patients have been frequently studied because of the presumed "purity" of their amnesia, they, nevertheless, can learn and remember some information (*4*). For example, although they are often incapable of remembering previously processed events on demand (declarative memory), they, like some other amnestic patients, are capable of learning and then "remembering" (performing) many complex tasks (*5, 12–15*). In addition they are able to remember, on demand, at least some recently occurring events and are also sensitive to conditions that would ordinarily affect recall in unimpaired subjects (*16*). Patients with PD can demonstrate functionally equivalent memory failures. The impairment of PD patients, unlike that of KD patients, is progressive, owing to continued neuropathological deterioration, and also seems related to how well these patients can obtain access to and use their previously acquired knowledge in processing ongoing events. We hypothesized that KD patients with severe impairments in recent memory could nonetheless effectively gain access to knowledge structures in semantic memory. In contrast we predicted that semantic memory functions would be impaired in PD patients and the extent of that impairment would be directly related to the severity of episodic memory failures. That is, unlike KD patients, PD patients were predicted to fail to remember because they cannot gain access to knowledge structures necessary for appreciating and encoding ongoing events.

The study was completed in two stages. Patients selected for further study were first evaluated neurologically, psychiatrically, and neuropsychologically. From this sample, patients were chosen in matched pairs on the basis of demographic characteristics, as well as comparable impairments in memory. Memory impairments were measured both clinically and psychometrically, as well as with laboratory tests of learning and memory. The psychometric evaluation and measures used to match the memory impairment of KD and PD patients included the Wechsler Memory Scale (WMS) performance, a standard global clinical assessment procedure that relates memory performance to measures of intelligence (IQ). The premorbid IQ of PD patients was estimated to be well above average on the basis of weighted factors including age, sex, education, and occupation (*17*) and was not

Table 1. Characteristics of patients with progressive degenerative dementia (PD) and Korsakoff's disease (KD), presented as means ± standard errors.

Characteristic	Group		
	PD (N = 8)	KD (N = 8)	Control (N = 8)
	Demographic measures		
Age (years)	58 ± 3.2	57 ± 6.1	61 ± 4.4
Education (years)	15.7 ± 2.7	11.0 ± 2.5	13.6 ± 2.2
	Psychometric measures		
Wechsler memory scale	72.4 ± 8.1	73.3 ± 10.6	103.6 ± 7.2
	Experimental measures of episodic memory		
Prompted recall			
Recall of words (No.)			
Trials 1 to 5	4.0 ± 0.2	4.2 ± 0.4	7.3 ± 0.6
Trials 6 to 10	4.6 ± 0.3	4.9 ± 0.4	9.7 ± 0.8
Consistency of recall (proportion)			
Trials 1 to 5	0.19 ± 0.03	0.22 ± 0.05	0.72 ± 0.08
Trials 6 to 10	0.24 ± 0.04	0.27 ± 0.06	0.84 ± 0.07
Proportion recalled (of 20)			
Words	0.07 ± 0.04	0.08 ± 0.03	0.42 ± 0.08
Pictures	0.15 ± 0.05	0.11 ± 0.04	0.48 ± 0.01
	Frequency monitoring		
Index*	0.24 ± 0.008	0.26 ± 0.008	1.5 ± 0.01

*Discrimination between frequently and infrequently presented words. A score of 0 indicates inability to accomplish frequency judgments in memory.

significantly different from the IQ score of KD patients. The WMS confirmed the presence of at least a moderate impairment in memory in all of these patients (see Table 1). The laboratory memory-learning procedure used to evaluate patients included a task used by many laboratories to measure changes in episodic memory functions (*18, 19*) as well as other laboratory procedures previously developed in this laboratory to assess disturbances in learning and memory in various patient groups (*20, 21*). The commonly used episodic memory-learning task is one in which subjects are repeatedly presented the same 12 unrelated words until they could all be correctly recalled (a method in which subjects were selectively reminded of those words forgotten on previous recall trials until all words were recalled but for no more than ten learning-test trials). Other tasks, administered at other times, required subjects to listen to and then remember (i) random (unrelated) words, (ii) nominally equivalent unrelated pictures of objects, (iii) unrelated words presented one to four times; later recall of these items was tested along with judgments of how frequently they had been presented to the subject (*20, 21*). Demographic characteristics and various measures of episodic memory performance of matched KD and PD patients are summarized in Table 1.

Patients were then evaluated by four experimental techniques that might characterize access to knowledge in semantic memory. On separate occasions subjects were asked to (i) generate and say aloud appropriate words for 60 seconds in response to stimuli that were either single letters of the alphabet or category names (natural categories) such as four-footed animals or vegetables; (ii) search their semantic memory (knowledge) for a word that would complete 40 highly structured sentence frames such as: "The wet clothes were hung out to ____" or "Some say that a dog is man's best ____" (*22*); (iii) reply "yes" or "no" in judging which of two events would ordinarily occur first for common themes or activities such as, "If you were eating in a restaurant is this a correct sequence? First eat your food and then read the menu" (*23*); (iv) a script or prose in response to a stimulus "Tell me all the things you would do after getting up in the morning and before you leave the house" (*24*).

The KD and PD patients demonstrated similar and profound learning-memory impairments (i) compared with controls, (ii) on the basis of their WMS performance, (iii) in learning and recalling unrelated words under the prompted or selective reminding procedure (measured by both the number of words recalled and the consistency of their recall), (iv) in recall of random words and pictures presented once, and (v) in memory monitoring of how frequently each event had occurred (each of these results was statistically significant; $P < 0.001$). These findings are summarized in Table 1.

The PD patients, in contrast to both KD patients and control subjects, could think of few words that start with the same letter or belong to some organized natural category of information. They generated fewer than a third of the number of word responses to letters and categories of information generated by KD patients, who were indistinguishable from unimpaired controls [$F(2, 15) = 13.7$; $P < 0.001$]. All of the other measures of access to semantic memory, also clearly differentiated KD and PD patients from one another, but also indicated that KD patients were indistinguishable from unimpaired controls in performing tasks that required them to gain access to previously acquired knowledge. The PD patients were less able to complete sentences appropriately

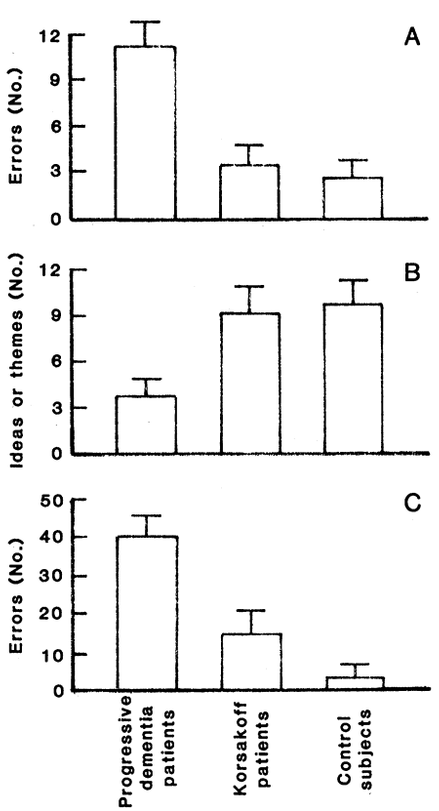

Fig. 1. Semantic memory processes in memory-impaired patients and unimpaired controls. Data are means ± standard errors. (A) Completion of sentence frames. (B) Scheme production. (C) Sequential organization of events within a scheme, ideas, and themes.

than both KD patients and controls [$F(2, 15) = 19.4$; $P < 0.001$] (Fig. 1A), although when errors were made they were semantically and logically related to the sentence context. The PD patients made far more errors than either KD or control subjects in sequencing activities that are part of more complex organized behaviors, such as ordering dinner in a restaurant [$F(2, 15) = 8.4$; $P < 0.01$] (Fig. 1B). However, like both KD patients and controls, the most frequent PD patient errors occurred for those events that would naturally occur close together as opposed to activities that are ordinarily most separate, such as ordering dinner, eating dessert. The PD patients were also less productive than KD or control subjects in generating ideas or themes that define activities in response to the question, "What are things you would do after getting up in the morning?" [$F(2, 15) = 10.6$; $P < 0.01$] (Fig. 1C). On this task they were particularly unproductive and most unlike KD and control subjects in thinking of the more infrequent types of activities or themes.

Impaired episodic memory performance as measured by the WMS and laboratory tests of learning and memory was unrelated to semantic memory performance in KD patients. In sharp contrast, the episodic memory impairment in PD patients was associated with a profound dysfunction in semantic memory functions. Despite the small number of PD patients studied there also appeared to be a consistent relationship between each measure of episodic and semantic memory; of the 16 such relationships tested, no correlation coefficient (r) fell below 0.51. A previous study, with a larger sample of PD patients ($N = 20$) did demonstrate a statistically significant relationship between generating words in response to letters or categories and similar measures of learning and memory ($r = 0.81$, $P < 0.01$) (*23*). Together, these findings provide consistent and convergent evidence that in PD patients memory failures are associated with loss of access to previous knowledge (semantic memory) and that this is not simply a function of impaired language processing (*25*). This is not the case in the equivalently profound episodic memory failures in KD patients. KD patients, and other types of amnestic patients, much like unimpaired subjects, can have reasonably intact access to their previous knowledge despite some impairment in remote memory (*26, 27*). Unlike the PD patients we tested, KD patients can also perform a variety of complex skills such as identifying and assembling complex perceptual figures, identifying words

from fragments and reading inverted text (*4, 5, 12–15*). Nevertheless, KD patients are as unsuccessful as PD patients in establishing permanent records of recently occurring episodic events.

The obvious failures in episodic memory that are readily apparent in Korsakoff's disease, in contrast to similar impairments in PD patients, seem to result from disruptions in different cognitive mechanisms, and these in turn may both be unlike other syndrome-related cognitive failures. For example, the learning-memory failures in depressed patients can resemble those of PD patients, but unlike PD patients they can effectively organize events in memory, and are most likely to demonstrate cognitive dysfunctions on tasks that require sustained activity and effort but not on tasks that can be performed relatively automatically (*21*). For depressed patients and for learning-impaired children, cognitive dysfunction may be linked to levels of motivation, arousal, and activation, which is not the case in PD patients. It is also possible that some forms of memory impairment may result from a disruption in the functional and anatomical linkage between the reward-reinforcement and memory systems of the brain (*21, 28*). The memory pathology of KD patients may be of this type. A preliminary analysis and synthesis of findings based on the relationships between neurochemical, neuroanatomical, clinical, and cognitive findings supports this hypothesis.

A number of drugs can disrupt information processing in unimpaired subjects, and mimic some of these different forms of impairments in memory and learning. For example, alcohol produces a Korsakoff-like memory impairment in unimpaired subjects (*4*). In contrast, cholinergic antagonists produce a dementia-like learning-memory impairment associated with a disruption in access to information in semantic memory (*29*), while cholinergic agonists have some, albeit small, facilitating effect on memory in some senile dementia patients (*30, 31*). Catecholamine antagonists also produce distinctive cognitive changes that resemble those seen in clinical depression, while catecholaminergic agonists, such as amphetamine, enhance similar component cognitive processes (*32, 33*). Neuropeptides when administered to impaired or unimpaired subjects also produce a distinctive pattern of changes in information processing (*34*).

These different findings all suggest that human learning and memory are determined by multiple and discrete psychobiological mechanisms. A disruption of any one of these component processes can result in superficially similar but nevertheless fundamentally different cognitive changes. "Amnesias" can be seen as a final common pathway for a variety of cognitive dysfunctions. The development of effective therapeutic strategies for treating common learning-memory impairments requires that we begin to appreciate and define some of these forms and mechanisms of cognitive dysfunctions.

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Spectral Consequences of Photoreceptor Sampling in the Rhesus Retina

Abstract. *Optical transforms were used to compute the power spectra of rhesus cones treated as arrays of image sampling points. Spectra were obtained for the central fovea, parafovea, periphery, and far periphery. All were consistent with a novel spatial sampling principle that introduces minimal noise for spatial frequencies below the Nyquist limits implied by local receptor densities, while frequencies above the nominal Nyquist limits are not converted into conspicuous moiré patterns, but instead are scattered into broadband noise. This sampling scheme allows the visual system to escape aliasing distortion despite a large mismatch between retinal image bandwidth and the Nyquist limits implied by extrafoveal cone densities.*

Like television and photography, vertebrate vision is based on discrete sampling of spatially continuous optical images. Spatial sampling of this sort can introduce two types of distortion: aliasing and noise (*1*). Aliasing is a moiré effect created by spatially regular sampling arrays, such as television rasters. Regular arrays allow perfect reconstruction of images whose spatial bandwidth does not exceed their Nyquist limit (half the sampling rate), but spatial frequencies above that limit are converted on a one-to-one basis into spurious low frequencies in the postsampling image. Noise is the analogous defect of spatially irregular sampling arrays, such as silver halide grains in photographic film. Perfectly random (Poisson) arrays have no Nyquist limit and produce no aliasing. The cost is a spectral scattering that affects high and low spatial frequencies