

Review Article

Korsakoff's syndrome

Introduction and history of the Wernicke-Korsakoff syndrome

The Korsakoff syndrome is defined as a disproportionate impairment in memory, relative to other aspects of cognitive function, resulting from nutritional (thiamine) depletion. Relatively small neuropathological lesions give rise to a severe amnesic syndrome. The neurochemical processes involved and the precise specification of the nature of the memory deficit remain topics of intense investigation.

Korsakoff (1887, 1889 a, b) described a syndrome of characteristic memory disturbance, witnessed in "not less than thirty" cases of chronic alcohol abuse, as well as 16 patients in whom alcohol had not played a role. He did not make any specific reference to Wernicke's syndrome, which had been described in 1881, but mentioned a prodromal state. Memory disturbance occurs in a setting of clear consciousness and characteristically "the memory of recent events...is chiefly disturbed", but in some cases memories "of the long past" (up to 30 years earlier) were also affected. Korsakoff emphasised the variability in the severity of the disorder and how events could be remembered "but not the time when they occurred". Confusion of "old recollections with present impressions", jumbled in temporal sequence, resulted in confabulation.

The neuropathology

There are petechial haemorrhages, endothelial proliferation, focal areas of parenchymal necrosis, demyelination, gliosis and variable degrees of neuronal loss in the paraventricular and peri-aqueductal grey matter, cerebellum, and the walls of the third and fourth ventricle. The mammillary bodies and the thalamus are among the sites commonly affected. Similar changes are sometimes found in post mortem studies of subjects with a history of alcohol abuse but lacking a Wernicke-Korsakoff diagnosis during life. The latter group show cortical atrophy, acute or "active" pathological changes (haemorrhages, endothelial proliferation), but more commonly chronic "inactive" changes (necrosis, gliosis). Gross atrophy, reduced neuron count, and increased hydration of the frontal lobes are commonly observed in alcoholic subjects at autopsy, particularly those with a diagnosis of Wernicke-Korsakoff syndrome.

The precise location of the lesions responsible for the amnesia is controversial. The balance of the more recent evidence appears to suggest that the critical areas in memory formation are a circuit comprising the hippocampus, entorhinal and perirhinal cortex, mammillary bodies, mammillo-thalamic tract and the anterior nucleus of the thalamus. Variable degrees of atrophy of brain tissue is a consequence of chronic alcohol abuse, even in the absence of Wernicke's encephalopathy (Kril and Halliday, 1999), therefore changes in cellular density should be interpreted with some caution. Harding *et al* (2000) compared the brains of 5 alcoholic patients with Wernicke's encephalopathy who did not develop profound amnesia ('Wernicke only') with those of 8 patients who became severely amnesic ('Korsakoff'). They found that neurodegeneration of the mammillary and medial dorsal thalamic nuclei was substantial in both groups, but that neuronal loss in the anterior (principal) thalamic nuclei was found consistently only in the Korsakoff

group. This suggested that damage in the anterior thalamus is critical for the development of amnesia, a finding consistent with some studies of thalamic infarction (von Cramon *et al*, 1985).

Neurochemistry of the Korsakoff's syndrome

Disorientation and confabulation show a favourable response to thiamine therapy in very early Korsakoff cases (Bowman *et al*, 1939). The onset of symptoms, which included mental changes in 78% of cases and loss of recent memory in 61%, generally occurred after 6-14 weeks, similar to beriberi but before the symptoms of other vitamin deficiencies. The combination of thiamine deficiency and the direct neurotoxic action of alcohol may be required to produce a persistent memory loss (Freund, 1973; Butters & Cermak, 1980) and the response to treatment seems to be determined by the aetiology, the age of the patient (Tallaksen *et al*, 1993), the abruptness of the onset and the rapidity with which treatment is instituted. Moreover, alcohol reduces both the absorption of thiamine and the activity of the enzyme which converts it to its active form. Transketolase is an enzyme which requires thiamine pyrophosphate (TPP) as a co-factor. A hereditary abnormality of transketolase metabolism might predispose some alcoholics to the Korsakoff syndrome (Blass & Gibson, 1977). TPP, the active form of thiamine, appears to be involved in DNA synthesis as well as three enzymatic reactions which are essential for glucose metabolism and neurotransmitter production (Witt, 1985). The metabolic heterogeneity of different brain regions might explain why some areas are more vulnerable to thiamine depletion than others. Six neurotransmitter systems are affected by thiamine depletion, whether by reduction of TPP-dependent enzyme activity, or by direct structural damage, and four of these neurotransmitters, acetylcholine, glutamate, aspartate and gamma-aminobutyric acid (GABA), are directly related to glucose metabolism.

Neuro-imaging studies

There is ventricular enlargement with sulcal widening in alcoholics, usually worse in Wernicke-Korsakoff patients. Research studies indicate a significant correlation between sulcal widening and overall cognitive impairment, especially frontal sulcal enlargement. Jacobson and Lishman (1987) found that the degree of third ventricular enlargement, which presumably reflects thalamic and hypothalamic pathology, correlates significantly with the severity of memory impairment, and Kopelman *et al* (2001) found significant correlations between MRI measures of thalamic volume and anterograde memory performance. Colchester *et al* (2001) found significantly reduced thalamic volumes on MRI in Korsakoff patients with evidence also of mammillary body atrophy, whereas the temporal lobes, hippocampi and parahippocampal gyri did not differ significantly from healthy controls. These findings contrasted with the MRI results in another group of amnesic patients who had underlying temporal lobe pathology, secondary to herpes encephalitis. Reed *et al* (2003) reported white matter hypermetabolism on fluoro-deoxy-glucose PET with relative hypometabolism in the diencephalic and medial frontal grey matter.



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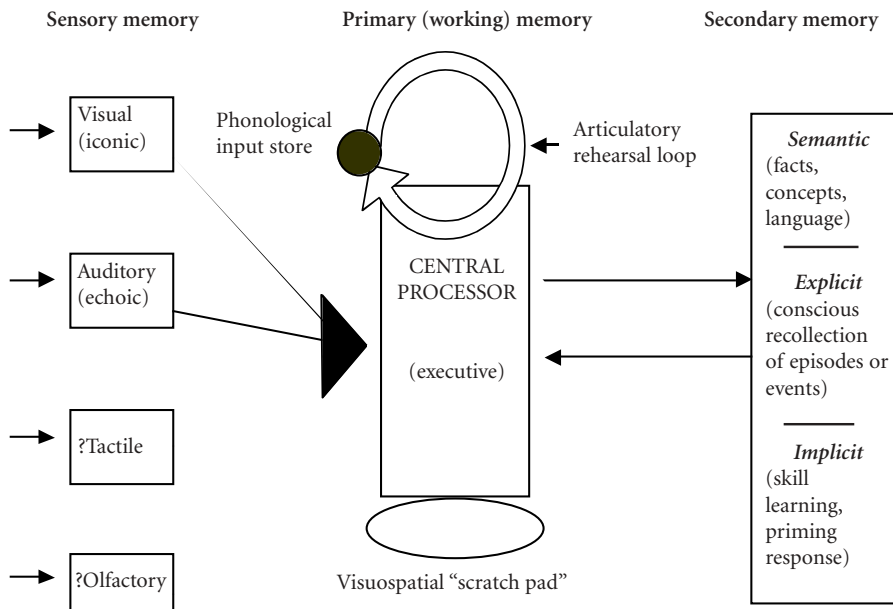
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Neuropsychology of the alcoholic Korsakoff syndrome

FIGURE 1. Current concepts in memory research.



Jacobson and Lishman (1987) reported a variable degree of impairment on a standard IQ test in alcoholic brain damaged patients indicating a continuum between patients with disproportionate impairment of anterograde memory and those with a more generalised cognitive decline (alcoholic dementia). There is also considerable evidence of frontal lobe or "executive" dysfunction in Korsakoff patients and various aspects of their memory complaints may be related to this.

There are many investigations showing that performance on span tests (verbal and non-verbal) is preserved in the Korsakoff syndrome. Performance on short-term forgetting tasks is much more variable on both verbal and non-verbal tasks. Some authors have postulated that this variability in performance is correlated with the degree of frontal lobe dysfunction and others have argued that these impairments are correlated with left-hemisphere and right-hemisphere cortical atrophy respectively, as measured on CT scans.

The explicit component of secondary memory refers to consciously aware memories for events or episodes. Korsakoff patients have a severe deficit in acquiring such explicit memories, but their problem does not seem to result from accelerated forgetting of previously acquired memories (at least on testing of recognition memory). Implicit memory refers to learning of which the subject is not consciously aware. It encompasses simple conditioning tasks, the acquisition and retention of perceptuo-motor skills (procedural memory) and priming, which refers to the facilitation of a particular response to cues by an earlier stimulus. Korsakoff patients show preserved implicit memory. The implicit memory system is mediated by cortical structures (priming) and/or subcortical

TABLE 1. Neuropsychology of Korsakoff's syndrome.

Primary/ working memory	Relatively intact (span test, "short term" forgetting)
'Psychological' encoding	
Semantic	Deficits probably insufficient to account for amnesia
Contextual	Deficits incidental to amnesia rather than core feature?
'Complex associations'	Currently under investigation
'Physiological consolidation'	Difficult to assess in man
Retention/storage/forgetting/ retrieval	Intact if learning accomplished Deficits secondary to encoding/consolidation
Priming/procedural learning (Skills)	Preserved
Retrograde amnesia	Extensive impairment (25 years or more with temporal gradient)

structures (procedural memory), distinct from the impaired explicit memory system, mediated by limbic-diencephalic structures. There is also some evidence of preserved affective or evaluative memory responses, possibly mediated by amygdaloid circuitry.

Semantic memory is a conglomerate term referring to knowledge of language, concepts, and well-rehearsed facts. Korsakoff patients show relative preservation of performance on semantic memory tests compared with Alzheimer or other dementia patients. However, they are often impaired at speeded tasks such as verbal fluency, and they usually fail to learn the names or definitions of words which have come into the language since the onset of the disorder.

Each memory type can have a retrograde and/or anterograde component. There is clearly extensive retrograde memory loss in the Korsakoff syndrome, extending back to 25-30 years. This loss includes memory for public or semantic information, facts about their own life, and autobiographical memory for incidents or events from the patient's past. All these aspects of retrograde memory show a temporal gradient, with relative sparing of the most distant memories, and the gradient is significantly steeper than that seen in dementing patients. The patients show a pronounced improvement on recognition memory testing for this "old" material, indicating a retrieval component to the disorder.

It is rare for florid and spontaneous confabulation to persist beyond the initial confusional Wernicke stage; it is likely to result from disorganised and disinhibited retrieval of memories and associations and, if persistent, it is associated with frontal lobe (rather than diencephalic) pathology. Table 1 summarises the pattern of preserved and impaired memory processes in the Korsakoff syndrome.

Conclusion

The Korsakoff syndrome is characterised by prominent memory and new learning impairment whilst other cognitive functions remain relatively intact. This clinical picture can be preceded by Wernicke's syndrome, but coma and an insidious onset are alternative initial manifestations of the disorder. The characteristic neuropathology is sometimes found at autopsy in alcoholic subjects who have never been diagnosed during life. The main lesions are in the periventricular and periaqueductal grey matter, and lesions in the thalami and mammillo-thalamic tracts and mammillary bodies damage neuronal circuitry which is known to be critical for memory formation. There has been controversy regarding the relative importance of these structures: Harding *et al* (2000) have recently indicated that neurodegeneration of the anterior principal nucleus of the thalamus is the only consistent lesion differentiating Korsakoff patients from others with Wernicke's encephalopathy. Neuro-imaging and autopsy studies have corroborated that cortical atrophy, particularly in the frontal lobes, is also present in many cases. The reason why some alcoholic subjects are more vulnerable to thiamine depletion and to developing the characteristic lesions is still poorly understood. Neuropathological studies indicate a severe deficit in anterograde explicit memory with intact or relatively well-preserved working memory, priming, procedural memory and the rate of long-term forgetting (at least on recognition memory testing). Whilst structural lesions and/or neurochemical deficiencies involving the limbic-diencephalic circuits produce anterograde amnesia, other factors, such as a retrieval deficit perhaps associated with frontal lobe atrophy, may account for the severe retrograde memory loss.

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