

Neuroanatomy and Neuropathology Associated with Korsakoff's Syndrome

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Abstract Although the neuropathology of Korsakoff's syndrome (KS) was first described well over a century ago and the characteristic brain pathology does not pose a diagnostic challenge to pathologists, there is still controversy over the neuroanatomical substrate of the distinctive memory impairment in these patients. Cohort studies of KS suggest a central role for the mammillary bodies and mediodorsal thalamus, and quantitative studies suggest additional damage to the anterior thalamus is required. Rare cases of KS caused by pathologies other than those of nutritional origin provide support for the role of the anterior thalamus and mammillary bodies. Taken together the evidence to date shows that damage to the thalamus and hypothalamus is required, in particular the anterior thalamic nucleus and the medial mammillary nucleus of the hypothalamus. As these nuclei form part of wider memory circuits, damage to the inter-connecting white matter tracts can also result in a similar deficit as direct damage to the nuclei. Although these nuclei and their connections appear to be the primary site of damage, input from other brain regions within the circuits, such as the frontal cortex and hippocampus, or more distant regions, including the cerebellum and amygdala, may have a modulatory role on memory function. Further studies to confirm the precise site(s) and extend of brain damage necessary for the memory impairment of KS are required.

Keywords Wernicke encephalopathy · Thiamin deficiency · Alcoholism · Diencephalon · Memory

The key neuropsychological features of Korsakoff's syndrome (KS), that are discussed in detail elsewhere in this issue, are profound deficits in memory for new material (anterograde) and temporally-graded deficits in remote memory (retrograde). The neuroanatomical regions that subserve these functions are a complex circuit of cortical and subcortical nuclei connected by white matter tracts. Although we have learned a great deal from the study of lesions in any one of these nuclei or tracts, focussing on a single site does not adequately reflect the degree of inter-connectedness of the circuit. Neuropathological examinations of well characterized patients with KS have yielded valuable information on both the type and topography of pathology in KS, however the site or sites of pathology that are both necessary and sufficient to cause KS have not been fully elucidated. Furthermore, the mechanism(s) of cell damage and the explanation for the regional vulnerability are not known. There is also controversy over the relative contribution of alcohol abuse and whether a number of different lesions affecting different nuclei can result in a similar clinical syndrome.

Neuropathological studies have the advantage of being able to detect small or subtle lesions below the resolution of imaging modalities, to allow the investigation of co-existing or contributory pathologies and to study multiple nuclei in the same individual; however, they are inherently retrospective and the interval between the onset of the disorder and autopsy is often prolonged. Adaptive changes, such as secondary degeneration of nuclei or fiber tracts following injury to interconnected brain regions, can alter the pathological picture. Such changes can obscure primary pathologies and

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may result in erroneous conclusions being drawn. A further drawback is the marked decline over the past decades in the number of autopsies being performed. This means that individuals with chronic disorders are often not autopsied, so the potential for more refined studies using improved histological and molecular techniques is reduced. Newly developed imaging techniques have enhanced the *in vivo* diagnosis of the Wernicke-Korsakoff syndrome (WKS) and, for the first time, allowed us to study in real time brain connectivity as well as anatomy. These significant advances would be made even more valuable if coupled with detailed histopathological assessments.

Neuropathology of WKS

Macroscopic examination of the brain in patients with KS reveals little overt pathology. Shrinkage and brown discoloration of the mammillary bodies and dilatation of the ventricular system are seen to varying degrees in the majority of patients. Rarely, grey discoloration indicative of necrosis is seen in the regions surrounding the third and fourth ventricles. The most striking microscopic feature is gliosis that results, in part, from an increase in packing density of cells due to atrophy of these regions. In most instances there is apparent sparing of neurons, although quantitative studies reveal fewer neurons in most regions compared with controls (see section below). Evidence of prior haemorrhage, indicated by the presence of hemosiderin-laden macrophages, and endothelial hypertrophy indicative of Wernicke encephalopathy (Harris et al. 2008) are seen in some patients.

Much of what we have learned of the distribution of pathology in the Wernicke-Korsakoff syndrome (WKS), and the correlates with clinical deficits, comes from the large autopsy series of Malamud and Skillicorn ($N=70$; (Malamud and Skillicorn 1956)) and Victor and colleagues ($N=245$; 82 with neuropathological examination; (Victor et al. 1989)). These series were collected in California between 1946 and 1956, and Massachusetts between 1950 and 1961, and are noteworthy for the extent of the neuropathological examination and the rich clinical data used for correlations. Table 1 outlines the characteristics of the groups studied. In both series the male to female ratio is approximately 2:1 and the mean age at onset is in the 50s, although the range from 20s to 70s. Malamud and Skillicorn (Malamud and Skillicorn 1956) studied inpatients from psychiatric facilities who were institutionalized due to “mental deterioration”. Sixty-two (90 %) had a history of alcoholism. In Victor and colleagues series (Victor et al. 1989), which was derived from general hospital admissions, only 2 patients were confirmed as not alcoholic. Of the remaining alcoholism was confirmed in 175.

Table 1 Characteristics and neuropathological findings in alcoholic WKS

	Malamud & Skillicorn	Victor et al.
N	70	245
Gender (M:F)	52:18	154:91
Mean age at onset (y)	58	51 (est.)
History of alcoholism N (%)	63 (90 %)	243 (99 %)
Neuropathology (%)		
Mammillary bodies	96	100
Dorsomedial thalamus	53	88
Pulvinar	4	85
Brainstem nuclei	23	55
Cerebellum	34	56

Neuropathological examination revealed lesions in the mammillary bodies of virtually all patients, however the frequency of lesions in other periventricular regions varied markedly between the two studies (Table 1). These differences in prevalence of lesions may reflect methodological differences in the neuropathological examination. For example, in many cases Victor and colleagues examined serial sections of periventricular regions increasing their probability of detecting abnormalities. Although both studies are extensive in the breadth of neuropathological examination neither comment on the severity of pathology or the involvement of various nuclei within a single patient. For these reasons it is difficult to develop a complete picture of the anatomical loci that are key to the clinical deficits in KS. Victor and colleagues conclude that it is involvement of the mammillary bodies, mediodorsal nucleus of the thalamus and medial pulvinar that correlates with the presence of amnesia in their series (Victor et al. 1989). The absence of pathology in the mediodorsal nucleus of the thalamus in 5 patients with Wernicke encephalopathy but no evidence of amnesia led to the final conclusion that this nucleus plays a key role in development of memory dysfunction.

Not all authors agree that damage to the mediodorsal nucleus of the thalamus is crucial for KS. Mair and colleagues (Mair et al. 1979) described 2 patients with well documented KS in that there was damage to the mammillary bodies and gliosis adjacent to the third ventricle but no apparent neuronal loss from the mediodorsal nucleus, or from elsewhere in the thalamus. The authors concluded, following an extensive review of the literature of the time, that the mammillary bodies are the key site of pathology in KS. A similarly extensive clinicopathological study of two cases by Mayes and colleagues confirmed the finding of gliosis adjacent to the third ventricle and sparing of the mediodorsal nucleus of the thalamus (Mayes et al. 1988).

Involvement of Memory Circuits in KS

Our current understanding of the nuclei and pathways involved in the various aspects of memory function has been derived from a combination of investigations using patients with brain lesions, behavioral studies, functional imaging and electrophysiology. These data have been enhanced with studies of animal models. Some of the principal brain areas involved in episodic memory are the hippocampal formation, mammillary bodies, anterior thalamic nucleus and cingulate cortex (Aggleton and Brown 1999). These regions are connected by the fornix, mamillothalamic tract and cingulum (Fig. 1).

In Aggleton and Brown's description of the circuitry of episodic memory they designate as central the hippocampus-anterior thalamus axis and then as secondary, a more diffuse and extended network of connections that involves the temporal and frontal cortices (Aggleton and Brown 1999). The anterior thalamus receives direct input from the hippocampus via the fornix and indirect input from the hippocampus via the mammillary bodies and the mamillothalamic tract (Fig. 1). Disruption to these connections is at the heart of anterograde amnesia, although there is likely involvement of other midline thalamic nuclei. Connections between the anterior thalamus and frontal lobe (prefrontal and cingulate cortices), reciprocal connections between the frontal lobe and medial temporal cortices and between the mediodorsal thalamus and medial temporal cortices provide modulatory influences on memory function. Lesions in these cortical regions and the cingulum

have a less marked effect on memory function (Aggleton and Brown 1999). Furthermore, some authors have highlighted the modulatory role of the amygdala (Mair et al. 1979; Richardson et al. 2004).

Quantitative, postmortem studies in KS are rare and the sample sizes small. Using unbiased stereological techniques we compared the brains of KS patients ($N=8$) with those from WKS patients with pathological evidence of thiamin deficiency but without amnesia ($N=5$), alcoholics without WKS or amnesia ($N=5$), and normal controls ($N=6$) (Harding et al. 2000). When compared with controls, non-amnesic alcoholics showed no significant reduction in either the volume or neuron number in the mammillary body, anterior principal or mediodorsal nuclei of the thalamus (Table 2). WKS patients without amnesia showed significantly fewer neurons in both the mammillary bodies (53 % of control mean) and mediodorsal thalamus (52 % of control mean), but not the anterior principal nucleus. Compared with controls, KS patients showed both smaller volume and fewer neurons in all three nuclei (Table 2; Fig. 2; (Harding et al. 2000)).

By contrast, compared with controls the volume of the hippocampus is smaller in alcoholics, including those with KS, but there is no difference in neuron number in any of the sub-regions including the CA1 (Harding et al. 1997). Interestingly, the smaller volume is a result of less white matter rather than a grey matter deficit and relates to whether or not the alcoholic patient was drinking at the time of death or had remained abstinent, but was independent of amnesic state

Fig. 1 A schematic diagram of the brain regions and connections involved in memory. The major hippocampus-anterior thalamus axis (shaded) involves the hippocampus, anterior thalamus, mammillary bodies and cingulate cortex and is connected by the fornix, mamillothalamic tract (MTT) and cingulum. The extended connections involving the amygdala, mediodorsal thalamus, and temporal and frontal cortices have a modulatory role (for description see (Aggleton and Brown 1999))

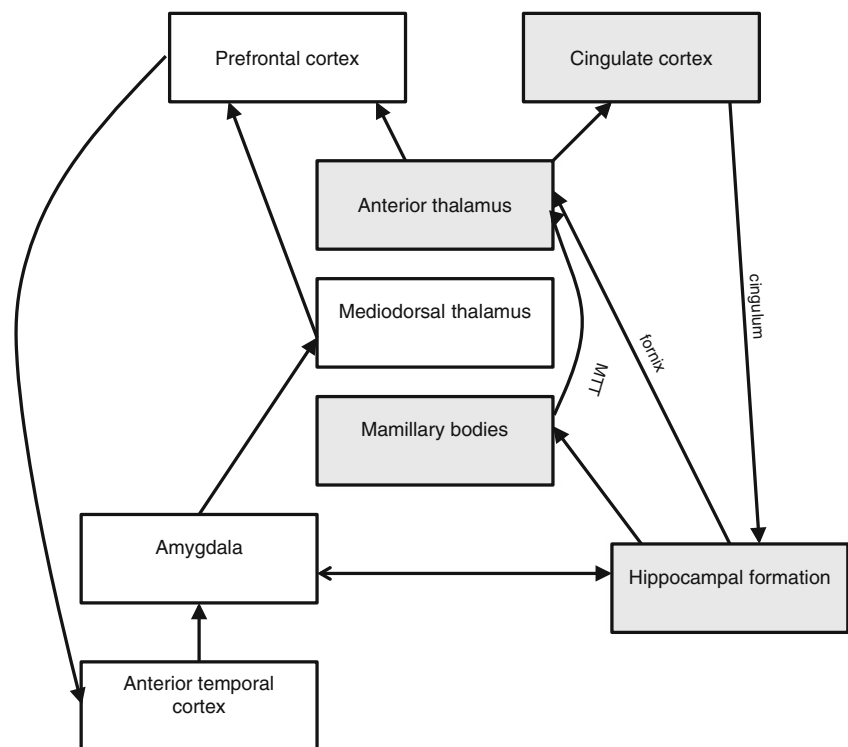


Table 2 Quantitative neuropathological assessment of brain regions involved in memory function in KS in comparison with alcoholics without KS and those with thiamin deficiency but no amnesia (WE). Values expressed as percentage of control mean

Region	Volume			Neuron number			Ref
	Alcoholic	WE	KS	Alcoholic	WE	KS	
Mediodorsal thalamus	100	88	56 ^a	100	52 ^a	36 ^a	1
Anterior principal thalamus	93	87	63 ^a	100	86	47 ^a	1
Mammillary bodies	89	78	33 ^a	98	53 ^a	32 ^a	1
Dorsolateral prefrontal ctx (BA8)				77 ^a	80 ^a	84	2
Primary motor ctx (BA4)				93	81	85	2
Hippocampal CA1				100	–	100	3
Cerebellar vermis	84	100 ^b	–	79	75 ^b	–	4
Basal nucleus of Meynert	–	–	–	100	76 ^a	79 ^a	5

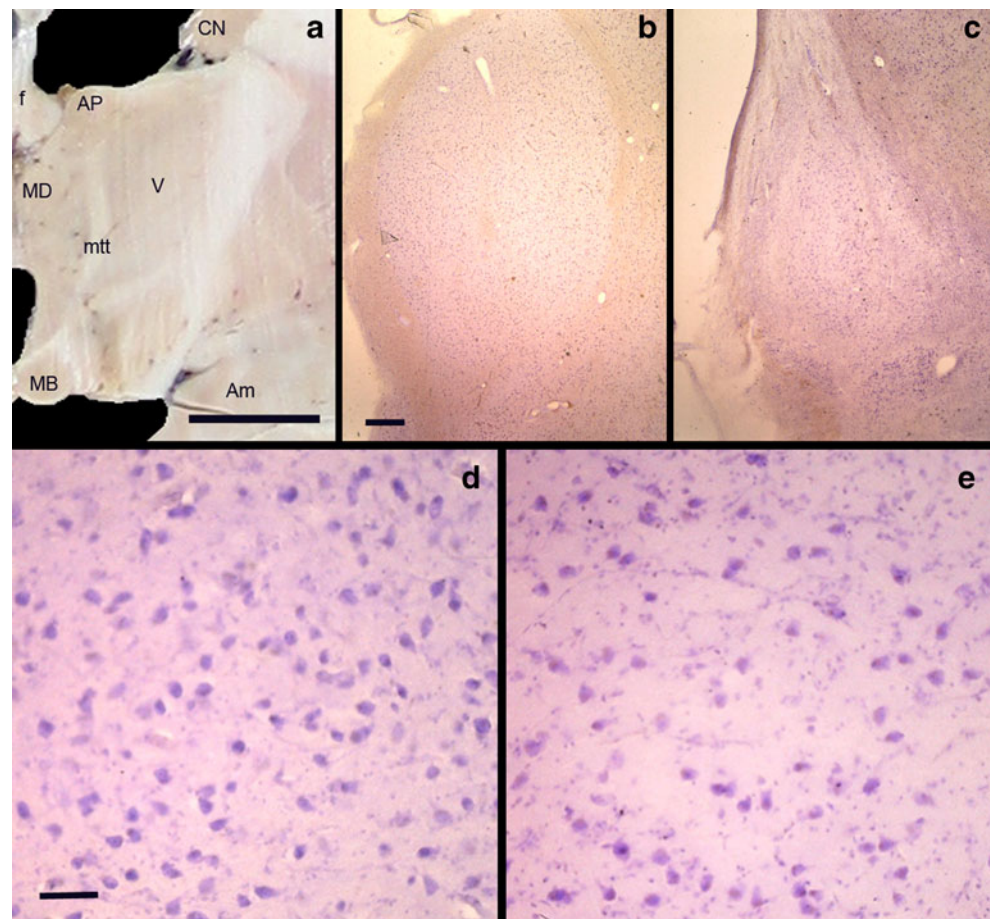
^a significantly reduced compared with control values. ^b 3 of 6 WE cases had memory impairment.

References: 1 = Harding et al. 2000; 2 = Kril et al. 1997; 3 = Harding et al. 1997; 4 = Baker et al. 1999; 5 = Cullen et al. 1997

(Harding et al. 1997). In the cortex, the volume of the cingulate cortex in KS is similar to controls (Kril et al. 1997), and there is no difference in neuron density in alcoholics with WKS (Kril and Harper 1989), although the latter were not selected to include only KS patients. The only cortical region where atrophy is identified at postmortem is the dorsolateral

prefrontal cortex (Kril et al. 1997). Alcoholics show approximately 20 % fewer neurons in this region but this is equivalent in all alcoholic groups regardless of the presence or absence of KS (Kril et al. 1997). Atrophy and neuron loss from the amygdala is equivalent in WKS patients with and without amnesia (Kril & Halliday, unpublished data). In

Fig. 2 (a) A photograph of a coronal section through the diencephalon of a normal brain showing the nuclei involved in memory circuits. Nuclei labelled are AP = anterior principal nucleus of the thalamus; MD = mediodorsal nucleus of the thalamus; MB = mammillary body (medial mammillary nucleus of the hypothalamus). The tracts connecting these nuclei are the mamillothalamic tract (mtt) and fornix (f). The caudate nucleus (CN) and amygdala (Am) are also labelled. Photomicrographs of the anterior principal nucleus of the thalamus in a control subject (b, d) and KS patient (c, e). The volume of the nucleus is smaller in KS (c) compared with the control (b). A decreased density of neurons and increased density of glia can be seen in KS (E). Bar in A=1 cm. Bar in B=1 mm (equivalent for C). Bar in D=50 μ m (equivalent for E)



response to the report by Arendt and colleagues (Arendt et al. 1983) that neuron loss from the cholinergic basal forebrain is important for the development of KS, we undertook a 3-dimensional study of this region in WKS patients with and without amnesia (Cullen et al. 1997). We showed that compared with controls neuron number is reduced, but that it did not differ between groups (Cullen et al. 1997) (Table 2).

Taken together these studies suggest that damage to the anterior principal nucleus of the thalamus is required for the clinical manifestation of KS; however, as the mammillary bodies, and mediodorsal nucleus of the thalamus are also damaged in these patients it is not possible, from these studies, to determine whether it is the anterior nucleus alone or a combination of two or all three nuclei that is required for KS.

KS in Malnourished Patients Without Alcoholism

Although it is well established that thiamin deficiency results in Wernicke encephalopathy in both alcoholic and non-alcoholic populations, and the underlying neuropathology is the same in both groups, KS is rarely seen in those without a history of alcoholism (Kopelman 1995; Homewood and Bond 1999)

This may be a reflection of the relative rarity in recent decades of thiamin deficiency outside the alcoholic population or suggest an etiological role for alcohol-related brain damage in KS. Alternatively, it could reflect differences in the natural history of thiamin deficiency in alcoholic and non-alcoholic subjects brought about, in part, by the exacerbation of thiamin deficiency by alcohol consumption (Butterworth 1989; Kopelman 1995; Thomson and Marshall 2006). Alcoholic patients who develop Wernicke encephalopathy require larger doses of thiamin for successful treatment implying more severe thiamin deficiency (Cook et al. 1998). It has been also hypothesized that thiamin deficiency in non-alcoholic subjects may be more readily identified at an earlier stage of disease as symptoms are more clearly recognized in those without obvious signs of alcohol misuse (Kopelman 1995; Thomson and Marshall 2006). This results in an earlier and more active treatment response. Furthermore, WKS in alcoholics may result from multiple sub-clinical episodes of thiamin deficiency (Harper and Kril 1994) whereas the insult in non-alcoholic individuals is usually a single episode.

Although they are rare, reports of KS in non-alcoholic subjects provide useful insights into the anatomic substrate (s) of the disease. Unfortunately, however, the majority of reports do not include pathological confirmation of disease or investigation of the extent and severity of neuropathology (Parkin et al. 1991). Nevertheless, the improved diagnosis of WKS with neuroimaging has allowed the topography of lesions in these patients to be explored.

One of the clearest descriptions of thiamin deficiency in non-alcoholic subjects comes from de Wardener and Lennox's description of 52 prisoners-of-war (De Wardener and Lennox 1947). Of the 31 patients who survived the initial episode of Wernicke encephalopathy, 29 recovered following treatment with thiamin or thiamin-rich foods and one recovered without treatment. Only a single patient showed no improvement in mental symptoms, despite physical recovery, suggesting a persistent amnesia.

Recently, Karaiskos and colleagues (Karaiskos et al. 2008) described a 44 year old man with poor dietary food intake who developed dysphagia followed by confusion, disorientation and ultimately a reduced level of consciousness. His symptoms resolved quickly following intravenous thiamin administration; however, he showed the marked anterograde and retrograde amnesia characteristic of KS. T2 and FLAIR MRI sequences, performed at the onset of mental signs, showed symmetric signal hyperintensities in the medial thalami, periaqueductal grey matter and floor of the fourth ventricle. A repeat MRI following treatment, and performed prior to discharge from hospital 2 months after onset of symptoms, showed no hyperintensities. Caulo and colleagues (Caulo et al. 2005) describe a 34 year old man with malnutrition due to oesophageal stenosis following surgery for cancer. The patient developed Wernicke encephalopathy and then, 5 days later, KS that persisted at re-assessment 5 months later. Initial FLAIR sequence MRI, performed 7 days after onset of Wernicke encephalopathy, showed signal hyperintensities in the medial thalamus, mammillary bodies and fornix. These hyperintensities were no longer visible on a repeat MRI performed 5 months after onset of symptoms.

Other Pathologies Resulting in KS

In addition to KS in patients with established nutritional deficiency, there are other examples of neuropathological lesions that give rise to a severe amnesic syndrome, disproportionate to any other cognitive impairment, similar to KS. These cases are not alcohol dependent nor do they have thiamin deficiency and include lesions of traumatic, neoplastic and vascular origin. It has been argued that the term KS is best reserved for those cases with persistent memory impairment and the characteristic pathological changes of thiamin deficiency, while the term "amnesic syndrome" be used for other etiologies (Kopelman 2002). The similarities and differences in amnesic disorders of different etiologies have been reviewed by Kopelman (Kopelman 2002); however, the similarity in memory deficits suggests that much can be learned from these cases. A significant limitation of many of these studies is that they do not have neuropathological assessments and, when present, these assessments

are qualitative rather than quantitative. Furthermore, the complexity of the anatomical regions damaged often makes interpretation of such studies difficult. Simple descriptions of the anatomical disruption caused by the pathological processes are inadequate as it has been shown that routine assessment of some regions, such as the anterior principal nucleus of the thalamus and cerebral cortex, can overlook critical volume and neuronal density changes found in quantitative studies (Kril et al. 1997; Harding et al. 2000). Although the literature contains numerous case reports of KS-like features following a variety of neurological insults, only those that shed light on the neuroanatomical substrates of KS are reviewed here.

Two historical case reports of penetrating injuries to the brain, one with a miniature fencing foil (patient NA; (Teuber et al. 1968)) and another with a snooker cue (patient BJ; (Dusoir et al. 1990)), show marked anterograde amnesia with relative preservation of other cognitive abilities, similar to KS. In each case the implement entered through the nostril and penetrated the basal regions of the brain. In BJ a structural MRI revealed bilateral damage to the hypothalamus, including the mammillary bodies, but no damage to the thalamus (Dusoir et al. 1990). CT scanning of NA performed 17 years after the injury (Squire and Moore 1979) showed damage to the left mediodorsal thalamus; however, subsequent MRIs performed 26 and 27 years after the injury showed more extensive damage that included many of the intralaminar nuclei of the thalamus, the ventral lateral and ventral anterior nuclei, ventral parts of the mediodorsal nucleus, the posterior hypothalamus and bilateral mammillary bodies (Squire et al. 1989). In addition, there was damage to parts of the anterior temporal lobe and amygdala. Importantly, the fiber tracts of the internal medullary lamina, mamillothalamic tract and postcommissural fornix were also disrupted. The extent of the damage, together with the secondary degeneration over time, damage to white matter tracts and the temporal lobe, make it difficult to assess the relative contribution of diencephalic nuclei to the memory impairment seen in this patient. Although there are other reports in the literature of amnesia similar to KS following traumatic brain injury (Jarho 1973; Brion et al. 2001) imaging and neuropathology are either unavailable or uninformative in these cases.

Cases with clinical syndromes similar to KS have also been described following a range of neurovascular insults. KS following dominant hemisphere thalamic infarction was described in 5 patients by Cole and colleagues (Cole et al. 1992). In one patient the lesion involved the mediodorsal and anterior principal nuclei of the thalamus with uncertain involvement of the mamillothalamic tract. More extensive involvement of the thalamus was seen in three of the remaining cases, including bilateral involvement on one case, and the lesion was not able to be precisely located in

the fourth. Bilateral infarcts involving the mamillothalamic tracts were described in a 56 year old man with acute onset of anterograde and retrograde amnesia (Yoneoka et al. 2004). Interestingly, the infarcts were of different ages with the right being remote and the left acute, suggesting a pivotal role for the left hemisphere. The patient was followed for only 6 months but showed no improvement in his memory function. Renou and colleagues (Renou et al. 2008) describe a 66 year old man with MRI evidence of infarction of the genu of the corpus callosum and the anterior columns of the fornix, bilaterally. The patient presented with acute onset of anterograde and retrograde amnesia and neuropsychological assessment confirmed KS. Diffusion tensor tractography performed 11 days after presentation showed marked degeneration of commissural fibres and disruption of frontal connections. At 1 year follow-up the severe amnesia remained.

Similarly some tumours, because of their anatomical position, are more likely to cause symptoms similar to KS. There are case reports of KS-like syndromes in patients with craniopharyngioma (Yarde et al. 1995), following removal of colloid cysts of the third ventricle (Kononov et al. 1998; Tsivilis et al. 2008), and other periventricular tumours such as lymphomas (Toth et al. 2002) that impinge on hypothalamic and thalamic structures. One such example is the case report by McEntee and colleagues (McEntee et al. 1976) where amnesia was observed in a patient with a bilateral thalamic tumour that involved the mediodorsal nuclei, but spared both the mammillary bodies and anterior thalamic nuclei. However, the complexity of the anatomical regions involved in such cases, the often diffuse spread of the tumour and the brain's reaction to the tumour makes interpretation difficult and mean these cases do not contribute greatly to our understanding of the anatomical substrate of KS.

Cerebellar Involvement in KS

In recent years it has been shown that the cerebellum, in addition to its established role in motor control, is involved in cognition. Correlations between motor dysfunction and cerebellar pathology have been well documented using radiological (Sullivan et al. 2000; Sullivan et al. 2006) and neurological (Allsop and Turner 1966) studies. It has also been postulated that cerebello-cerebral disconnection could have a role in the memory and executive dysfunction of KS (Wijnia and Goossensen 2010; Zahr et al. 2010). Fewer cerebellar Purkinje cells compared with controls have been demonstrated in alcoholics (Phillips et al. 1987) including those with WKS (Phillips et al. 1990; Baker et al. 1999). Although in this study cases of KS were not analyzed separately, the marked loss of Purkinje cells in thiamin deficient alcoholics with mental state signs (Baker et al.

1999) adds support to the hypothesis that disruption of cerebello–cerebral pathways might contribute to neurocognitive dysfunction in KS. Nevertheless, the relative contributions of thiamin deficiency and alcoholism remain to be fully elucidated.

Animal Models of KS

A number of animal models of alcohol-related disorders have been developed (reviewed by (Vetreno et al. 2011)). Pyridoxamine induced thiamin deficiency (PTD) in the rat is a well validated experimental model to study the pathophysiology of human Wernicke encephalopathy where the histological lesions generally mirror those seen in the human disorder. If rats are allowed to progress through a severe bout of thiamin deficiency, they develop lesions in the anterior and midline thalamus as well as the mammillary bodies (Zhang et al. 1995; Pfefferbaum et al. 2007). Furthermore, these animals show impaired memory function (Langlais and Savage 1995) and older animals demonstrate greater susceptibility to brain damage (Pitkin and Savage 2001). The PTD model has assisted researchers to address the relative contribution of different anatomical regions to the memory deficits in KS.

In addition, animal models have also been used to establish the relative contribution of alcohol to KS. Experiments in chicks exposed to both thiamin deficiency and ethanol have shown that they develop irreversible memory impairment, even after thiamin replacement. By contrast, the memory of chicks exposed to thiamin deficiency alone returns to normal following correction of thiamin deficiency. Thus, there is some experimental evidence that alcohol permanently damages the thiamin-depleted brain to a greater degree than thiamin depletion alone (Ciccia and Langlais 2000; Crowe and El-Hadj 2002). White matter also appears to be more susceptible to the combined effects of thiamin deficiency and ethanol exposure. Rats exposed to PTD plus ethanol had greater thinning of myelin in the corpus callosum than did those that received only PTD treatment (He et al. 2007).

Conclusions

Despite considerable evidence for the involvement of the diencephalon in the memory impairment of KS, some uncertainty still exists as to the precise location of the minimum lesion required. The absence of pure, focal lesions in humans has meant that reports from a variety of diseases, involving various combinations of nuclei and their connections, have been used to infer the neuroanatomical basis of KS. Taken together, the studies reviewed above would

suggest that damage to the thalamus and hypothalamus are required, in particular the anterior thalamic nucleus and the medial mammillary nucleus of the hypothalamus. This damage can be achieved either by direct involvement of the nuclei or damage to the major connections, namely the fornix and mamillothalamic tract. Although damage to other parts of the circuit, such as cortical regions of the frontal and medial temporal lobes, or other modulatory loci such as the cerebellum and amygdala, may have a contributory effect it would appear that in isolation lesions of these regions are insufficient to result in KS. A combination of rigorous neuropsychological assessment, longitudinal *in vivo* neuroimaging and quantitative neuropathology is required to provide the definitive answer to the question of the neuroanatomical substrates for the various cognitive and function impairments seen in KS.

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