Functional Neuroimaging of Cortical Dysfunction in Alcoholic Korsakoff's Syndrome

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Abstract

■ Many neuropsychological investigations of human memory have focused on the amnesic deficits of alcoholic Korsakoff's syndrome. Structural neuroimaging suggests that the syndrome results from midline diencephalic damage, but functional neuroimaging has the potential to reveal additional neuropathology that may be responsible for cognitive dysfunction. Accordingly, high-resolution positron emission tomography (PET) was used to measure regional cerebral metabolic rates for glucose utilization in five alcoholic Korsakoff patients and nine alcoholic control subjects. Results from a continuous recognition test administered during the radiotracer uptake period indicated that all subjects performed normally with respect to immediate memory, whereas Korsakoff patients demonstrated a marked memory impairment in delayed recognition. PET results from the Korsakoff group showed a widespread decline in glucose metabolism in frontal, parietal, and cingulate regions, suggesting that these functional abnormalities in the cerebral cortex contribute to the memory impairment. Hippocampal glucose metabolism did not differ between the groups. Thus, the evidence did not support the hypothesis that parallel brain dysfunctions are responsible for the similar amnesic symptomatology after hippocampal and diencephalic damage. We hypothesize that the amnesic dysfunction of Korsakoff's syndrome depends on a disruption of thalamocortical interactions that mediate a function critical for normal memory storage. ■

INTRODUCTION

The ways in which memory functions break down after neurological insult provide a rich source of insight into the normal mechanisms for storing information in the brain. Impairments of the ability to remember facts and events can be highly selective, in which case a wide variety of other mental functions are entirely preserved. The evidence implies that the integrity of a specific set of brain areas is necessary for remembering facts and events but not for other types of memory. These brain areas include structures in the medial temporal region, the midline diencephalon, and the basal forebrain (for reviews, see Schacter & Tulving, 1994).

The usual reasoning behind this approach is as follows. An association between a structural brain lesion and a discrete amnesic deficit is taken to imply that a crucial cognitive operation is normally performed within the brain area that is damaged. For example, bilateral lesions in the CA1 field of the hippocampus (in a patient who became amnesic following an ischemic episode during cardiac surgery) led Zola-Morgan et al. (1986) to infer that the intact hippocampus performs a process required for normal memory. However, this sort of inference gives rise to many further questions. How can we understand the critical cognitive process? What is the role of that process in relation to other memory functions? How is that process implemented within the brain?

To address these theoretical issues, not only must the precise loci of critical structural damage be determined, but functional changes in remaining brain areas must also be assessed. In other words, both anatomical and physiological evidence are required. For example, func-

tional changes at sites remote from the lesion have been demonstrated in stroke patients (e.g., Baron, 1989; Szelies et al., 1991). Clinical-pathological correlations associating particular patterns of brain damage with memory dysfunction can be misleading if the altered functioning of other brain areas is not taken into account. Here, we use functional neuroimaging to investigate neural dysfunction in the most prevalent form of amnesia, Korsakoff's syndrome.

Korsakoff's Syndrome

Korsakoff's syndrome occurs most commonly after prolonged alcohol abuse accompanied by inadequate nutrition (for reviews, see Joyce, 1994; Kopelman, 1995; Mair, 1994; Talland, 1965; Victor, Adams, & Collins, 1989). A low dietary intake of thiamine is thought to combine with alcohol-induced impairments in thiamine absorption and metabolism to impair the action of several thiamine-dependent enzymes, eventually leading to cell death (Butterworth, 1989). The mechanism of cell death is unclear but may involve impaired energy metabolism, build-up of lactic acid, or excitotoxic glutamate release. Korsakoff's syndrome is sometimes referred to as the Wernicke-Korsakoff syndrome because it tends to follow the acute phase of Wernicke's encephalopathy, which refers to the symptom complex of disordered eye movements, ataxia of gait, and confusion. These symptoms can effectively be treated with the administration of thiamine such that the acute confusional state of Wernicke's encephalopathy clears. Occasionally, early treatment can prevent the progression to the Korsakoff syndrome. Otherwise, a memory disorder is revealed when the acute symptoms recede. The amnesia is thus thought to be an outcome of structural brain damage and to be largely irreversible. Attempts to explore neuropharmacological therapies have yielded mixed results (Martin et al., 1995; Moffoot et al., 1994; O'Carroll et al., 1994).

In addition to memory problems, Korsakoff patients show characteristic cognitive deficits in temporal discrimination, spatial organization, initiative, abstract reasoning, and other functions. Motor disorders of alcoholic cerebellar degeneration can occur either along with Korsakoff's syndrome or independently and probably derive from the same disease process (Victor et al., 1989). Korsakoff's syndrome has been observed in nonalcoholic, nutritionally compromised patients (e.g., Beatty, Bailly, & Fisher, 1988; Becker et al., 1990; Parkin et al., 1991), and although some of this evidence is equivocal, the earlier literature attests to the contribution of nonalcoholic causes (Kopelman, 1995). Therefore, alcoholism is not a necessary forerunner of Korsakoff's syndrome. Related amnesic disorders can occur after medial diencephalic damage caused by stroke, tumor, or trauma (Butters & Stuss, 1989; Graff-Radford et al., 1990).

Neuropathology of Korsakoff's Syndrome

The classic monograph of Victor et al. (1971) provided an extensive corpus of pathological evidence on Wernicke's encephalitis and Korsakoff's syndrome. Patients who died in the acute Wernicke stage showed bilaterally symmetrical lesions in the paraventricular regions of the thalamus and the hypothalamus, midbrain periaqueductal gray, floor of the fourth ventricle, and superior cerebellar vermis. Microscopic examination showed loss of myelinated fibers and nerve cells along with proliferation of glia and macrophages, and occasional evidence of hemorrhage. The most consistent lesion was found in the mammillary bodies. Evidence from patients who died in the chronic Korsakoff stage was similar except for an association between amnesia and involvement of the medial dorsal nucleus of the thalamus. The pathological evidence thus led to the conclusion that "the lesions responsible for the memory disorder are those of the medial thalami rather than of the mammillary bodies" (Adams & Victor, 1993, p. 856).

Yet, the neuropathological literature on Korsakoff's syndrome faces several interpretive problems. (1) Some damage may be incidentally rather than causally associated with amnesia. (2) Lesion locations responsible for amnesia may differ across patients. (3) Damage to fibers of passage may be critical. (4) The amount of damage to an area may need to pass some threshold in order to produce cognitive symptoms. (5) Many reports do not include complete assessments of both the neuropathology and the memory disorder.

In fact, there are many apparent conflicts in the neuropathological literature. For example, there is disagreement about which portions of the thalamus are critical—the medial magnocellular portion of the dorsomedial nucleus and perhaps the pulvinar (Victor et al., 1989), the lateral parvocellular portion of the dorsomedial nucleus (Markowitsch, 1982), or anterior and midline areas including the paratenial nucleus (Mair, Warrington, & Weiskrantz, 1979; Mayes et al., 1988). On the whole, the human literature does not allow definitive conclusions regarding the roles of various medial thalamic components. Another hypothesis, based on studies in rats, is that the critical damage involves lateral portions of the internal medullary lamina, which affects the dorsomedial nucleus as well as intralaminar and paralaminar nuclei (Mair, 1994).

Furthermore, several hypotheses imply that nonthalamic damage is critical. One idea is that conjoint damage to the medial thalamus and the mammillary bodies, or to significant portions of dual limbic-diencephalic pathways, is critical (Butters, 1984; Mishkin, 1982; Von Cramon, Hebel, & Schuri, 1985). Alternatively, McEntee and Mair (1978) proposed that Korsakoff's amnesia results from brainstem damage that interrupts the ascending norepinephrine system, a view supported by findings of decreased levels of corresponding metabolites in Korsa-

koff patients, results from drug studies, and results from animal studies (McEntee & Mair, 1990; but see Halliday, Ellis, & Harper, 1992, for conflicting results). Another idea is that cholinergic innervation from the basal forebrain plays a critical role (Arendt et al., 1983; Butters, 1985; but see Mayes et al., 1988, for conflicting results).

Other neuropathological studies have shown midline diencephalic changes in 2–3% of all autopsies (Harper, 1983; Victor & Laureno, 1978), a much higher percentage than would be predicted given the lower incidence of Korsakoff's syndrome diagnosed in the general population. This finding suggests either that the syndrome often goes undetected or that the apparent pathological changes are not sufficient to give rise to the syndrome. The idea that Korsakoff's syndrome can develop gradually is consonant with the clinical literature and also supported by pathologic results from intermittent thiamine deprivation in monkeys (Witt & Goldman-Rakic, 1983).

Importantly, gross cortical pathology does not appear to be a consistent feature of the syndrome. Although observed in many Korsakoff patients (Lishman, 1981; Victor et al., 1989), several detailed case studies failed to find significant cortical pathology (Mair et al., 1979; Mayes et al., 1988). On the whole, the recent literature on postmortem pathology does not provide strong support for the idea that cortical damage is critically associated with the memory disorder.

Structural neuroimaging studies of Korsakoff patients have confirmed the existence of midline diencephalic lesions (Blansjaar et al., 1992; Charness & DeLaPaz, 1987; Jernigan et al., 1991; Squire, Amaral, & Press, 1990) and revealed indications of cortical atrophy (Carlen et al., 1981; Jacobson & Lishman, 1990; Jernigan et al., 1991; Shimamura, Jernigan, & Squire, 1988). In these studies, volume losses in cortical areas were often not more severe in Korsakoff patients than in non-Korsakoff alcoholics, although Jernigan et al. (1991) observed disproportionate volume loss in orbitofrontal and medial temporal areas. Some investigators have accounted for the cortical findings by postulating a dual basis for the cognitive impairments of Korsakoff's syndrome: (a) diencephalic damage due to thiamine deficiency, leading to amnesia, and (b) cortical atrophy probably due to alcohol neurotoxicity, leading to additional problems (e.g., Jacobson & Lishman, 1990; Moscovitch, 1982; Shimamura et al., 1988; Shimamura & Squire, 1986; Squire, 1982). Nonetheless, the nature, etiology, and relevance of cortical factors in Korsakoff's syndrome remains controversial.

Tests of Hypotheses via Functional Neuroimaging

Three hypotheses can be formulated to describe the neural dysfunction responsible for the amnesic symptoms in Korsakoff's syndrome. The first and simplest hypothesis is that the relevant functional damage is limited to the midline diencephalon. A second hypothesis is that additional brain areas in the medial temporal region are affected. For example, Butters & Stuss (1989) suggested that diencephalic amnesia in general may arise from disrupted connections between the diencephalon and medial temporal lobe structures. Indeed, some structural evidence is suggestive of hippocampal involvement (Jernigan et al., 1991; Mayes et al., 1988; Victor et al., 1989). Furthermore, this scenario would explain the common observation that diencephalic amnesia and bitemporal amnesia are indistinguishable on neuropsychological grounds. Despite intuitive appeal, the empirical basis for this hypothesis is presently weak. A third alternative is that functional impairments are widespread, encompassing multiple cortical areas.

Evidence from structural neuroimaging or from postmortem histology cannot adequately test these alternatives. These sources of evidence are incomplete, because the functioning of remaining brain tissue is not taken into account. Relevant physiological evidence can be provided by functional neuroimaging with positron emission tomography (PET) and the radiotracer F-18-fluorodeoxyglucose (FDG). Due to the strong similarity between FDG and glucose, FDG is taken up by brain cells in proportion to their metabolic requirements, which is in turn proportional to level of neuronal activity (Phelps et al., 1979). Because FDG is not readily metabolized further, PET can provide 3-dimensional localization of neuronal activity that occurs following radiotracer injection.

In this study, we compared Korsakoff patients to age-matched alcoholic control subjects who were not amnesic. In each individual, four PET scans were sequentially obtained using a single-slice tomograph specially constructed to yield high spatial resolution. Radioactivity from PET and from arterial blood sampling were used to obtain quantitative measures of regional cerebral glucose utilization. These indirect measures of neuronal activity thus provided indications of the functional integrity of various brain regions.

Given that PET results are influenced by the cognitive state of the subject during the radiotracer uptake period, we controlled cognition using a behavioral challenge procedure that taxed multiple cognitive functions, including the memory functions of interest. Beginning just prior to the FDG injection, each subject saw a list of words presented one at a time, with some words appearing in the list more than once. The subject read each word and decided whether it had appeared before. The entire test lasted approximately 20 minutes, which covered the time during which the majority of FDG was taken up in the brain (Phelps et al., 1979).

RESULTS

Behavioral Results

The behavioral results fell into two categories—memory performance measures obtained during the PET scan

procedure and neuropsychological performance measures obtained during separate testing sessions. The latter category was included in order to thoroughly characterize the patients' impairments in memory and other cognitive functions. A battery of standardized and special-purpose tests was used. A summary of scores from these tests is shown in Table 1. General tests such as the WAIS and the Mini-Mental Status Exam showed decrements in the patient group. However, an estimate of premorbid IQ did not differ between groups,[1] suggesting that the alcoholic group was a well-matched control group.

The memory impairment in the Korsakoff group was evident in scores from several standardized memory tests. For example, two-choice recognition judgments in the Warrington Recognition Memory Test for words yielded a range of scores in the Korsakoff group (25–36) that was well below that in the alcoholic group (41–50). Tests of other cognitive functions showed additional impairments in the Korsakoff group, such as in copying simple geometric objects and in abstract reasoning as assessed in sorting tests. Language capabilities were good, but slight deficits were detected in the Boston Naming Test and the Token Test. Note that the patient selection criteria focused on patients with relatively circumscribed memory deficits, so that patients with more global cognitive impairments (i.e., patients with diagnoses of alcoholic dementia) were excluded from this group.

The expected patterns of memory performance were also demonstrated during the PET procedure. Korsakoff patients performed well when immediate memory was sufficient to guide performance, but poorly when memory was tested with a significant delay between acquisition and retrieval. Figure 1 shows the forgetting functions for the two groups over delays up to approximately 1 min. Mean scores in the two groups did not differ significantly for delays of 1 or 2 trials [$t(12) = 0.7$ and $t(12) = 0.2$, respectively], whereas they did for delays of 4, 8, and 16 trials [$t(12) = 5.5$, $t(12) = 6.2$, $t(12) = 8.8$, respectively, $p < 0.0001$ for each].

Figure 2 compares the key memory scores from the behavioral challenge. The immediate memory score was computed by averaging across the two shortest delays.

Table 1. Mean scores from neuropsychological testing for both groups (ranges in parentheses). Group differences significant at the 0.05 level are indicated by a *. See text for abbreviations.

Measure	*Korsakoff Group*		*Alcoholic Group*		
General					
Full-scale IQ (WAIS-R)	91	(80–108)	111	(93–117)	*
Mini-mental status exam (maximum = 30)	23	(18–25)	29	(28–30)	*
IQ estimate (NART)	114	(108–121)	113	(94–128)	
Memory					
Word recognition (maximum = 50)	30	(20–36)	46	(41–50)	*
Face recognition (maximum = 50)	30	(26–38)	42	(36–47)	*
WMS-R General Memory Index	58	(50–76)	110	(92–123)	*
WMS-R Delayed Recall Index	52	(50–56)	103	(93–144)	*
MAS list acquisition recall score	32	(23–40)	54	(32–64)	*
Public events recognition (maximum = 100)	65	(47–73)	75	(57–97)	
Release from proactive interference	1.3	(1.1–1.7)	1.6	(1.2–2.4)	
Reading speed priming	17	(−3–35)	17	(8–25)	
Other					
Visuospatial construction (maximum = 11)	9.0	(7–11)	10.7	(10–11)	*
Wisconsin card sort test (maximum = 6)	3.2	(0–6)	5.3	(2–6)	
California card sort test (maximum = 48)	26	(22–32)	35	(24–42)	*
Stroop interference test	−3.9	(−17.2–4.7)	−0.4	(−7.0–5.7)	
Boston naming test (maximum = 60)	48	(43–56)	56	(44–60)	*
Token test (maximum = 44)	41	(39–43)	44	(43–44)	*
Verbal fluency test	37	(26–45)	35	(21–54)	
Lifetime alcohol consumption (kg)			1153	(299–3165)	

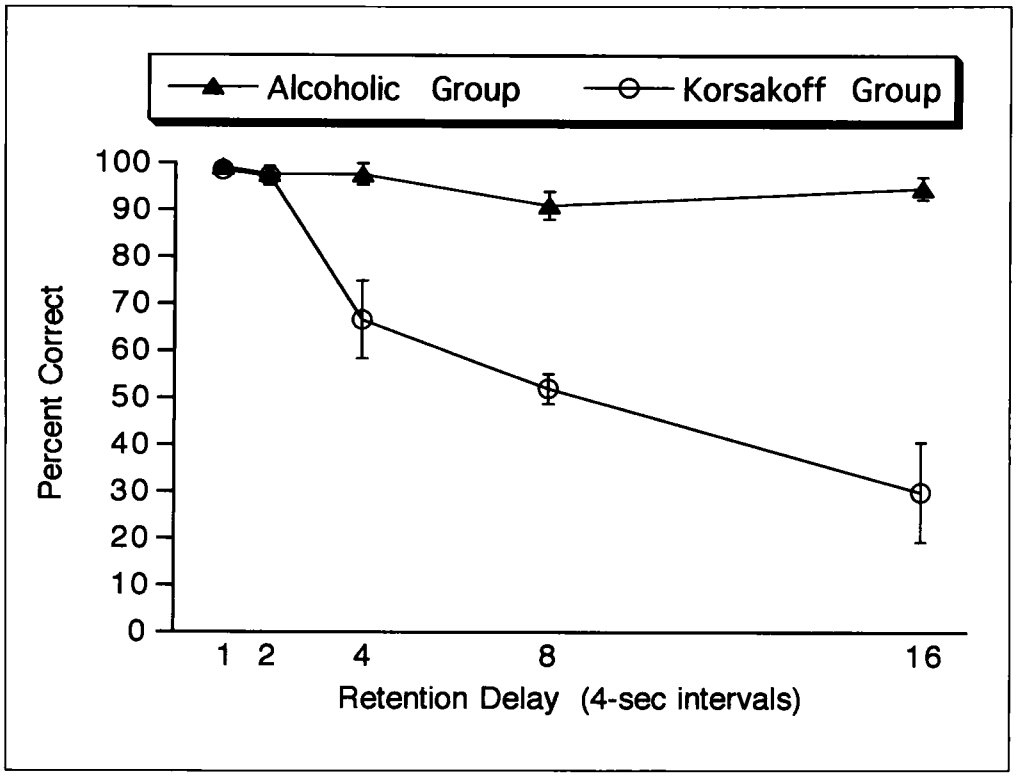

Figure 1. Recognition results from the behavioral challenge given during the radiotracer uptake period for the Korsakoff and alcoholic groups. Percent correct scores are shown for words that were repeated after a delay that varied from 1 to 16 trials, which corresponds to a retention delay up to about 1 min. Error bars show standard errors of the mean.

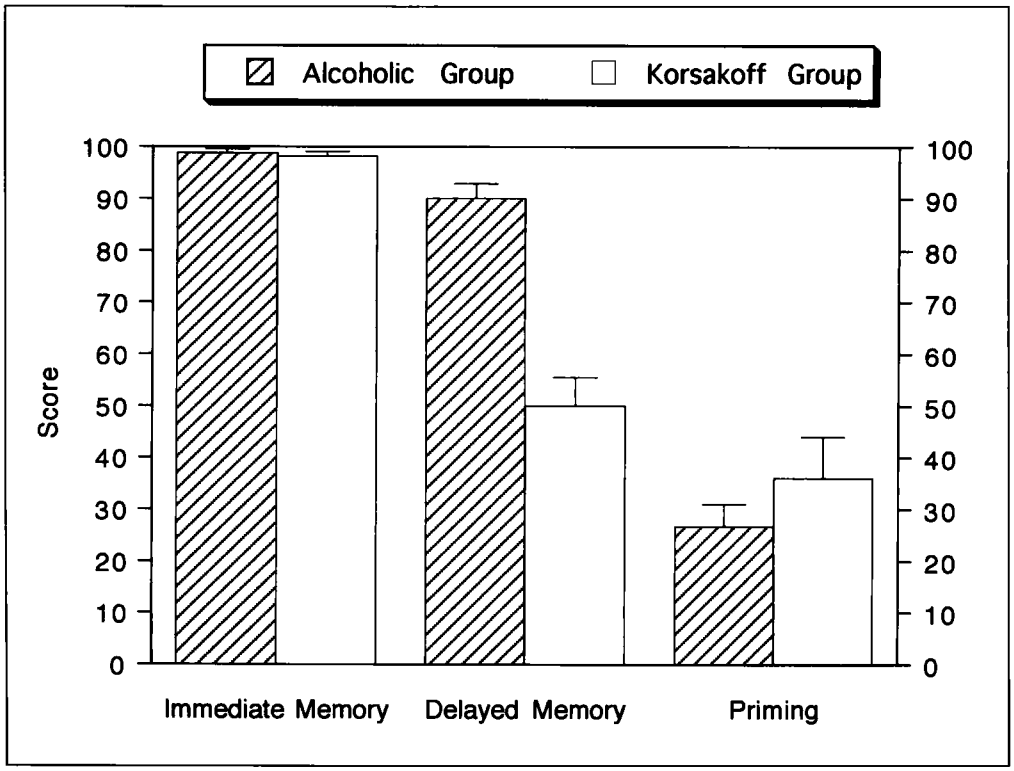

Figure 2. Memory scores for the Korsakoff and alcoholic groups from tests given during the radiotracer uptake period. Immediate and delayed memory scores were from the continuous recognition test. The priming score was the percentage of stems in the stem-completion test completed to form previously studied words. The baseline score in the priming test was 10%. Error bars show standard errors of the mean.

The delayed memory score was computed by averaging across the three longer delays and correcting for guessing on the basis of false alarm rate (the percentage of new words for which an incorrect response was given). False alarm rate did not differ significantly between groups [1.6% in the Korsakoff group, 4.6% in the alcoholic control group, $t(12) = 1.1$]. The priming score was derived from the stem-completion test given after the recognition test. Half of the stems in this test corresponded to words seen in the recognition test and half were used to compute the baseline completion estimate, which was 10%. Both groups showed a priming effect,

in that the percentage of stems completed with words from the recognition test exceeded the baseline level. Neither the immediate memory score [$t(12) = 0.8$] nor the priming score [$t(12) = 1.1$] differed between groups. In contrast, the delayed memory measure was significantly lower in the Korsakoff group than in the alcoholic control group [$t(12) = 7.2, p < 0.0001$].

PET Results

Figure 3 shows PET images from a Korsakoff patient, along with structural images and renderings derived from magnetic resonance imaging (MRI). An MRI-guided procedure (see **Methods**) was used to select an initial imaging plane parallel to the long axis of the hippocampus so as to maximize the hippocampal volume in the image. The first image thus included the following five regions on each side: hippocampus, anterior temporal cortex, posterior temporal cortex, medial occipital cortex, and lateral occipital cortex. Subsequent images were from parallel planes separated by 15–20 mm. The second image included: thalamus, striatum, orbitofrontal cortex, insula, superior temporal cortex, and posterior parietal cortex. The third image included: anterior cingulate, inferior frontal cortex, pericentral cortex, anterior parietal cortex, and posterior cingulate. The fourth image included: anterior cingulate, middle frontal cortex, and pericentral cortex. PET results were averaged across the third and fourth images for two regions (anterior cingulate and pericentral cortex). Structural images were later selected via a coregistration procedure to correspond to each patient's PET images. Thus, precise anatomical in-

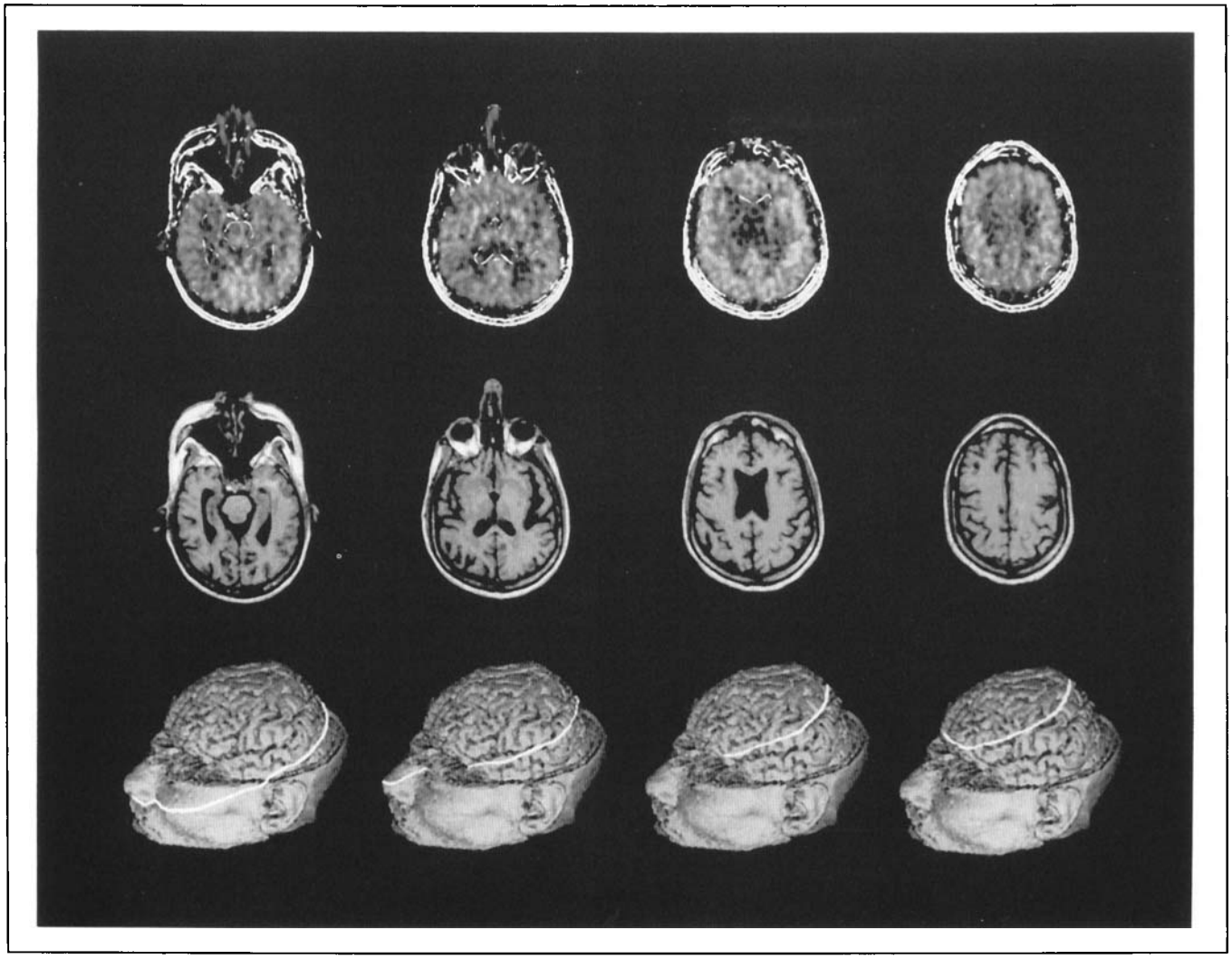

Figure 3. PET and MRI scans of the four imaging planes from one Korsakoff patient. (This patient was not included in the study group because insufficient vascular supply to the hand from the ulnar artery made use of an arterial line risky, so absolute measures of regional cerebral metabolism could not be obtained.) PET scans are shown in the top row (slice thickness = 6 mm). The hippocampal scan (far left) was obtained first and the other three scans were obtained by moving the patient 15–20 mm per scan. White outlines were derived from corresponding MRI scans, as selected via the coregistration procedure and shown in the middle row (slice thickness = 1–2 mm). Surface renderings with cortical gyri exposed and a line depicting the imaging plane are shown in the bottom row.

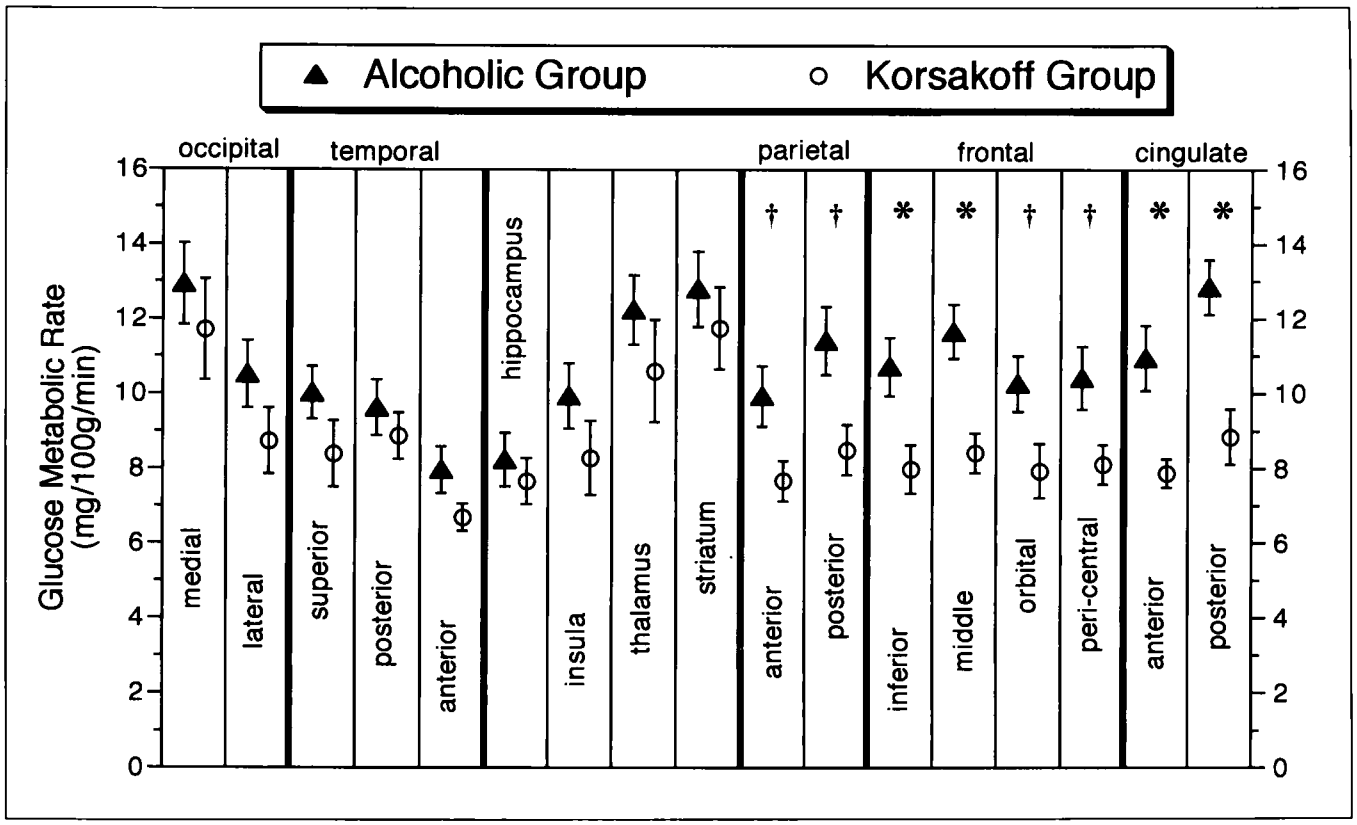

Figure 4. Measures of glucose utilization in discrete brain regions for the Korsakoff and alcoholic groups. Group differences significant at the .05 level are indicated by a * at the top of the column. Marginal group differences with $p < 0.082$ are indicated by a † at the top of the column. Error bars show standard errors of the mean.

formation from MRI was used to guide the quantification of the PET results.

Regional cerebral metabolic rate for glucose (rCMRglc) was computed for each anatomical region. These rCMRglc values were averaged across left and right sides, as no significant laterality effects were found. Mean rCMRglc values for the two subject groups are shown in Figure 4. For every brain region analyzed, mean rCMRglc was numerically lower in the Korsakoff group than in the alcoholic group. Further analyses focused on how rCMRglc varied across different anatomical regions.

In comparisons between the two groups, statistically reliable differences were found for four brain regions: inferior frontal [$t(12) = 2.4, p \leq 0.0364$], middle frontal [$t(12) = 3.2, p < 0.0084$], anterior cingulate [$t(12) = 2.7$, $p < 0.0184$], and posterior cingulate [$t(12) = 3.4, p < 0.0051$]. For the following four brain regions, marginally nonsignificant differences were found: anterior parietal [$t(12) = 1.9, p < 0.0764$], posterior parietal [$t(12) = 2.1$, $p < 0.0625$], orbitofrontal [$t(12) = 2.1, p < 0.0628$], and pericentral [$t(12) = 1.9, p < 0.0818$]. Results from the thalamic region failed to show a statistically significant difference between groups, possibly because of the small size of the pathology in the midline thalamus and the fact that the thalamic region sampled primarily posterior thalamus. Regions in which rCMRglc was most similar between the two groups included the striatum and several temporal lobe regions, including the hippocampus.[2]

Results from Individual Patients and Correlational Findings

The hypometabolism in the Korsakoff group can also be viewed in individual subjects, as shown in Figure 5. In parietal, frontal, and cingulate regions, rCMRglc values for most of the Korsakoff patients were well below the mean of the alcoholic group. Hypometabolism was also seen in other regions, but less consistently. In the hippocampus, for example, rCMRglc values in the Korsakoff patients were within the range of those from the alcoholic group. Note that the Korsakoff patient with the highest glucose metabolic rates ("Korsakoff 1" in Fig. 5) suffered from an amnesic impairment as severe as that in the other Korsakoff patients (e.g., delayed memory scores were 41, 61, 47, 64, and 37 for patients 1-5, respectively). Correlational analyses were used to investigate these effects further, combining data from all 14 subjects: five Korsakoff patients and nine alcoholic control subjects.

First we present correlational results using behavioral measures. Scores on the delayed memory measure from the behavioral challenge correlated significantly with

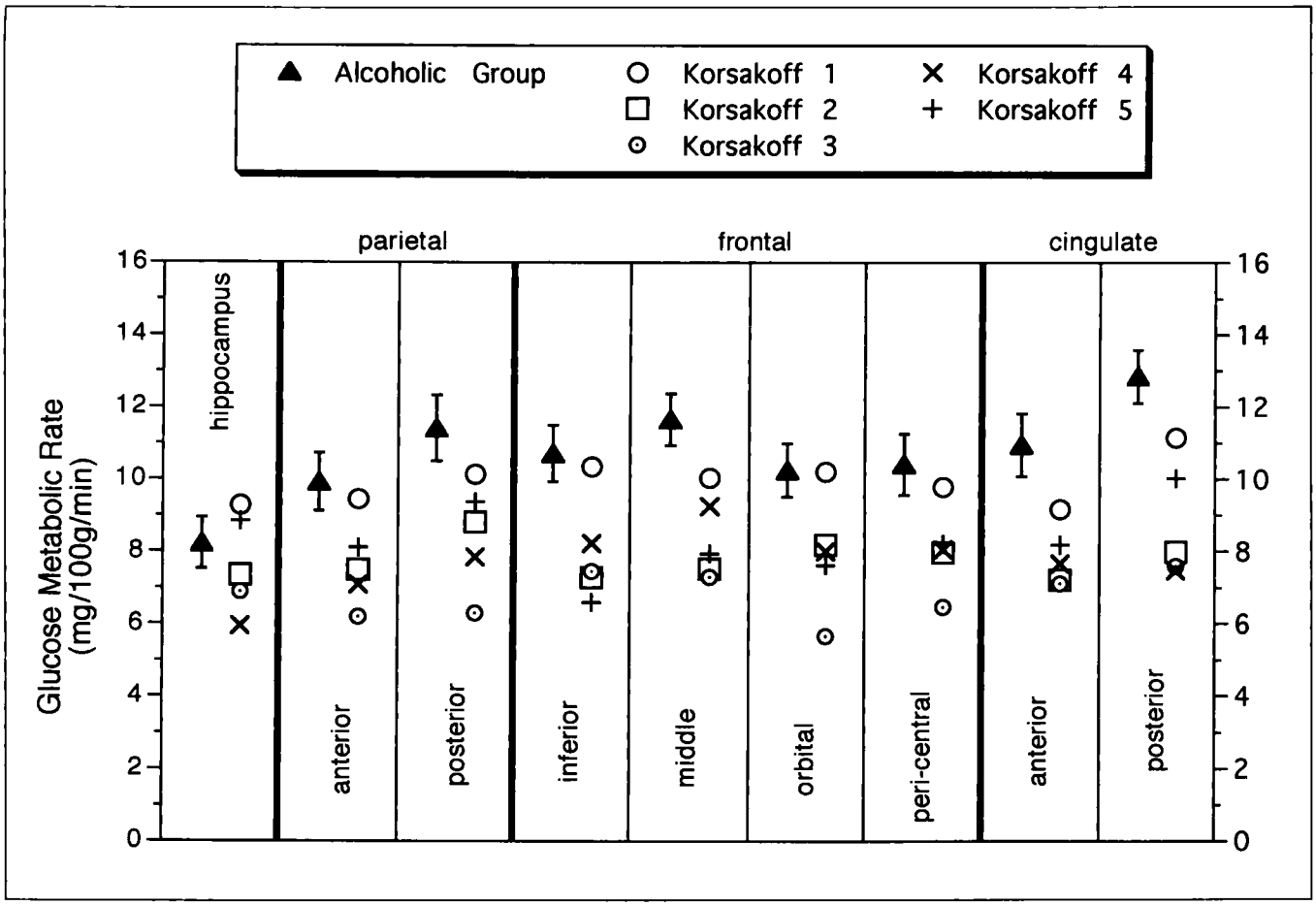

Figure 5. Measures of glucose utilization for individual Korsakoff patients compared to the mean for the alcoholic group. Results are shown for parietal, frontal, and cingulate areas, in addition to the hippocampus.

scores on the Warrington Recognition Memory Test for words (r = 0.94) and with scores on the mini-mental status exam, which is also sensitive to patients' memory deficits (r = 0.89). Scores on the immediate memory measure, in contrast, were not correlated with scores on the Warrington recognition memory test for words (r = –0.07), the mini-mental status exam (r = –0.25), nor with scores on the delayed memory measure (r = 0.5). Furthermore, none of these measures correlated with age (delayed memory score r = –0.02; Warrington Recognition Memory Test for words r = –0.02; mini-mental status exam r = 0.27; immediate memory score r = –0.47).

Both immediate and delayed memory measures obtained during the PET procedure showed significant positive correlations with rCMRglc values from a large number of brain regions (r's .53, see Table 2). For the immediate memory measure, correlations were found with medial and lateral occipital, anterior and posterior temporal, anterior and posterior parietal, insula, and pericentral regions. In contrast, rCMRglc values from a different set of regions were correlated with delayed memory scores. This set of regions was similar to the set of regions in which rCMRglc was most hypometabolic in the Korsakoff group: inferior, middle, and orbitofrontal, pericentral, anterior and posterior cingulate, and anterior and posterior parietal. There were thus distinct correlational patterns for immediate memory versus delayed memory.

DISCUSSION

Three alternative conceptualizations of the neural dysfunction responsible for the amnesic impairments of Korsakoff's syndrome can be contrasted as follows: (1) Relevant functional damage is limited to midline diencephalic regions. (2) The hippocampus and adjacent areas in the medial temporal region are also dysfunctional. (3) Widespread functional impairments in the cerebral cortex accompany structural damage in the diencephalon. Our results from PET measures of cerebral glucose utilization suggest that multiple cortical regions are dysfunctional in Korsakoff syndrome, thus supporting the third hypothesis.

Korsakoff's Syndrome and the Hippocampus

The pattern of hypometabolism found in Korsakoff's syndrome was not what would be predicted by hypothe-

Table 2. Correlations between glucose metabolic rates and memory scores. Correlations significant at the .05 level are indicated by a *.

Brain region	*Immediate memory*	*Delayed memory*
medial occipital	* 0.58	0.24
lateral occipital	* 0.62	0.42
superior temporal	0.53	0.46
posterior temporal	* 0.64	0.33
anterior temporal	* 0.59	0.33
hippocampus	0.52	0.17
insula	* 0.54	0.39
thalamus	0.32	0.32
striatum	0.50	0.27
anterior parietal	* 0.55	* 0.56
posterior parietal	* 0.54	* 0.61
inferior frontal	0.41	* 0.65
middle frontal	0.51	* 0.63
orbitofrontal	0.40	* 0.58
pericentral	* 0.57	* 0.58
anterior cingulate	0.38	* 0.67
posterior cingulate	0.24	* 0.65

ses that place hippocampal dysfunction at the core of amnesia. For example, in reviewing the literature on diencephalic amnesia, Butters and Stuss (1989) suggested that

> "although the dorsomedial nucleus of the thalamus and the mammillary bodies of the hypothalamus are often considered the *critical neurological entities* involved in diencephalic amnesia, there is now increasing evidence that this amnesic syndrome may also involve other subcortical structures (e.g., basal forebrain) and/or fiber tracts (e.g., mammillothalamic tract and internal medullary lamina) connecting the diencephalon with mesial temporal lobe structures."

This conception provides an explanation for the high degree of similarity between amnesic impairments following diencephalic versus medial temporal damage.

The question of whether hippocampal damage is a significant feature of Korsakoff's syndrome has remained open for many years. Postmortem neuropathology has shown hippocampal involvement in some cases, but it is not by any means a universal feature of the syndrome (Mayes et al., 1988; Victor et al., 1989). Alterations in the size of the hippocampus are generally not observed with structural neuroimaging (e.g., Squire et al., 1990). However, hippocampal neuronal loss has been observed as a result of direct neurotoxic effects of alcohol consumption (Freund, 1973; Walker et al., 1980). Yet, in a PET-FDG study of chronic alcohol-dependent patients, no trend for changes in the hippocampus was found (Gilman et al., 1990), but the authors were cautious in interpreting this negative finding due to the limited spatial resolution of their PET scanner relative to the small size of the hippocampus.

Recently, Fazio et al. (1992) suggested that a disruption of the same neural circuitry is responsible for several different types of amnesia, based on PET-FDG findings. This conclusion would imply that hippocampal dysfunction accompanies Korsakoff's syndrome. The key findings were comparisons between a group of 11 amnesic patients and a group of 10 control subjects. The amnesic group was hypometabolic in several brain areas, including hippocampus, thalamus, cingulate, and frontal-basal regions. The amnesic group, however, included two Korsakoff patients, three stroke cases, five anoxia cases, and one encephalitis case. Due to the heterogeneity of the amnesic group, the results reported by Fazio et al. (1992) are equivocal with regard to the question of whether any of these disease processes affect functions in areas other than the known sites of structural damage.

The present study was specifically designed to assess whether Korsakoff's syndrome gives rise to hippocampal dysfunction. Importantly, the patient group was limited to amnesic patients with Korsakoff's syndrome. In addition, the PET procedure had sufficient spatial resolution to reveal hippocampal abnormalities. The efficacy of the 2.6-mm resolution of the tomograph was demonstrated in prior evaluations in which structures as small as the superior colliculi and external capsule were resolved (Valk et al., 1990). The MRI-PET coregistration procedure, combined with high spatial resolution, ensured that hippocampal metabolism was specifically quantified. Of course, these arguments apply only to the extent that functional abnormalities in the hippocampus would give rise to altered glucose metabolism. Nonetheless, the findings do not support the hypothesis that the hippocampus is the focus of either a direct or indirect effect of the Korsakoff pathology. Glucose utilization in the hippocampus was nearly the same in the Korsakoff and alcoholic groups.

Several alternative explanations for this result must also be considered. One possibility is that hippocampal dysfunction was present in the Korsakoff patients, but that it was also present in the alcoholic control subjects to an equal extent. Another alternative is that the behavioral challenge used in our experiment caused the Korsakoff patients to engage their hippocampi to a relatively greater extent, thereby surmounting metabolic differences that would otherwise have been evident. This alternative is unlikely.[3] The finding that immediate memory scores were virtually identical in the two groups argues that motivational and attentional factors during

the radiotracer uptake period did not differ between Korsakoff patients and alcoholic control subjects. Finally, hippocampal function may have been disrupted in Korsakoff patients while glucose metabolism in the hippocampus remained normal, within the limits of the sensitivity of the PET measures. Effects may have been obscured because of the small size of the hippocampus combined with a relatively lower proportion of gray to white matter. However, the absence of significant hypometabolism in any portion of the temporal lobe in the Korsakoff group, combined with the presence of hypometabolism in other regions, suggests that the amnesic disorder is not a consequence of altered hippocampal function.

Korsakoff's Syndrome and the Cerebral Cortex

Does cortical dysfunction in Korsakoff's syndrome contribute causally to the memory impairment, or does it merely add additional symptoms that bear no obligatory relationship to amnesia? The hypothesis that cortical damage is instrumental in leading to the symptomatology of Korsakoff's syndrome has a checkered history, displaced by an emphasis on the idea of parallel neuropathology in Korsakoff's syndrome and Wernicke's encephalopathy (see Victor et al., 1989 for a detailed historical account). Despite the fact that many early investigators emphasized cortical pathology, the perceived importance of the cortex waned in the face of the Wernicke-Korsakoff connection. Lishman (1981, pp. 3 and 14) noted that

> "cortical lesions in Korsakoff's psychosis have come increasingly to be ignored or to be mentioned only in passing, and one suspects that intensive studies of cortical regions have latterly become unfashionable. . . . [T]he sum total of evidence points to the possibility that we have been too far seduced by the Wernicke-Korsakoff syndrome, and by rigid conceptions of its pathological substrate; and that we have tended as a result to overlook cortical damage in alcoholics, both clinically and at autopsy."

Another facet of the issue of whether cortical pathology contributes to Korsakoff's syndrome is the central role often afforded the frontal lobe. A variety of Korsakoff symptoms—apathy, lack of initiative, lack of insight, poor organization of behavior, poor recency judgments, and failure to release from proactive interference—lend themselves to interpretations in terms of frontal dysfunction (e.g., Butters, 1984; Moscovitch, 1982; Squire, 1982). Accordingly, when cortical pathology has been discussed, the frontal lobes have often been emphasized and pathology in other cortical areas de-emphasized.

Widespread cortical atrophy in Korsakoff's patients has been observed using structural neuroimaging, and findings include increases in the size of the interhemispheric fissure and the ventricles (Jacobson & Lishman, 1990), decreases in frontal cerebrospinal fluid (Shimamura et al., 1988), reduced volumes of cortical gray matter (Jernigan et al., 1991), and sulcal enlargement (Wilkinson & Carlen, 1980; but see Jacobson & Lishman, 1990 for conflicting findings). One difficulty in interpreting these effects is that they could arise from multiple causes, including head trauma, hepatic encephalopathy, anoxia, hypoglycemia, or direct neurotoxic effects of alcohol. Indeed, cortical abnormalities in nonamnesic alcoholics are commonly observed with CT (e.g., Pfefferbaum et al., 1988; Ron et al., 1982) as well as with PET (e.g., Sachs et al., 1987; Volkow et al., 1992). For example, hypometabolism in alcoholic patients measured with PET-FDG was described as comprising "bilateral medial bands extending anterior to posterior from the frontal poles to about the junction of the frontal and parietal lobes" (Gilman et al., 1990), thus encompassing the frontal lobe and the anterior cingulate.

PET studies of Korsakoff's syndrome have yielded mixed results. In one study, a group of patients with alcohol-related mental disorders (seven with Korsakoff's syndrome and three with alcoholic dementia) were compared to a group of normal subjects, and no differences in unnormalized cortical glucose metabolism were found (Martin et al., 1992). This result is surprising in light of the present findings and the fact that an earlier study using three of the same patients found significant metabolic reductions across 46 regions overall and in numerous cortical areas (Kessler et al., 1984). A subsequent study of nine Korsakoff patients (including some from Martin et al., 1992) also failed to find group differences in regional glucose metabolism, except for a trend toward cerebellar hypermetabolism (Joyce et al., 1994). However, normalized metabolic rates were depressed in medial cortical regions, namely the anterior cingulate and precuneus, and these effects remained significant when measures of cortical atrophy (nearby increases in interhemispheric size) were used as covariates. The decreased cingulate activity was interpreted by Joyce et al. (1994) as a remote effect of diencephalic pathology, mediated by a disconnection of Papez circuitry. In a study using single photon emission computed tomography (SPECT), Korsakoff patients showed a tendency toward reduced blood flow in various cortical areas, except posterior temporal cortex (Hunter et al., 1989). In another PET study of Korsakoff patients, significant reductions in regional glucose utilization were found in all brain locations (Heiss et al., 1992). However, these patients were apparently still in acute stages of the disease. Xenon contrast CT (Hata et al., 1987) and measures of total cerebral metabolism and blood flow (Shimojyo, Scheinberg, & Reinmuth, 1967) have also revealed reductions in relatively acute stages.

The present results suggest that widespread cortical dysfunction continues in the chronic stages of Korsakoff's syndrome. Abnormalities were particularly prominent in the frontal lobe, anterior cingulate, and posterior

cingulate, and trends in the same direction were apparent in the parietal lobe and, to a lesser extent, portions of the occipital and temporal lobes. It should be emphasized that evidence of cortical dysfunction was not limited to the frontal lobe. Previous PET studies may have missed cortical effects of this sort, in part due to poor spatial resolution such that signals from gray and white matter were mixed, and also because analyses of glucose utilization normalized to whole brain values could obscure cortical effects.

One possible interpretation of the cortical effects we found is that they reflect a greater extent of alcohol abuse in the Korsakoff group than in the alcoholic control group. Lifetime alcohol consumption is difficult to assess accurately, but estimates were obtained in the alcoholic control subjects. However, these estimates were not correlated with rCMRglc measures. Given that premorbid drinking levels for the Korsakoff patients were impossible to verify, the possibility that drinking levels were not matched cannot be excluded.

Further insights can be derived from the correlational analyses, in that the different findings with respect to the immediate and delayed memory measures (Table 2) can be taken as evidence for two separable pathological processes. Significant correlations between delayed memory and glucose metabolism in frontal, parietal, and cingulate regions may reflect critical neuropathology underlying the amnesic deficits, as also reflected in the group comparisons. On the other hand, correlations between immediate memory and glucose metabolism in multiple widespread regions may reflect a generalized influence of alcohol abuse on cognitive functioning. Despite the small sample size, the contrast between the two patterns of correlations is striking. Correlations have previously been detected between atrophy measures and general intellectual impairment in other samples (e.g., Carlen et al., 1981; Jacobson & Lishman, 1990). Interestingly, a correlation was found between performance of alcoholic patients on the Wisconsin Card Sort Test and rCMRglc in the region of the anterior cingulate (Adams et al., 1993). The authors concluded that hypometabolism in the anterior cingulate resulted from patients' chronic alcohol intake.

Glucose hypometabolism in the cerebral cortex may arise for a variety of reasons: loss of neurons, synapses, or cortical atrophy (Friedland, Brun, & Budinger, 1985; Herscovitch et al., 1986); altered glucose transport or phosphorylation (Friedland et al., 1989; Jagust et al., 1991); or specific neurochemical changes such as thiamine-related enzymatic changes (Butterworth, Kril, & Harper, 1993). Perhaps the most parsimonious explanation for the Korsakoff patients' cortical hypometabolism is cortical atrophy. Because PET measurements were made for regions defined on an individual basis by the border of the anatomical region, smaller regions of cortex would not necessarily yield different results from larger regions of cortex. Nevertheless, atrophic changes could involve decreases in neuronal density beyond decreases in gross tissue volume.

Given that cortical metabolic activity was diminished in the Korsakoff patients, two possible contributing factors can be distinguished.

1. Alcohol may directly and permanently produce neuronal damage in the cortex, as in cases of long-term alcoholism. Alcohol neurotoxicity could contribute to the clinical presentation but not be an essential factor in the amnesic syndrome. Alcohol consumption may be particularly harmful to the cortex because of concurrent thiamine deficiency. Other common concomitants of alcoholism (head injury, anoxia, etc.) could also mediate cortical effects directly.
2. Structural damage in the diencephalon could give rise, indirectly, to dysfunction in cortical areas. Neuropathological evidence is consistent with the generalization that multiple thalamic nuclei and fibers of passage are affected. Thus, widespread cortical regions could be affected remotely.

Whereas alcoholic Korsakoff's syndrome may represent a combination of diencephalic pathology resulting from thiamine deficiency plus cortical pathology resulting from other alcohol-related factors, we hypothesize that *an indirect influence of diencephalic damage on cortical function plays an essential role in the amnesic impairment.* Direct, alcohol-related cortical pathology would thus not be a necessary condition for the syndrome; diencephalic pathology would be sufficient. This scenario can readily explain variations of Korsakoff's syndrome in the absence of alcoholism, wherein only the diencephalon is directly affected, and it is consistent with the failure of Victor et al. (1989) to find evidence supporting a contribution from direct toxic effects of alcohol. Our PET results are also in agreement with this hypothesis.

A more specific test of whether diencephalic damage remotely disrupts cortical function would be to study patients with nonalcoholic Korsakoff's syndrome to determine whether they show similar patterns of cortical hypometabolism. The hypothesis that the memory impairment arises from a disruption of thalamocortical processing would also predict that cortical dysfunction can result from diencephalic damage due to stroke. Several reports attest to this phenomenon. Sandson et al., (1991) described a constellation of behavioral disturbances typical of patients with frontal lesions in a patient with a discrete infarct in the left medial thalamus. SPECT showed reduced perfusion in the ipsilateral frontal lobe. Pepin and Auray-Pepin (1993) reported on three cases with unilateral thalamic infarcts that produced memory and cognitive deficits, and SPECT also showed dorsolateral frontal hypoperfusion. The authors suggested that cortical dysfunction was secondary to loss of thalamocortical afferents, particularly related to damage to the rostroventral internal medullary lamina, along with dam-

age to the ventral anterior nucleus and the mammillothalamic tract. Other reports of remote effects of thalamic damage have also appeared (e.g., Baron, 1989; Heiss et al., 1992; Szelies et al., 1991). One other notable study concerned a patient with transient global amnesia (Goldenberg et al., 1991). During the attack, SPECT showed reduced blood flow in the thalamus, especially on the left, along with cortical hypoperfusion, whereas 40 days later these effects were shown to have subsided, except for some residual left frontal hypoperfusion. Therefore, it is reasonable to speculate that diencephalic damage in Korsakoff's syndrome also produces remote effects in the cerebral cortex. Nonetheless, this speculation will require further tests, both in patients and in animal models of Korsakoff's syndrome.

Thalamocortical interconnections must normally contribute in some manner to the consolidation process whereby memory traces achieve long-term storage in the cortex. Many theories of amnesia suggest that a failure of consolidation is at the root of the memory disturbance (see Mayes & Downes, in press; Paller, in press). This consolidation process presumably depends on interactions between cortical areas and circuitry in the medial temporal region, particularly the hippocampus. Many questions about consolidation remain to be answered, such as how hippocampal-neocortical interactions promote memory storage. One suggestion is that multiple sources of feedback to the cortex are required. First, results of neocortical processing of sensory information are carried through multiple streams to the medial temporal region. Subsequently, neural feedback is directed back to cortical regions where information is stored. This feedback may require multisynaptic projections to cortical regions via both (1) hippocampal and entorhinal areas and (2) thalamic nuclei. The thalamic connections may reach cortical regions directly as well as through the frontal lobe. Processing in the frontal lobe may play a particularly important role with respect to retrieval strategies and in maintaining information in working memory. Dual feedback pathways may be critical such that consolidation is not effective in the absence of either the medial temporal component or the diencephalic component. In Korsakoff's syndrome, critical diencephalic pathways are damaged thus disabling a specific type of thalamocortical processing. Amnesia results because the cortical destinations of damaged thalamic projections are not sufficiently activated at times when that activation is needed to promote memory storage.

Summary

Our chief conclusion is that the neural dysfunction responsible for the memory disorder of Korsakoff's syndrome is not limited to the diencephalon. We suggest that the amnesia is related to abnormal cortical function, which was manifest in our patients by decreased glucose metabolism. Our results failed to support the hypothesis that Korsakoff's syndrome entails loss of function in temporal lobe areas such as the hippocampus. Instead, functional impairments encompass major portions of the frontal and parietal lobes and the cingulate. The cortical dysfunction may have arisen *directly,* as a consequence of alcohol neurotoxicity and thiamine deficiency, and/or *indirectly,* as a consequence of structural damage in the diencephalon affecting thalamocortical interconnections. This evidence from high-resolution functional neuroimaging thus provides important clues for understanding the mechanisms underlying declarative memory and its disorders.

METHODS

Subjects

Two groups of subjects were studied: alcoholic Korsakoff's patients and nonamnesic subjects with histories of excessive alcohol consumption for 20 years or more. Five patients with Korsakoff's syndrome were selected through medical facilities in the San Francisco Bay area. Each patient displayed a relatively circumscribed amnesia due to Korsakoff's syndrome and was in generally good health. Exclusion criteria were: continued alcohol consumption; clear evidence of dementia; history of other neurological disorder (including significant head trauma); history of major psychiatric disorder; and current use of medications with central nervous system effects. Medical problems resulted in exclusion only if they were judged to be likely to affect cognition. Nine nonamnesic alcoholic control subjects were recruited through fliers at local alcohol treatment centers or related establishments, using the same exclusion criteria.

The alcoholic control subjects were selected such that mean age and years of formal education in the two groups did not differ significantly. In the Korsakoff group, the mean age was 54 years, with 14 years of education. In the alcoholic control group, the mean age was 56 years, with 15 years of education. In the Korsakoff group, four patients were right-handed and one was left-handed; in the alcoholic group, six subjects were right-handed and three were left-handed. All Korsakoff patients were male, whereas eight alcoholic control subjects were male and one was female.

The Geriatric Depression Inventory was given to all subjects. Mean scores were 6.2 in the Korsakoff group and 3.7 in the alcoholic group. Three Korsakoff patients received scores between 7 and 10, indicating mild to moderate levels of depression. Medical history and neurological examination were used to rule out other disorders, and each subject participated after giving informed consent.

Neuropsychological Assessment

Neuropsychological evaluations, done in most cases in advance of brain scanning, included the following tests (corresponding to results in Table 1).

General Tests

- Wechsler Adult Intelligence Scale-Revised (9 of 11 WAIS-R subtests)
- Mini-Mental Status Exam
- North-American version of the National Adult Reading Test (NART), which provided a premorbid IQ estimate

Memory Tests:

- Warrington Recognition Memory Test (50 two-choice recognition trials for words and for faces)
- Wechsler Memory Scale-Revised (all WMS-R subtests)
- Memory Assessment Scales (word learning MAS subtests)
- Public Events Recognition Test for the 1950s, 1960s, and 1970s (Cohen & Squire, 1981)
- Release from Proactive Interference Test, in which recall of four-item lists was compared across trials in which the items came from a repeated semantic category versus a new category (higher score indicates more release from interference)
- Reading Speed Priming Test, in which word pairs were read in a study phase and then again in a test phase (priming measure computed as decrease in reading time for studied versus unstudied words taken as a percentage of average reading time)

Other Tests:

- Visuospatial Construction Test, in which subjects copied four line drawings, the most complicated of which was a cube
- Wisconsin Card Sort Test (score is mean number of categories achieved)
- California Card Sort Test (score derived from one card set)
- Stroop Interference Test, in which color-naming speed was measured for three lists and a measure was derived to indicate the extent to which interference from word meaning slowed color-naming speed (more negative implies more interference)
- Boston Naming Test, in which drawings of common objects were named
- Token Test, which measured verbal comprehension
- Verbal Fluency Test, in which subjects were allotted 60 sec to name words beginning with a particular letter (C, F, and L in three consecutive blocks)
- Lifetime Alcohol Consumption Estimation, an interview measure used in alcoholic control subjects (Pfefferbaum et al., 1988)

Imaging Procedures

MRI was used to verify that none of the subjects had any unsuspected neuropathology, to select imaging planes, and to assist in region identification in the analysis of the PET results. The first step in the imaging protocol was to obtain a 3-dimensional MRI data set of T1-weighted images (voxel size 1 mm × 1 mm × 2 mm). This was done using a 0.5-Tesla IBM-MIT-LBL scanner and a 3-D gradient recalled echo sequence (TE = 14.3, TR = 30). Images could be reconstructed in any plane, and we selected a plane parallel to the long axis of the temporal lobes and intersecting maximal hippocampal volume. This plane will be referred to as the hippocampal slice.

The PET protocol used the standard FDG method and a single-slice tomograph with 600 BGO crystals, an in-plane resolution of 2.6 mm full width at half maximum, and an axial resolution of 6 mm (Valk et al., 1990). The subject was fitted with a percutaneous arterial line in the left or right radial artery and an intravenous catheter in the contralateral antecubital vein. The subject was then seated next to a peristaltic pump. Blood was withdrawn and transferred from the radial artery to thin Teflon tubing wrapped around a plastic scintillator beta-detector. Arterial blood withdrawal was begun immediately prior to radiotracer injection, initially at 10 ml/min for 5 min and then at 2 ml/min for the next 25 min. The radiotracer consisted of a 5–10 mCi intravenous injection of FDG.

At 30 minutes postinjection, the patient was moved to the PET scanner and positioned to target the hippocampal slice. Positioning was accomplished using laser markers and the MRI surface rendering of the patient's head with a superimposed line representing the hippocampal slice (see Fig. 6). Positioning for the other three slices was accomplished by moving the patient 15–20 mm per scan. Data were acquired over 10-min periods, each preceded by a 3-min transmission scan used to make attenuation corrections.

Due to the fact that errors in positioning or slight patient movements can lead to differences between the locations of preselected MRI slices and the obtained PET images, a coregistration procedure was used to obtain corresponding MR images. In this process, we used anatomical information from PET scans of glucose metabolism as well as from PET transmission scans showing features such as the location of the skull. The MR image with the best correspondence was selected from the 3-dimensional data set. For example, a filtered version of an MR image can be superimposed on a PET image, as shown in Figure 3, making it possible to shift the location and orientation of the MR image until pairs of images are in register.

Regions were outlined using coregistered images. This was done by a neuroanatomist (O.P.) who was blind to all other patient characteristics and who used MR images

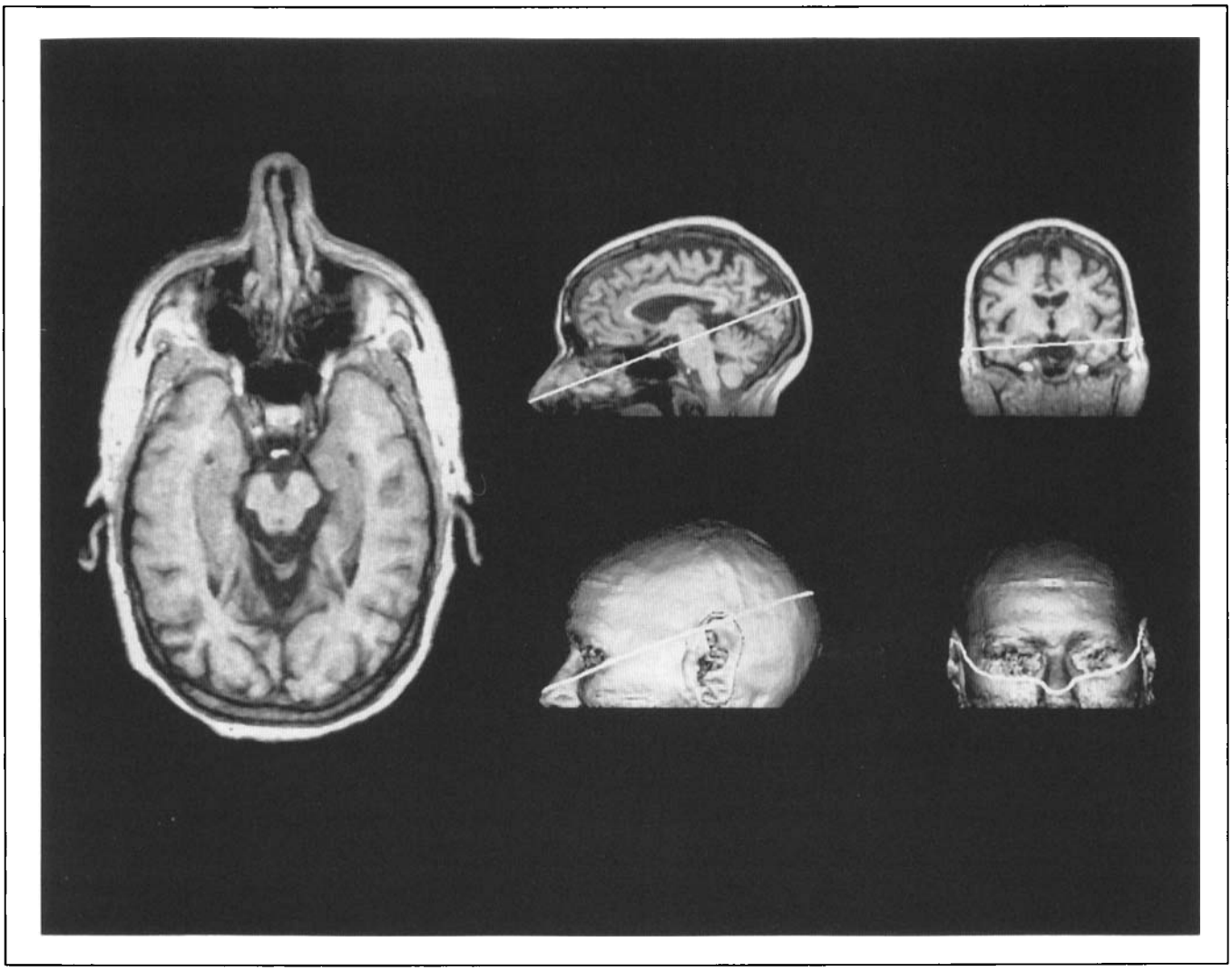

Figure 6. MRI results showing the method of slice selection. The location of the hippocampal slice (left) is shown by a white line in saggital and coronal planes (top right) and on surface renderings (bottom right).

from multiple levels to determine where boundaries between regions should be placed. Immediately following each PET study, a radioactive standard was used to calibrate the arterial blood sampling apparatus and the PET scanner. Values for rCMRglc were computed using the arterial input function, calibration factors, and the operational equation with rate constant $k_4 = 0.0068$ (Phelps et al., 1979) and rate constants k_1, k_2, and k_3 determined previously with the same PET scanner (Jagust et al., 1991).

Behavioral Challenge

To control cognitive functions during the radiotracer uptake period, a behavioral challenge involving a continuous recognition memory test was used. A few minutes prior to the FDG injection, instructions for the behavioral challenge were given to the subject along with some brief practice designed to ensure that the performance requirements were understood. In the test, each subject saw a list of words that began 10–20 sec prior to the injection and lasted at least 20 min. The subject read each word aloud and said "old" or "new" according to whether they thought the word had or had not appeared before. Each word appeared 4 sec after the onset of the prior word or after the response if the response took longer. An experimenter listened to the subject's responses and registered them in the computer. Retention delays embedded in the list were 1, 2, 4, 8, and 16, where 1 signified repeating a word immediately after the initial presentation, 2 signified repeating a word such that it was the second word to appear after the initial presentation, and so on. A set of 30 words were repeated at the shortest delay, whereas 15 words were repeated at each of the longer delays. Thus, a large proportion of the "old" trials were within the span of immediate memory, and accordingly, even severely amnesic patients could follow the instructions, give correct "old" and "new" responses over short delays, and maintain the task set during the entire test. Recognition testing was based

on 180 trials (90 words presented twice). Mixed in with these words were an additional 20 filler words, each of which occurred four times. There were also two buffer words at the beginning of the list and two buffer words at the end of the list, which thus included 264 trials in total.

At the conclusion of the continuous recognition test, a stem-completion priming test was given. This test was given as an implicit memory test, as subjects were not informed that their memory was being tested. A printed list of 40 three-letter stems was presented to the subject with instructions to complete each out loud with the first word to come to mind, and to proceed as fast as possible down the list giving a word for each stem. Half of these stems corresponded to the 20 filler words from the recognition test, e.g., as MOT corresponds to MOTEL. Furthermore, there were two sets of filler words, although each subject saw only one of these sets during the recognition test. The specific words comprising these two sets of filler words were selected such that each started with a unique three-letter stem that could be completed to at least five common words. Stems from the set of filler words not displayed were used to obtain a baseline measure of completion—the a priori probability that a list word would be given as a completion. The priming score was the percentage of completion responses that matched the corresponding filler word from the recognition test.

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Notes

1. The IQ estimate was derived from patients' attempts to pronounce words that break standard phonetic rules. Assuming that scores on this test are not strongly affected by the disease, a rough estimate of premorbid intelligence can be derived. However, some investigators have suggested that this measure underestimates IQ in Korsakoff patients (O'Carroll et al., 1992). Nevertheless, the similarity between the IQ estimates in the two groups suggests that any deficits in the Korsakoff group relative to the control group cannot be explained as an outcome of a possible bias in subject selection for lower baseline intelligence levels in patients than in controls, independent of the disease process.

2. Between-group comparisons were also made using data normalized to mean rCMRglc across all brain regions sampled. *Z*-scores were still significantly lower in the Korsakoff group than in the alcoholic group for three regions: anterior cingulate [−0.3 vs. 0.2, $t(12) = 2.2, p < 0.0478$], posterior cingulate [0.2 vs. 1.2, $t(12) = 3.2, p < 0.008$], and posterior parietal [−0.1 vs. 0.2, $t(12) = 2.2, p < 0.0494$]. *Z*-scores were significantly higher in the Korsakoff group than in the alcoholic group in posterior temporal cortex [0.2 vs. −0.5, $-t(12) = 5.0, p < 0.0003$] and in the anterior half of the hippocampus [−0.5 vs. −1.4, $t(12) = 2.7$, $p < 0.0207$]. The interpretation of normalized results is complicated by the difficulty of ascertaining whether global metabolic rates differ across individual subjects for relevant or irrelevant reasons. However, the normalized results underscore the necessity of obtaining absolute rather than relative measures of glucose utilization in order to understand the neural dysfunctions.

3. A behavioral challenge similar to that in the present experiment was used in a PET study of Alzheimer's disease (Kessler et al., 1991). The difficulty of the visual recognition test was adapted to each individual's capabilities (whereas in the present study the preponderance of short-delay items functioned to equalize the perceived difficulty across groups). PET results obtained during the visual recognition test versus during an uncontrolled resting state yielded similar group differences between patients and controls. This evidence is thus consistent with the idea that the use of a behavioral challenge does not alter the patterns of differences between patient groups.

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