

Inferring Function from Structure: Relationship of Magnetic Resonance Imaging-Detected Hippocampal Abnormality and Memory Function in Epilepsy

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Although temporal lobectomy is an effective alternative treatment for many patients with medication-resistant epilepsy, the risk of cognitive morbidity is not inconsequential. The ability to predict cognitive outcome is increasingly dependent on convergent information from multiple sources, including direct (e.g., Wada test) and indirect (e.g., psychometric testing) functional assessments along with magnetic resonance imaging studies that detect structural abnormalities. This brief review summarizes the relationship between imaging and function at baseline and predicting cognitive outcome following temporal lobectomy.

Introduction: Hippocampal Model of Memory and Assessment of Function

Evidence for a crucial role of the hippocampus in memory comes from a variety of sources. The most compelling and relevant are the reports of memory impairment in patients with bilateral hippocampal damage (1–6). Although clinical lore equates the memory impairment suffered by these patients with the dense amnesia suffered by the most well known patient, (H.M.), there is actually a spectrum of memory disturbances reported (7).

In one of the first reports of amnesia following bilateral temporal lobectomy, Scoville (3) described the “grave loss of recent memory” experienced by two of his patients. Each of these patients demonstrated a complete loss of the ability to

retain new information in long-term memory. Although able to hold information in short-term memory, this information was lost the moment their attention was diverted from the task at hand. Despite the inability to form lasting new associations and memories, other aspects of cognition remained remarkably well preserved. A subsequent analysis of 10 patients (including the two patients in the original report) led to the conclusion that the bilateral hippocampal lesion was the critical variable in producing the memory impairment (4).

At the same time that Scoville was analyzing the outcome of his series of patients, a similar pattern of memory impairment was observed in patients that had undergone unilateral temporal lobectomy (5). Penfield and Milner reported two cases from among a larger series of temporal lobectomies that demonstrated a persistent “grave, unexpected, generalized loss of recent memory” following left temporal lobectomy. Because a large number of patients that underwent unilateral temporal lobectomy did not develop severe anterograde memory deficits, the assumption was made that there was an undetected lesion in the contralateral hippocampus. When the left hippocampus was removed, this produced the functional equivalent of bilateral hippocampal lesions. This hypothesis was later confirmed in one of Penfield and Mathieson’s (6) patients when an autopsy revealed pathological changes in the right hippocampus that were consistent with hippocampal sclerosis.

Because unilateral resections did not appear to produce significant deficits unless there was bilateral damage and surgery was emerging as a viable treatment option, it became critical to identify patients in whom surgery in one temporal lobe posed a risk of severe memory impairment. In 1962, Milner et al. (8) reported on use of intracarotid amobarbital to anesthetize one hemisphere, thereby producing a reversible model of the effects of the planned surgery. This test became the method of choice for assessing the “functional reserve” of the hippocampus contralateral to the proposed surgery. This procedure (the intracarotid amobarbital procedure [IAP], or “Wada” test) provides a more direct assessment of hippocampal function than is possible with traditional assessment of memory. Although a complete review of the controversies regarding the Wada test is beyond the scope of this brief review, numerous lines of evidence have emerged that support the validity of the IAP as a measure of hippocampal function, including a correlation of IAP memory performance with hippocampal EEG changes recorded following injection (9) and reduced metabolism following injection of amobarbital (10,11), as well as neuronal cell loss (12) determined from resected tissue.

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In the decades that followed, assessment of functional reserve remained the primary means of evaluating risk of amnesia in temporal lobectomy candidates. However, increasing awareness of the more subtle changes in memory that accompanied unilateral temporal lobectomy gradually led to a paradigm shift toward assessment of “functional adequacy” (13). Although severe amnesic syndromes were rare, it was much more common that follow-up assessment revealed a pattern of memory performance that varied depending on the side of surgery. In patients undergoing temporal lobe resections in the language-dominant hemisphere, a clinically significant but subtotal loss of verbal memory was common. The degree of memory impairment appeared to be inversely related to the level of function before surgery. Patients with greater capacity before temporal lobectomy were at risk for larger declines (14,15).

The degree of memory impairment observed on psychometric testing was also correlated with pathology in the hippocampus determined from resected tissue (16,17). Patients exhibiting classic signs of mesial temporal sclerosis (MTS) (severe neuronal loss, gliosis) demonstrated less decline following surgery than patients in whom pathological specimens revealed less pathology or were normal. A linear relationship between the degree of hippocampal cell loss and functional outcome was also observed (18). Thus, these methods appear to confirm the early observations that the critical lesion for memory impairment is the hippocampus.

Sass et al.’s (16–18) studies demonstrated that the direct relationship between memory and the extent of damage to the hippocampus before and after surgery were replicated using a variety of different methods (19–21). However, a correlation of memory dysfunction with pathological status of resected tissue poses a limitation for determination of preoperative risk based on knowledge of the degree of pathology.

The emergence of modern imaging techniques provided a valuable tool for *in vivo* detection of the pathological changes associated with epilepsy. In medial temporal lobe epilepsy, the most common pathological finding is MTS (22). The pathological features of MTS (cell loss and gliosis) may be manifested as hippocampal formation atrophy and increased signal intensity on T2-weighted images (23). Methods of quantifying magnetic resonance imaging (MRI) changes, such as quantified volumetric ratios, may increase the sensitivity of MR to these changes (24,25). Because the pathological changes associated with MTS are also associated with memory loss, it is reasonable to assume that there would be some relationship between the degree of MRI-detected hippocampal pathology and the degree of memory impairment. This was confirmed in several studies investigating the IAP memory assessment, as well as neuropsychological investigations of memory. Three modes of investigation are discussed: the correlation of MRI

with IAP memory, baseline neuropsychological assessment, and MRI findings for prediction of outcome and MRI with neuropsychological testing in patients with bilateral hippocampal atrophy.

IAP Memory and Volumetrics

IAP memory test results are correlated with MRI-detected features of MTS, including hippocampal volume and increased T2 signal. In an early study, Loring et al. (26) observed a significant correlation between MRI hippocampal volume measurements and IAP memory performance. In their study, asymmetry of IAP memory performance was significantly correlated with MRI hippocampal volume asymmetry. Baxendale et al. (27) studied the relationship of IAP memory results to hippocampal volumetric measurements and hippocampal T2 relaxometry. These authors also found that MRI measures of asymmetry (e.g., right volume minus left volume) were significantly related to IAP memory asymmetries in patients with unilateral hippocampal sclerosis, although simple correlations of volume with IAP memory performance were not significant. Similarly, asymmetry in the T2 signal intensity was correlated with asymmetry in memory performance.

Both of these studies indicated that the disparity between hemispheric performance is a more important indicator than absolute performance of either the ipsilateral or contralateral hemispheres. Furthermore, the results of Loring et al. (26) indicated that the combination of structural (MRI) and functional measurements (IAP) was a stronger indicator of lateralized dysfunction than either method alone. The implications of this are threefold. First, the asymmetry measure necessarily takes into account both functional adequacy (memory ipsilateral to proposed surgery) and functional reserve (memory in unoperated hemisphere). More importantly, the results suggest that the procedures are nonredundant, and each contributes uniquely to the assessment of functional adequacy and functional reserve. The absence of simple correlations between quantitative measures and IAP memory performance indicates that structure is not necessarily equal to function with respect to the Wada test.

Association of Baseline Neuropsychological Function with MRI Findings

Several authors have attempted to address the complexity of the relationship between MRI defined structure and psychometrically defined function through multivariate approaches. These approaches take into account demographic variables such as age and gender, as well as epilepsy-specific variables, including age of seizure onset, history of febrile convulsion, or other risk factors.

Lenz et al. (28) examined the MRI findings, neuropsychological test results, and pathological findings in a sample of temporal lobectomy patients. In this first report on the relationship of MRI-determined structure with cognitive function, these authors confirmed that the volumetric changes not only predicted the side of seizure onset, but also correlated with the degree of pathologically verified neuronal loss in hippocampal cell fields. The volumetric measurements of the hippocampus, expressed as both raw volume measures and as a right–left ratio to determine asymmetry, were significantly correlated with measures of verbal learning and recall. However, the memory test scores were only related to the asymmetry ratio and the left hippocampal and temporal lobe measurements. There were no significant relationships between right temporal lobe or hippocampal volume measurements and memory performance. A similar pattern was observed by Kilpatrick et al. (29) in a sample of 25 patients with MTS. They found that left hippocampal atrophy (expressed as a ratio) was correlated with impaired memory for both verbal and nonverbal memory. However, right hippocampal atrophy was not related to any of the memory tests.

Failure to observe significant correlations of right temporal lobe volumes with memory measures may be related to the often reported variability in nonverbal memory outcome following temporal lobectomy. However, Trenerry et al. (30,31) suggested that gender differences in cerebral organization may play a role. When volumetric and memory data obtained from men and women were analyzed separately, preoperative verbal memory was significantly correlated with both left and right hippocampal volumes in women with left TLE. Furthermore, a gender effect was also demonstrated for visual memory, with significant correlations between right hippocampal volumes in women, but not men. Baxendale et al. (32) also failed to obtain a direct relationship between MRI measures of hippocampal structure and neuropsychological variables. However, when demographic and disease variables (age at onset of seizures, chronological age, duration of epilepsy) were included in a regression model, significant relationships of hippocampal volume with memory measures emerged. Although gender was not analyzed in the Baxendale et al. study, the results are consistent with the Trenerry study in that both found the addition of demographic variables enhanced the structure–function relationship.

The finding of correlations between *in vivo* measures of structural integrity and memory is useful if they can predict the functional consequences of temporal lobectomy. Although prospective studies have yet to be reported, retrospective analysis appears to confirm the hypothesis that resection of a relatively larger left hippocampus is associated with greater decline in memory following surgery (33). The association of memory decline with structural changes was mediated by gender and

side of surgery (31). More recently, Wendel et al. (34) reported that increased T2 signal in the left hippocampus is associated with poor verbal memory outcome, regardless of the side of surgery. Increased left hippocampal T2 was associated with a better verbal memory outcome in patients undergoing left temporal lobectomy. However, when there was increased T2 in the left hippocampus in right temporal lobectomy patients, verbal memory outcome is worse. This makes intuitive sense in that increased left hippocampal T2 in dominant TLE is an indicator of diminished verbal memory function or decreased functional adequacy of the epileptogenic temporal lobe. Conversely, increased left T2 in nondominant TLE is an indicator of diminished functional reserve. These authors report that the association with verbal memory outcome and T2 signal abnormality is independent of the volume measurements, as volume measurements were not significant in their multivariate model.

Many volumetric studies use ratios to identify asymmetry in hippocampal volume and memory dysfunction. However, volumetric measures that use asymmetries to identify seizure laterality may fail to identify patients in whom bilateral hippocampal atrophy is present (35). Furthermore, the risk of cognitive morbidity may be greater in this group, given the higher probability of diminished functional reserve associated with bilateral atrophy. Identification of significant verbal memory impairment in these patients may be important for lateralizing seizure onset (36). Sawrie et al. demonstrated that in patients with bilateral atrophy, the odds of correct lateralization using percent retention of verbal information increased to 36.11 compared with 1.67 for patients with symmetric, nonatrophic hippocampi. Although patients with bilateral atrophy demonstrated significantly worse verbal memory performance before surgery, they were still at greater risk for significant exacerbation of the memory impairment following left temporal lobectomy (37,38). These studies appear to confirm that there is a spectrum of memory disturbance associated with bilateral dysfunction. Bilateral hippocampal atrophy poses a greater risk to verbal memory but is not necessarily associated with profound anterograde amnesia like that of H.M. The factors that mitigate the degree of impairment in these cases remain unknown.

Summary and Conclusions

Several conclusions may be drawn regarding the relationships between MRI measures of hippocampal pathology and behavioral measures of functional capacity. Structure–function correlations provide a useful tool for understanding memory function in epilepsy surgery candidates. However, the evidence does not indicate that identification of structural abnormalities alone is an adequate means of assessing functional status. Direct relationships between structural measures are modest at best and leave a significant proportion of variance unex-

plained. The strongest associations are obtained when functional as well as structural assessments include both hemispheres and use multivariate approaches that include disease-related demographic variables. Continued investigation into the combination of these techniques, along with additional application of other functional measures (e.g., PET, SPECT) and newer technologies such as functional MRI, will improve identification of surgical candidates that have the highest probability of seizure control without cognitive morbidity.

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