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Reorganization of Verbal Memory Function in Early Onset Left Temporal Lobe Epilepsy

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The purpose of this investigation was to examine the issue of reorganization of verbal memory function following early insult to the left mesial temporal region. It was hypothesized that reorganization of memory function was most likely to occur in those patients with an early age of seizure onset who have a more limited degree of extra-hippocampal neuropathology. Fifty-four patients with epilepsy of unequivocal left temporal lobe origin were classified into four groups on the basis of the presence/absence of hippocampal sclerosis and degree of postoperative seizure relief. Measures of verbal learning and memory as well as nonmemory measures were administered both before and 6 to 8 months after anterior temporal lobectomy. Findings were consistent with the reorganization proposal. The clinical and theoretical significance of the findings are discussed.

INTRODUCTION

People with complex partial seizures of temporal lobe origin (TLE) do not constitute a homogeneous group, but instead demonstrate considerable variability in ictal semiology, etiology, EEG characteristics, extent and nature of metabolic and physiologic disturbance, underlying neuropathology, and other characteristics (Engel, 1993; Kligman & Goldberg, 1975; Paradiso, Hermann & Robinson, 1995; Tizard, 1962; Wieser, 1983; Williamson, Wieser & Delgado-Escueta, 1987). It is therefore not surprising that there is also variability in memory function, a primary cognitive consequence of TLE (Chelune, 1995; Dodrill et al., 1993; Hermann et al., 1995).

Recent reports have shown that the presence or degree of hippocampal sclerosis, a primary neuropathological substrate of unilateral mesial temporal

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lobe epilepsy (Gloor, 1991), is a critical factor mediating the heterogeneity in both adequacy of preoperative memory function as well as the severity of pre- to postoperative memory decline. Patients without evidence of significant hippocampal pathology (assessed via MR volume imaging, neuronal cell counts in CA subfields, or conventional diagnosis of hippocampal sclerosis) exhibit better presurgical memory functioning compared to those with sclerosis, but exhibit considerably greater pre- to postoperative memory decline (Hermann et al., 1994b; Oxbury & Oxbury, 1989; Rausch, 1987; Sass et al., 1994; Trenerry et al., 1993). To date, these findings have been observed almost exclusively for patients who undergo left (dominant) ATL, and the morbidity appears to be specific to particular components of verbal memory (e.g., declarative episodic memory but not immediate memory) (Chelune, 1995; Hermann et al., 1994b; Sass et al., 1992). Thus, hippocampal sclerosis is a lesion of considerable relevance to the neuropsychology of epilepsy.

Not all patients with unilateral TLE have hippocampal sclerosis, but those who do appear to have several reliable clinical features including an earlier age at onset of epilepsy (Engel, 1993; Wieser et al., 1993). In the Memphis ATL series ($n = 88$), 65% of TLE patients with histopathologically confirmed hippocampal sclerosis had seizure onset before age 5, compared to 8% of patients without hippocampal sclerosis (unpublished observation). Thus, TLE patients with hippocampal sclerosis exhibit a distinct lesion associated with an early age of seizure onset. These factors might be expected to have implications for cognitive development and the potential for cerebral reorganization of function.

Cerebral reorganization refers to the compensatory neuronal takeover of a cognitive function secondary to an insult to the neural systems which typically mediate that function. It is generally acknowledged that cerebral reorganization is most likely to occur in the context of an early age of brain insult (Hecaen & Albert, 1978; Lennenberg, 1968). Evidence for functional reorganization with early onset seizures has been reported, primarily concerning interhemispheric transfer of language function in the context of structural lesions in the left neocortex (Rausch, Boone, & Ary, 1991; Sass et al., 1995; Strauss, Wada & Hunter, 1992).

However, the majority of patients with (left) hippocampal sclerosis (without neocortical injury) show the conventional pattern of speech dominance, and it is unclear if and to what extent reorganization of higher cognitive functions takes place in the absence of a hemispheric change in speech dominance. Recent reports examining pre- to postoperative changes in visual confrontation naming ability following left ATL (in left hemisphere speech dominant patients) have suggested the possibility of intrahemispheric reorganization of language function among those with either an early age of risk factors for epilepsy (Saykin et al., 1995; Stafiniak et al., 1990), or early age at onset of recurrent seizures (Hermann et al., 1994a). Similar age of onset/

verbal memory outcome findings have been reported following left ATL (Hermann et al., 1995; Saykin et al., 1989; Wolf et al., 1994), but have not been considered within the framework of cerebral reorganization.

Implicit in the concept of cerebral reorganization is the availability of intact compensatory neural regions. Thus, for reorganization of hippocampally mediated memory functions to occur among early onset left TLE patients, related neuronal systems outside the left hippocampus would need to be functionally capable of subserving memory. We hypothesize that one potential marker of the functional integrity of extra-hippocampal neuronal systems is whether seizures continue after ATL. Although the majority of well-selected surgical candidates show substantial benefit from surgery, not all individual are rendered completely seizure-free (Engel et al., 1994; King et al., 1994; Spencer & Inserni, 1991). Given a *standard surgical approach*, we believe it is reasonable to suggest that the epileptogenic zone extends beyond the margins of the resection in those patients who continue to have seizures. As such, a more diffuse epileptogenic and neuropathologic process is implied which would limit the availability of functional neuronal resources available for reorganization.

To date, seizure outcome has not been used as a marker for the distribution/severity of underlying neuronal dysfunction and its potential relevance to reorganization of memory function has not been considered. However, given this line of thinking, one would expect reorganization to be most likely to occur among TLE patients with evidence of an early brain insult *and* a seizure-free outcome. That is, patients with hippocampal sclerosis with a fairly focal lesion. In contrast, individuals with an early brain insult and poor seizure outcome would be less likely to show evidence of cerebral reorganization.

In order to test this hypothesis, we suggest that reorganization of function would be implied by three pieces of evidence. First, among patients with hippocampal sclerosis, the *preoperative* memory performance of patients rendered seizure-free should be superior to that of patients not rendered seizure-free. If ongoing postoperative seizures imply that significant neuropathology resides outside the zone of resection, then fewer neuronal resources should be available for reorganization, and preoperative memory performance should suffer accordingly. Second, patients with hippocampal sclerosis who are rendered seizure-free should exhibit superior *postoperative* performance compared to patients who undergo resection of a nonsclerotic hippocampus (regardless of their surgical outcome). Patients without hippocampal sclerosis have a mean age at onset of seizures (around 20 years of age) which is well beyond any optimal window of plasticity. The significant postoperative memory decline that has been reported in these patients suggests that the resected structure was (at least partially) functional, and the task examined was dependent on the functional status of the hippocampus. Superior postoperative memory performance by seizure-free patients with hippocampal sclerosis (seizure-free), who have a substantially longer duration of epilepsy, would be strongly suggestive of cerebral reorganization. Finally, if reorganization of hippocampally mediated memory functions has occurred, then there should be minimal pre- to postoperative memory change following hippocampal resection among seizure-free patients with sclerosis. In summary, if reorganization of function has occurred, those memory measures that show a significant decline following resection of non-sclerotic hippocampus (i.e., hippocampally mediated tasks) should be relatively well preserved, both pre- and post-operatively, in seizure-free patients with hippocampal sclerosis.

We examined these hypotheses in the pre- to postoperative performance of 54 left TLE patients with confirmed left hemisphere speech dominance. Subjects were divided into four groups based on the presence/absence of verified hippocampal sclerosis and degree of seizure relief (seizure-free, not seizure-free). Pre- to postoperative verbal memory performance was examined using several indices which have been demonstrated to be sensitive to left hippocampal function. Also included were measures of executive function and spatial orientation, functions not primarily mediated by the mesial temporal lobe, in order to determine the specificity of findings to memory ability.

METHOD

Subjects

The sample consisted of 54 patients who underwent partial resection of the left (dominant) anterior temporal lobe for treatment of intractable seizures of temporal lobe origin and for whom a grading of hippocampal pathology could be derived. Patients in this study met the following criteria: (1) nonretarded (WAIS-R Full Scale IQ > 69), (2) no MRI lesions other than hippocampal sclerosis, and (3) left hemisphere dominant for speech as demonstrated by intracarotid amobarbital testing. In all cases, the patients' seizures were verified as being of unilateral temporal lobe origin by long-term EEG/video monitoring of spontaneous seizures using invasive (bilateral subdural strip electrodes) recordings (Wyler et al., 1984). All determinations as to the localization and lateralization of the ictal onset were made independently by the electroencephalographer, blinded to the results of the neuropsychological testing.

Seizure outcome was determined by the neurosurgeon, blinded to the results of the neuropsychological evaluation. Patients were classified into a rigid dichotomous classification (seizure-free, not seizure-free). Auras were considered as simple partial seizures, and patients reporting auras were rated not seizure-free, as were patients who may have unilaterally reduced their medication intake and suffered a seizure, experienced a seizure with illness, and other such circumstances. The rationale for this classification is that only those patients who are rendered completely seizure-free represent exemplars of the most complete resection of epileptogenic cortex.

Surgical Specimens

All patients underwent ATL under general anesthesia. After routine exposure of the temporal lobe the surgeon undertook resection of anterior lateral temporal neocortex, leaving the temporal horn of the lateral ventricle exposed along its anterior length. This resection included the superior through inferior temporal gyri, leaving hippocampus, parahippocampus and fusiform gyri. The fusiform gyrus was then resected leaving only hippocampal and parahippocampal gyri. A single silver clip was applied to the anterior edge of the hippocampus, and then the hippocampus and parahippocampal gyrus were removed *en bloc* to at least the anterior margin of the cerebral peduncle. Two silver clips were applied to the posterior margin of the hippocampus. By placing the single and double silver clips on the anterior and posterior margins, the specimen could be aligned after fixation to facilitate serial sectioning perpendicular to its long axis. The entire dissection of hippocampus was done using the operating microscope. After removal, the specimen was placed in formalin, fixed, and then serially sectioned along its long axis, which, although it is somewhat curved, was mainly oriented along the anterior–posterior axis. Patients did not undergo postresection MRI, so quantification and confirmation of the surgeon's estimates of resection were not available.

Hippocampal Grading System

The hippocampal pathology grading system was based on review of serial sections of hippocampus removed *en bloc* (see description below). After reviewing the entire hippocampal specimen, the sections showing the most severe involvement were used to grade pathology. The grading system yields the following categories:

Grade 0: No hippocampal pathology present. None of the conditions which describe the following grades were met.

Grade 1: Mild mesial temporal damage. Mild damage (gliosis with slight [<10%] or no neuronal dropout) involving sectors CA1, CA3, and/or CA4 of hippocampal pyramidal cell layer.

Grade 2: Moderate mesial temporal damage. Moderate damage (gliosis with moderate [10–50%] neuronal dropout) involving sectors CA1, CA3, and/or CA4 of hippocampal pyramidal cell layer. (If involvement is limited to CA3 and CA4, the lesion can be designated ''end folium sclerosis'').

Grade 3: Moderate to marked mesial temporal damage. (Hippocampal sclerosis or ''classical'' Ammon's horn sclerosis): Severe damage (gliosis with >50% neuronal dropout) involving sectors CA1, CA3, and CA4 of hippocampal pyramidal cell layer but sparing CA2, the resistant sector.

Grade 4: Marked mesial temporal damage. (Hippocampal sclerosis or ''total'' Ammon's horn sclerosis). Severe damage (gliosis with >50% neuronal dropout) involving all sectors of hippocampal pyramidal cell layer. The fascia dentata, subiculum, parahippocampal gyrus may also be involved.

Throughout the investigation, neuropathological analysis was carried out while blinded to neuropsychological results, and vice versa. Left and right temporal lobe groups were classified into two groups based on the neuropathology results: No/mild hippocampal sclerosis (Grades 0 and 1 combined) versus Moderate/marked hippocampal sclerosis (Grades 3 and 4 combined). This is a meaningful dichotomy which has been found to be predictive of the adequacy of preoperative memory function and pre- to postoperative memory change (Hermann et al., 1992; Hermann et al., 1994b; Seidenberg et al., 1996), and subsequently will be referred to as HPSC− and HPSC+ respectively. HPSC+ (Grades 3 and 4) essentially corresponds to ''classical'' hippocampal sclerosis, and HPSC− essentially corresponds to absent hippocampal sclerosis since Grade 1 describes such minor cell loss. Patients with Grade 2 were deleted because this is the least frequently occurring classification and they fall intermediate between what is clearly hippocampal sclerosis and what is not convincing hippocampal sclerosis.

Based on the examination of the hippocampal specimens and data on seizure outcome, four groups were composed: (1) No hippocampal sclerosis, seizure-free (HPSC− SF); (2) No hippocampal sclerosis, not seizure-free (HPSC− NSF); (3) hippocampal sclerosis present,

TABLE 1
Characteristics of Left ATL Groups

	HPSC− SF (N = 13)	HPSC− NSF (N = 10)	HPSC+ SF (N = 19)	HPSC+ NSF (N = 12)
Age	34.2 (9.4)	30.5 (9.8)	30.3 (6.8)	30.1 (10.5)
Education	14.3 (2.4)	12.3 (2.5)	12.9 (1.9)	11.1 (2.4)
Gender				
Male	6	6	7	6
Female	7	4	12	6
Age of onset	21.6 (10.9)	19.1 (11.8)	6.6 (7.0)	6.8 (7.4)

seizure free (HPSC+ SF); and (4) hippocampal sclerosis, not seizure-free (HPSC+ NSF). As shown in Table 1, these groups did not differ in chronological age [$F(3, 50) = 0.63$, $p > .10$], but there was a significant difference in years of education [$F(3, 50) = 4.43$, $p < .01$], with the HPSC+ NSF group having fewer years of education than the HPSC− SF group. As expected, age of onset was also significantly different between the four groups [$F(3, 50) = 10.26$, $p < .001$]. Patients with hippocampal sclerosis (HPSC+), regardless of surgical outcome, had an earlier age of onset (mean = 6.7 years) than those without hippocampal sclerosis (HPSC−) (mean = 20.5 years).

Memory Measures

We have previously identified measures from the California Verbal Learning Test (Delis et al., 1987) that are sensitive to left hippocampal function, and selected indices are included here for investigation: Total Words Recalled (Trials 1–5), Short Delay Free Recall (SDFR), Long Delay Free Recall, Percent forgetting (Trial 5 minus SDFR/Trial 5), and Discriminability. Also included is the overall score from the Paired-Associate Learning subtest from the Wechsler Memory Scale (Wechsler & Stone, 1945) in order to examine generalizability of findings across memory tests.

Nonmemory Measures

Included was the Wisconsin Card Sorting Test (Heaton, 1981) as a measure of executive function and the Judgement of Line Orientation Test (Benton, Hamsher, Varney, & Spreen, 1983) as a measure of spatial orientation. Previous findings have indicated that these measures are not associated with hippocampal integrity (Hermann & Seidenberg, 1995; Hermann, Seidenberg, Haltiner, & Wyler, 1995; Trenerry & Jack, 1994).

RESULTS

Means and standard deviations for the pre- and postoperative performance of the four groups are shown in Tables 2 and 3. The pre- and postoperative scores were examined via Group × Time (4 × 2) repeated-measures analyses of variance (ANOVA), and post-hoc contrasts were conducted using the Newman–Keuls procedure.

TABLE 2
Performance of Left ATL Groups Prior to Surgery

	HPSC− SF (N = 13)	HPSC− NSF (N = 10)	HPSC+ SF (N = 19)	HPSC+ NSF (N = 12)
Verbal memory				
CVLT total words	44.1 (10.4)	43.9 (10.3)	43.4 (10.3)	33.9 (11.4)
CVLT short delay free	9.3 (4.5)	9.3 (2.3)	7.5 (3.9)	5.2 (3.8)
CVLT long delay free	8.8 (4.5)	8.9 (3.2)	7.4 (3.6)	6.1 (4.1)
CVLT discriminability	87.1 (14.1)	91.6 (6.7)	89.2 (7.4)	76.4 (14.4)
CVLT % forgetting	18.0 (29.4)	16.5 (18.2)	33.2 (26.3)	40.5 (31.7)
WMS paired associates	15.2 (3.7)	14.8 (3.9)	13.9 (3.6)	11.1 (4.5)
Nonmemory				
Line orientation	23.2 (6.0)	24.6 (2.0)	23.1 (3.5)	21.4 (5.4)
WCST PR[a]	21.0 (14.7)	10.9 (9.1)	16.1 (13.7)	35.5 (19.3)

[a] Wisconsin Card Sorting Test—Perseverative Response.

Memory Measures

All five of the CVLT indices as well as the WMS Paired-Associate measure showed a significant Group × Time interaction effect (all p's $< .01$). Figure 1 illustrates the pattern of pre- to postoperative memory performance observed for the four groups for the memory indices.

Preoperatively, the HPSC+ NSF group obtained the lowest score across all memory indices, and was significantly lower than both the HPSC− SF and HPSC− NSF groups (all p's $< .05$). The HPSC+ NSF group performed worse than the HPSC+ SF group across all memory indices, with significance reached for CVLT Total Words Recalled and Discriminability (all p's $< .05$). There were no significant preoperative differences between the HPSC+ SF group and either of the HPSC− groups (SF or NSF).

TABLE 3
Performance of Left ATL Groups after Surgery

	HPSC− SF (N = 13)	HPSC− NSF (N = 10)	HPSC+ SF (N = 19)	HPSC+ NSF (N = 12)
Verbal memory				
CVLT total words	31.5 (10.6)	33.5 (10.4)	41.7 (11.2)	34.7 (11.1)
CVLT short delay free	4.8 (3.1)	5.3 (3.9)	7.4 (3.4)	5.7 (3.3)
CVLT long delay free	4.8 (3.2)	4.3 (3.2)	7.4 (3.4)	5.0 (3.8)
CVLT discriminability	78.3 (10.9)	82.1 (11.3)	88.8 (8.2)	80.8 (10.9)
CVLT % forgetting	38.0 (27.0)	35.8 (27.9)	29.2 (20.9)	33.1 (34.4)
WMS paired associates	9.7 (2.1)	8.3 (2.3)	12.1 (3.7)	8.5 (4.3)
Nonmemory				
Line orientation	24.0 (5.2)	25.4 (2.8)	24.8 (3.5)	20.4 (5.4)
WCST PR[a]	12.2 (12.2)	8.0 (10.3)	11.8 (13.3)	21.4 (11.2)

[1] Wisconsin Card Scoring Test—Perseverative Response.

Postoperatively, the left HPSC+ SF group had the highest scores across all the memory measures, while both of the HPSC− groups (SF and NSF) performed at levels similar to the HPSC+ NSF group. The HPSC+ SF group obtained significantly higher scores on CVLT Total Words, Long Delay Free Recall, Discriminability, and WMS Paired-Associates than both the HPSC− groups (p's $< .05$), and the remaining memory indices showed the same pattern of results.

Significant pre- to postoperative declines were observed on all memory indices for both HPSC− groups (SF and NSF) (all p's $< .05$), and the extent of decline was quite similar for these two groups. None of the pre- to postoperative memory changes were significant for either of the HPSC+ groups (SF or NSF).

Nonmemory Measures

For preoperative Wisconsin Card Sort (WCST) performance a significant Group and Time effects were found (p's $< .01$), but the interaction effect was not significant ($p > .10$). The HPSC+ NSF group produced significantly more perseverative responses than the other three groups (p's $< .05$), and no other significant group differences emerged. Figure 2 provides a display of these scores for the four groups.

Preoperative performance on the Judgment of Line Orientation Test (JLO) revealed a marginal significant Group effect ($p = .08$), along with nonsignificant effects of Time and the Group × Time interaction (p's $> .10$). The HPSC+ NSF group had the lowest scores at both testings.

Predictors of Cognitive Change following ATL

Regression analyses were conducted to examine the relationship between cognitive outcome and age of onset of recurrent seizures. For these analyses the patients' pre-operative score and seizure outcome were entered first so that the residualized age at onset effects could be determined. The semi-partial correlations values for age of onset and the cognitive measures are reported in Table 4 for the left HPSC+ and HPSC− groups separately.

For the left HPSC+ group (SF and NSF combined), age of seizure onset was a significant predictor of postoperative CVLT Total Words Recalled, Short-Delay Free Recall, Long Delay Free Recall, Percent Forgetting, and WMS Paired Associates. In each instance, an earlier age of seizure onset was associated with better verbal memory outcome. In contrast, age of seizure onset was not significantly correlated with postoperative scores on the WCST or the JLO.

For the HPSC− group (SF and NSF combined), age of seizure onset was not significantly related to any of the postoperative memory indices or the nonmemory measures.

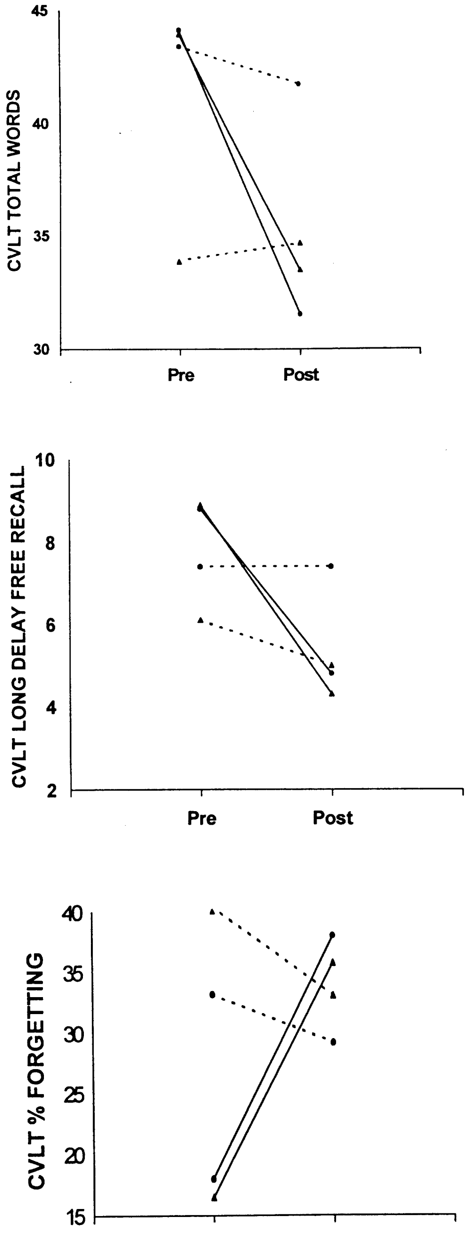
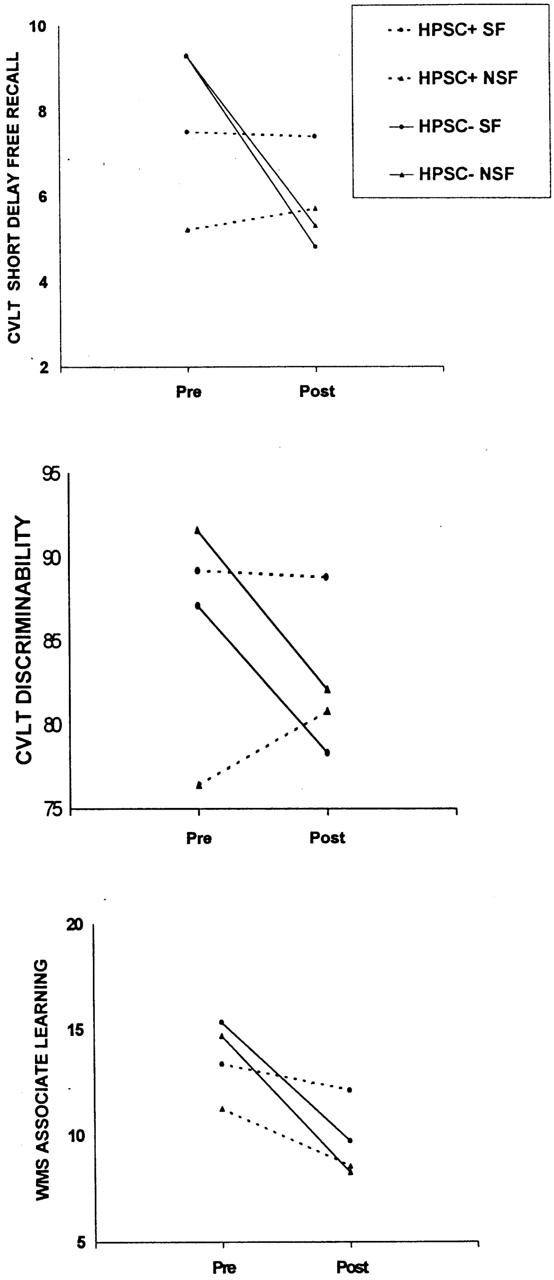


FIG. 1. Pre- and post-ATL memory scores for the four groups.



HPSC+ SF
HPSC+ NSF
HPSC- SF
HPSC- NSF
CVLT SHORT DELAY FREE RECALL
10
8
6
4
2
Pre
Post
CVLT DISCRIMINABILITY
95
90
85
80
75
Pre
Post
WMS ASSOCIATE LEARNING
20
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Pre
Post

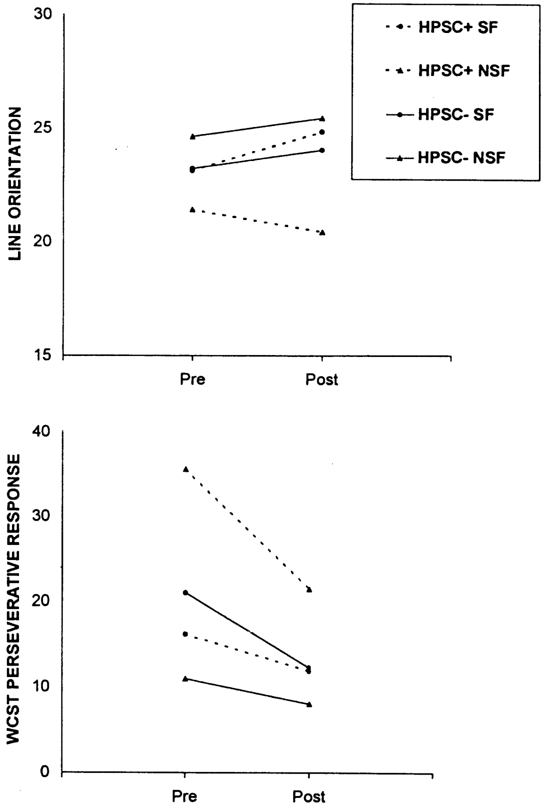

FIG. 2. Pre- and post-ATL nonmemory scores for the four ATL groups.

DISCUSSION

We proposed that reorganization of traditional mesial temporal lobe memory functions in unilateral TLE requires both an early and very focal hippocampal lesion. Several findings from this study were consistent with this proposal. However, before reviewing these results, several fundamental features of this study deserve comment. First, patients were excluded if they showed MRI evidence of any lesions with the exception of mesial temporal sclerosis. Thus, a primary variable distinguishing the groups was the presence or absence of histopathologically verified hippocampal sclerosis. Comparability in surgical attack, lack of neocortical lesions, and other features help to insure that group differences can be attributed to the neuropathological status of the mesial temporal region. Second, epilepsy centers differ as to how surgical outcome is defined. Most centers consider patients who continue to experience auras as seizure-free. That was not the case here. Ongoing seizure activity, even simple partial, implies that epileptogenic tissue remains

TABLE 4
Semipartial Correlations of Age of Seizure Onset with Memory and Nonmemory Measures

	Left HPSC− ($N = 23$) Age of onset	Left HPSC+ ($N = 31$) Age of onset
Verbal memory		
CVLT total words	−.23	−.32*
CVLT short delay free	−.26	−.44**
CVLT long delay free	−.12	−.40**
CVLT discriminability	−.12	−.07
CVLT % forgetting	−.17	−.47**
WMS paired associates	−.15	−.27*
Nonmemory		
Line orientation	.05	.15
WCST PR[a]	.03	.03

[a] Wisconsin Card Sorting Test—Perseverative Response.
** $p < .01$, * $p < .05$.

outside the zone of resection, a crucial consideration in this study. Surgical outcome was rated by the surgeons, blinded to the neuropsychological test results, and this information was garnered well before the current hypotheses were developed. Third, surgical outcome was used as an inferential marker of the degree to which dysfunctional neuronal systems remained outside the zone of surgical resection. It is entirely possible that pathologic (nonfunctional) tissue also remains in those who become seizure-free as well as those who did not become seizure-free; however, our assumption was that it would likely be a more diffuse region of pathology among those who continued to have seizures. Fourth, there are different measurement techniques (e.g., MRI hippocampal volumes, neuronal cell counts, qualitative ratings) employed to determine hippocampal sclerosis and the thresholds of neuronal loss used to categorize the presence/absence of hippocampal sclerosis also may vary across epilepsy centers. We have presented in detail (see Methods section) the procedure used in the current study to arrive at the diagnosis of hippocampal sclerosis.

The pattern of findings observed for the HPSC+ SF group is quite consistent with the proposal that reorganization of memory function is more likely to occur in the context of an early occurring focal brain insult. First, the HPSC+ SF group performed at a level similar to the HPSC− groups prior to surgery, while the HPSC+ NSF group did not. None of the memory measures examined prior to ATL showed a significant difference between the HPSC+ SF group and the two HPSC− groups. This finding is particularly impressive given that the HPSC+ SF group had significantly longer-standing epilepsy than the HPSC− groups (24 years versus 12 years), and had clear significant pathology in the hippocampus whereas the HPSC− groups are known to have an at least partially functional hippocampus (given their pre- to post operative decline). More important, following left ATL the HPSC+ SF group's memory performance did not change and was superior to both the HPSC− groups. Given that resection of the mesial temporal lobe region occurred for all subjects, the better memory outcome observed for the HPSC+ SF group suggests that other neural systems were mediating the target memory functions.

The performance of the HPSC+ NSF group is also consistent with the notion that in the presence of more diffuse neuropathology, reorganization of function would be less likely to occur, despite the presence of an early brain insult. HPSC+ NSF patients were more impaired than the HPSC+ SF group on both memory and nonmemory measures both before as well as after ATL. Other studies have also reported a relationship between poorer postoperative seizure outcome and preoperative evidence of diffuse neuropsychological impairment (Helmstaedter, Hufnagel & Elger, 1992; Hermann & Seidenberg, 1995; Lieb et al., 1982).

Thus, the overall pattern of findings for the HPSC+ SF and HPSC+ NSF groups is consistent with expectations based on the occurrence of cerebral reorganization of memory function in the context of an early onset, but fairly focal lesion. We could find no differences between the HPSC+ groups, other than seizure outcome that could account for these findings. The HPSC+ groups did not differ in severity of hippocampal pathology (Grade 3 vs Grade 4), age of seizure onset, duration of disorder, or education level. There was a higher proportion of females in the HPSC+ SF group, but the pattern of findings reported above remained the same when males and females were examined separately. However, given the limited sample size available when broken down by sex, our power to detect possible sex differences was clearly limited. The only difference clearly evident between these groups was their seizure outcome. Given that a comparable surgical attack was utilized for all patients, it appears reasonable to propose that seizure outcome reflected the distribution or diffuseness of the underlying epileptogenic region. The extent of such disturbances would then have an impact on the capability of other neuronal systems to compensate and assist in taking over the functions associated with the primary hippocampal lesion, presumably taking place at an early age.

The potential for functional reorganization would not be expected for those individuals without evidence of an early onset hippocampal lesion (i.e., HPSC− patients with a mean age at onset of approximately 21 years). The substantial decline in memory performance shown by the HPSC− confirms that functional tissue (at least in part) had been removed and is consistent with previous research indicating a clear inverse relationship between performance on verbal memory tasks and the degree of left hippocampal neuronal loss (Hermann et al., 1994b; Rausch, 1987; Sass et al., 1994; Trenerry et al., 1993). Furthermore, the decline in performance was specific to memory functions and was not seen on measures of executive function or spatial orientation. Indeed, following ATL, the HPSC− groups performed at a level comparable to the HPSC+ NSF group on the memory indices but were significantly better on the nonmemory measures examined in this study. It is worth noting too, that the decline in memory performance following ATL was similar for both the HPSC− groups, regardless of seizure outcome. Thus, the removal of functional hippocampal tissue rather than the continuation of seizure activity was the critical variable in producing the substantial memory morbidity.

We should note that our proposal concerning reorganization of memory function is not necessarily predicated on any assumptions concerning the cause–effect relationship between hippocampal sclerosis and seizures, but our findings are not irrelevant to this issue. The question of whether hippocampal sclerosis is the neuropathological end-state of intractable temporal lobe epilepsy versus a primary etiologic lesion continues to be debated and evidence can be mounted for either viewpoint (Holmes, 1991). Thus, we do not assume that the extent/severity of hippocampal sclerosis observed at time of resection in our HPSC+ groups (as adults) necessarily reflected the state of the hippocampus at the time that seizures began to occur. We do, however, think it is reasonable to suggest that the presence of an early age of recurrent seizures among those with tissue verified hippocampal sclerosis (at time of surgery) signals the presence of a discrete hippocampal lesion early in development, and that this lesion sets in motion the reorganization process. Subsequent ongoing seizure activity over an extended period of time can add to the degree of gliosis and neuronal loss in the hippocampus. This proposal is consistent with findings from MRI studies in children with unilateral TLE (Cendes et al. 1993; Grattn-Smith et al., 1993), studies reporting an association between age of onset but not duration of epilepsy with hippocampal sclerosis in unilateral TLE (Davies et al., 1996; Trenerry et al., 1993), and findings suggesting that an early precipitating event (e.g., head injury, febrile seizures, perinatal complications) contributes in large part to the extent of hippocampal sclerosis observed in adult surgical specimens (Mathern et al., 1995).

Three other points about our study deserve comment and have relevance to the proposal about reorganization of verbal memory which we have put forth: (1) the definition of age of seizure onset, (2) the inclusion of only left hemisphere speech dominant patients, and (3) MRI evidence of the absence of a structural neocortical lesion. First, by using age of recurrent seizures to define age of seizure onset, we have probably relied on a conservative estimate (i.e., later age) of the age at which the underlying brain insult which gave rise to seizures actually occurred. Thus, the underlying brain lesion may have been present for a period of time before recurrent seizures appeared. Even so, we noted earlier that over two-thirds of the TLE sample that come to surgery and have evidence of moderate–severe hippocampal sclerosis begin having recurrent seizures before age five years.

Second, the fact that the HPSC+ patients had left hemisphere language dominance in the context of an early age of seizure onset suggests that the seizures and the underlying insult which gave rise to the seizures did not influence the interhemispheric organization of speech. In addition, none of the patients had a structural cortical lesions revealed by MRI. If it is accepted that reorganization of memory function has taken place in the HPSC+ SF group, then it would appear that a shift of speech function to the right hemisphere is not a necessary precondition for verbal memory reorganization. It remains to be determined whether such reorganization of memory function has been intra- or interhemispheric in nature.

Previous reports in the epilepsy literature implicating interhemispheric reorganization have focused on the study of patients with atypical language organization. However, several reports examining patients with IAT evidence of left hemisphere language dominance have suggested the possibility of intrahemispheric reorganization for naming (Stafiniak et al., 1990) and verbal memory (Saykin et al., 1989). In a recent paper, Glosser et al. (1995) examined Wada Test-based memory performance for verbal and nonverbal material and could find no evidence of contralateral transfer of verbal memory function in left hemisphere speech dominant patients with early age of risk factors for epilepsy. Based on these results, it was proposed that reorganization of memory function took place in association with early onset mesial temporal lesions, and that the reorganization was intrahemispheric in nature. We also noted the absence of impaired performance on measures outside the verbal memory domain (e.g., visuo-perceptual) in the group which shows evidence for memory reorganization (i.e., left HPSC+SF group). Previous studies have suggested that interhemispheric reorganization of speech occurred at a cost to the abilities typically subserved by the contralateral hemisphere (Milner, 1974).

Overall, the results provide support for the notion of functional reorganization of verbal memory ability in a subset of patients with unilateral left TLE. This subset is characterized by an early age of recurrent seizures and a good seizure outcome following surgery. These results are consistent with the notion that factors such as hippocampal integrity, seizure outcome, and age of seizure onset appear to contribute to the nature and extent of variability in memory and cognitive functioning of individuals with unilateral TLE.

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