Risk to Verbal Memory Following Anterior Temporal Lobectomy in Patients With Severe Left-Sided Hippocampal Sclerosis

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Background: Previous investigations indicate low risk for memory loss following anterior temporal lobectomy (ATL) in patients with severe hippocampal sclerosis (HS) compared with patients with mild HS. However, these conclusions have been established primarily with group-level analyses.

Objective: To investigate individual base rate risk for verbal memory loss following ATL in patients who have pathologically verified mild, moderate, or severe HS.

Patients and Methods: One hundred fifteen patients with unilateral temporal lobe epilepsy (68 with left-sided and 47 with right-sided epilepsy) were included. Acquisition, retrieval, and recognition components of verbal memory, as measured by the California Verbal Learning Test, were assessed before and after ATL. Postoperatively, the degree of neuronal loss and reactive gliosis of the hippocampus was assessed via a 3-tiered rating system establishing mild, moderate, and severe pathologic features. Patients with preoperative magnetic resonance imaging–based evidence of lesions outside the mesial temporal area (side of surgical resection) were excluded.

Results: Neither seizure laterality nor severity of HS was associated with preoperative verbal memory performance. Postoperatively, the left-sided ATL group demonstrated significant decline across the acquisition (P<.01), retrieval (P<.001), and recognition (P<.001) verbal memory components compared with the right-sided ATL group. Patients who underwent left-sided ATL and had mild HS displayed the largest magnitude and percentage proportion of postoperative decline across all verbal memory components. However, 28 (48%) of the 58 patients who underwent left-sided ATL and who had moderate and severe HS displayed statistically reliable declines on retrieval aspects of verbal memory. Most patients undergoing right-sided ATL, regardless of the extent of hippocampal pathologic features, displayed no postoperative memory change.

Conclusions: Substantial individual heterogeneity of memory outcome exists across groups of patients undergoing ATL, with various degrees of pathologically verified HS. Patients undergoing left-sided ATL who have mild HS seem at greatest risk for broad-spectrum verbal memory decline. However, when examining outcome on a patient-by-patient basis, many patients undergoing left-sided ATL who have moderate to severe HS were also vulnerable to verbal memory loss. This risk seems selective to a retrieval-based aspect of verbal memory.

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individuals experiencing an earlier age of onset, thus having experienced seizures for an extended period, often exhibit a more neurologically compromised status and, therefore, demonstrate greater and more widespread deficits in cognitive functioning preoperatively. However, the earlier age of onset may also result in a reallocation of function to surrounding brain areas, thus explaining the less severe loss of memory function postoperatively. Therefore, in patients with severe HS, ATL results in the resection of tissue that is less functional. In contrast, those individuals who experience TLE onset at a later age are likely not as neurologically compromised and, thus, exhibit milder cognitive dysfunction preoperatively. However, for these individuals, ATL results in the removal of more functional brain tissue and, thus, yields greater risk to memory deficits postoperatively.

As previously described, research has consistently demonstrated significant changes in memory function following ATL. However, these findings have primarily been obtained by averaging performance across groups. Anterior temporal lobectomy outcome research has only recently attempted to characterize the extent of within-group heterogeneity found on neuropsychological measures. These studies have demonstrated substantial intragroup cognitive outcome variability for patients undergoing ATL. However, to our knowledge, the issue of individual levels of base rate change as related to the degree of HS has not been examined. The present study examines the individual-level (within-group) distribution of memory outcome in patients undergoing ATL who have various degrees of pathologically verified HS. Although group-level analysis provides valuable information about general tendencies in memory outcome, reliance on such examination may mask important heterogeneity of outcome within particular groups. The present study will particularly focus on whether patients with severe HS exhibit memory decline following ATL, even though as a group memory decline is not typically noted.

**METHODS**

Patients were selected for the present study from our epilepsy center's ATL series operated on between January 1, 1988, and April 30, 2000. All patients underwent standard preoperative diagnostic procedures. Videotape/electroencephalographic monitoring was used for all patients to analyze interictal electroencephalographic and ictal semiological features, and electroencephalograms of at least 3 seizures were recorded. Each patient underwent magnetic resonance imaging of the brain with a 1.5-T unit before surgery, including T2- and T1-weighted images in axial, coronal, and sagittal planes. All patients were determined to have a unilateral temporal lobe seizure origin by scalp or sphenoid electroencephalographic monitoring or epidural strip electrode implantation when necessary.

Inclusion criteria for patient selection were as follows: (1) aged 16 years or older, (2) Full Scale IQ score greater than 69, (3) right-handedness, (4) preoperative magnetic resonance imaging findings indicating only mesial temporal sclerosis, and (5) exclusive HS as determined by histopathological features. Patients with lesions outside the mesial temporal area were excluded (eg, tumor or developmental malformation).

Ten patients were left-handed (6 underwent left-sided ATL and 4 underwent right-sided ATL), but were included in the sample because they had intracarotid amobarbital (Amytal) procedure evidence of left hemisphere language dominance. Patients with intracarotid amobarbital procedure evidence of atypical language representation were not included.

The study sample consisted of 115 patients who underwent unilateral ATL for the treatment of intractable seizures (68 left-sided and 47 right-sided procedures). The resection included a neocorticectomy of the anterior 4.5 to 5.5 cm of the temporal lobe, sparing the superior temporal gyrus. The amygdala and the anterior two thirds of the hippocampus were resected and sent for pathological analysis. This surgical technique has been reported in detail previously.

Surgical tissue samples of the hippocampus were obtained for quantitative analysis by a single neuropathologist (C.P.). Specimens were fixed in formaldehyde and sectioned perpendicularly to the long axis as much as possible. After paraffin embedding, 6-μm-thick sections of the hippocampus were stained with hematoxylin-eosin and underwent immunohistochemical testing for the determination of glial fibrillary acidic protein. Regions demonstrating the most severe pathological involvement were used to grade the pathological features.

The degree of neuronal loss and reactive gliosis (HS) was assessed via a 3-tiered system of mild, moderate, and severe. Mild HS consists of a combination of mild quantitative astrogliosis by immunohistochemical analysis and less than 40% long-term neuronal dropout. Moderate HS includes a combination of moderate quantitative astrogliosis and neuronal loss between 40% and 75% of the normal population. Severe quantitative astrogliosis and more than 75% long-term neuronal loss characterize severe HS. These categorizations are similar to other classification systems used in the pathological study of HS.

All patients completed postoperative neuropsychological evaluations between 3 and 18 months after surgery (mean, 7.5 months; SD, 2.5 months).

**PREOPERATIVE ANALYSES**

A series of 2 (seizure laterality: left and right) by 3 (HS classification: mild, moderate, and severe) analyses of variance were performed to examine between-group differences for demographic and clinical variables (Table 1). Follow-up post hoc testing was performed in the event of a significant interaction or main effects.

**POSTOPERATIVE ANALYSES**

Analysis of postsurgery verbal memory incorporated a standardized regression-based (SRB) method. Using regression-based methods offers the advantage of controlling for test-retest artifacts, such as practice effect, between-subject differences in baseline performance, and regression to the mean, that confound standard repeated-measures analyses (ie, comparing raw score test differences between the preoperative and postsurgical times).
Table 1. Summary of Demographic, Intelligence Score, and CVLT Data for the Left- and Right-Sided ATL Groups, by HS Classification*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild (n = 10)</th>
<th>Moderate (n = 36)</th>
<th>Severe (n = 22)</th>
<th>Mild (n = 13)</th>
<th>Moderate (n = 23)</th>
<th>Severe (n = 11)</th>
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<tr>
<td>Age, y</td>
<td>34.8 (10.3)</td>
<td>33.2 (10.1)</td>
<td>35.9 (10.5)</td>
<td>30.9 (9.8)</td>
<td>36.7 (8.9)</td>
<td>33.3 (12.2)</td>
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<td>Education, y</td>
<td>11.2 (2.2)</td>
<td>12.1 (2.7)</td>
<td>12.4 (2.1)</td>
<td>13.2 (2.7)</td>
<td>12.3 (2.9)</td>
<td>11.0 (4.1)</td>
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<td>Age at first seizure risk, y</td>
<td>9.9 (10.6)</td>
<td>9.4 (11.7)</td>
<td>6.2 (7.1)</td>
<td>9.1 (6.9)</td>
<td>11.4 (11.4)</td>
<td>7.0 (5.1)</td>
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<tr>
<td>Age at seizure onset, y</td>
<td>11.2 (10.7)</td>
<td>13.8 (12.1)</td>
<td>11.3 (8.4)</td>
<td>10.2 (6.7)</td>
<td>14.0 (11.4)</td>
<td>8.1 (5.2)</td>
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<td>Seizure duration, y</td>
<td>21.2 (8.4)</td>
<td>20.1 (12.8)</td>
<td>24.6 (14.4)</td>
<td>20.6 (9.9)</td>
<td>22.7 (12.7)</td>
<td>30.6 (13.4)</td>
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<td>WAIS-R</td>
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<td>VIQ</td>
<td>82.0 (11.2)</td>
<td>85.6 (14.0)</td>
<td>86.3 (10.3)</td>
<td>90.7 (14.2)</td>
<td>89.2 (8.4)</td>
<td>87.9 (12.3)</td>
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<td>PIQ</td>
<td>84.8 (12.2)</td>
<td>85.3 (14.8)</td>
<td>91.8 (10.9)</td>
<td>91.1 (13.8)</td>
<td>90.7 (9.3)</td>
<td>81.9 (10.6)</td>
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<td>CVLT scores</td>
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<td>Preoperative</td>
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<tr>
<td>Acquisition</td>
<td>41.9 (10.5)</td>
<td>42.3 (13.2)</td>
<td>44.5 (10.1)</td>
<td>46.7 (10.5)</td>
<td>48.1 (12.2)</td>
<td>48.0 (12.4)</td>
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<td>Retrieval</td>
<td>8.1 (2.9)</td>
<td>7.6 (3.9)</td>
<td>7.7 (3.5)</td>
<td>9.2 (3.7)</td>
<td>8.7 (4.1)</td>
<td>8.6 (3.9)</td>
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<td>Recognition</td>
<td>88.4 (10.6)</td>
<td>87.5 (9.2)</td>
<td>89.4 (9.4)</td>
<td>89.7 (9.8)</td>
<td>90.2 (7.1)</td>
<td>91.9 (5.8)</td>
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<td>Postoperative</td>
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<tr>
<td>Acquisition</td>
<td>34.0 (20.1)</td>
<td>41.5 (12.8)</td>
<td>40.7 (12.2)</td>
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<td>50.0 (13.1)</td>
<td>49.7 (11.1)</td>
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<td>Retrieval</td>
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<td>6.9 (3.5)</td>
<td>7.0 (3.8)</td>
<td>9.6 (2.3)</td>
<td>10.2 (4.0)</td>
<td>10.2 (3.0)</td>
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<tr>
<td>Recognition</td>
<td>83.6 (9.0)</td>
<td>92.9 (32.7)</td>
<td>85.3 (11.2)</td>
<td>89.9 (9.1)</td>
<td>91.6 (9.0)</td>
<td>92.6 (4.2)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD). CVLT indicates California Verbal Learning Test; ATL, anterior temporal lobectomy; HS, hippocampal sclerosis; WAIS-R, Wechsler Adult Intelligence Scale–Revised; VIQ, Verbal Intelligence Scale Quotient; and PIQ, Performance Intelligence Scale Quotient.

Derivation of Verbal Memory Standardized Change Scores

The regression-based method develops a cognitive change score by first modeling change in unoperated-on control patients with epilepsy who have been tested at baseline and follow-up. The resultant regression models predict follow-up scores in an unoperated-on control sample with epilepsy based on baseline performance and other covariates, such as age, educational level, and sex. When the regression equation is applied to the test-retest data from a surgery sample, the difference between the predicted and observed follow-up scores (ie, residual) can be standardized using the SE of the estimate from the regression model. These standardized residuals are referred to as SRB change scores, reflecting change in SD units relative to the unoperated-on control group. Previously published regression equations for the CVLT were used.

By applying the SRB equations to our surgery sample, predicted follow-up scores and SRB change scores for the CVLT measures were calculated using the following equation:

\[ \text{SRB Change Score} = \frac{Y_o - Y_p}{SE_{est}} \]

where \( Y_o \) is the observed follow-up score; \( Y_p \), the predicted follow-up score; and \( SE_{est} \), the SE of the estimate.

The second phase of postsurgery analysis calculated a mean SRB memory change score for each group across each CVLT measure. Separate 2 \( \times \) 3 analyses of variance were performed to examine surgery side and HS classification for the 3 CVLT measures. Post hoc analyses were performed in the event of significant main or interaction effects.

A third phase of postsurgery analysis calculated base rates of change across each CVLT measure. This level of analysis provides individual-level determination of change. For the present study, statistically reliable change was based on SRB change scores that exceeded a \( z \) score of \( \pm 1.64 \) SDs (90% confidence interval, \( P < .05 \)). Thus, individual change scores that fell within the \( \pm 1.64 \) SD distribution of change scores were considered statistically common in unoperated-on populations with epilepsy. However, if the individual change score exceeded the \( \pm 1.64 \) SD range, the score was operationalized as statistically rare and viewed as representing a statistically reliable change. Base rate distributions for each CVLT measure were determined for the left- and right-sided ATL groups across the HS classifications. Nonparametric statistics (Kruskal-Wallis tests) were used to examine possible base rate distribution differences for each CVLT measure.

RESULTS

Preoperative Results

Demographic and Clinical Variables

Table 1 provides a summary of demographic, clinical, and CVLT scores for the left- and right-sided TLE groups across each HS classification. An analysis of variance revealed no significant interaction or main effects across the demographic or clinical variables. Groups did not differ across the Verbal or Performance Intelligence Scale Quotient measures.

CVLT Variables

No significant interaction (\( F_{3,110} = 0.84, P = .92 \)) or main effects were shown for the CVLT acquisition variable. The HS classification was not associated with acquisition scores (\( F_{3,110} = 0.16, P = .85 \)). A trend was observed for seizure laterality (\( F_{3,110} = 3.35, P = .07 \)), with patients with left-sided TLE having lower acquisition scores.

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No significant interaction (F5,110 = 0.01, P = .99) or main effects were found for the CVLT retrieval variable. The HS classification was not related to the retrieval measure (F5,110 = 0.14, P = .87). Seizure laterality was not associated with the retrieval measure (F5,110 = 1.70, P = .19).

Interaction (F5,110 = 0.01, P = .72) and main effects were not found for the CVLT recognition variable. Neither seizure laterality (F5,110 = 1.90, P = .17) nor HS classification (F5,110 = 0.43, P = .65) were related to the recognition variable.

**POSTOPERATIVE RESULTS**

**Group-Level Analysis**

Because of the variability in time to postoperative testing, we examined whether group-level differences existed as a function of time. Left- and right-sided ATL groups did not differ in average time to testing (P = .52). Time to postoperative testing did not differ according to HS classification (P = .40).

Analysis of variance results disclosed significant effects for side of surgery across each of the 3 CVLT SRB change scores (acquisition: F1,109 = 9.1, P < .003; retrieval: F1,109 = 25.8, P < .001; and recognition: F1,109 = 10.8, P < .001). The left-sided ATL group displayed poorer verbal memory compared with the right-sided ATL group. No interaction effects were found. The Figure presents mean SRB change scores by surgery group and HS classification. The mean SRB change scores for the right-sided ATL group ranged from −0.67 (retrieval: mild HS) to 0.49 (retrieval: severe HS). None of the SRB scores for the right-sided ATL group, regardless of HS, exceeded our a priori ±1.64 cutoff value. For the left-sided ATL group, decline was observed across each level of HS and for all 3 CVLT variables. The larger magnitude of performance decline by the left-sided ATL group with mild HS compared with the left-sided ATL groups with moderate or severe HS was notable. However, post hoc analyses did not reach statistical significance (acquisition: F2,65 = 0.89, P = .42; retrieval: F2,65 = 2.00, P = .14; and recognition: F2,65 = 1.90, P = .15).

**Individual-Level Analysis**

Base rate distributions of the 3 CVLT SRB change scores are presented in Table 2. Nonparametric analyses disclosed no differential pattern of proportion change for the left-sided ATL groups across HS classification. However, for each CVLT measure, patients who underwent left-sided ATL and who had mild HS displayed more individuals who declined (SRB change score < 1.64) compared with patients who underwent left-sided ATL and who had moderate or severe HS. For the acquisition measure, 60% of the patients who underwent left-sided ATL and had mild HS displayed reliable performance decline compared with fewer than 25% for the other 2 left-sided ATL groups. For the recognition measure, reliable change...
was found in 40% of the patients who underwent left-sided ATL and had mild HS compared with fewer than 20% in the other 2 groups. Although 70% of the patients who underwent left-sided ATL and who had mild HS displayed reliable decline on the retrieval measure, approximately 50% of the patients who underwent left-sided ATL and who had moderate and severe HS also displayed statistically reliable decline for this measure.

For the right-sided ATL group, the proportion of patients within each HS classification displayed statistically reliable change across the CVLT SRB change scores was nonsignificant ($P > .30$ for all). Overall, fewer than 10% of the patients who underwent right-sided ATL displayed reliable decline for the memory measures and most displayed no reliable change. When change was found, it occurred more frequently in the patients who underwent right-sided ATL and had mild HS.

**Additional Analyses**

As seen in Table 2, approximately 50% of the patients who underwent left-sided ATL and who had moderate and severe HS demonstrated statistically reliable declines on the CVLT retrieval measure. Previous studies have indicated that risk to verbal memory loss in groups of patients with moderate to severe HS is modest. A series of parametric and nonparametric analyses were performed to examine whether patients who underwent left-sided ATL who had moderate to severe HS ($n=28$) and exhibited CVLT retrieval SRB change score declines ($<−1.64$) differed in present age, age at seizure onset, age at first seizure risk (ie, febrile convulsion), preoperative CVLT retrieval score, history of generalized tonic-clonic seizures, and postoperative seizure outcome compared with those patients who underwent left-sided ATL who had moderate to severe HS ($n=30$) and did not exhibit significant CVLT retrieval score changes. The 2 groups did not differ statistically for any of the variables ($P > .05$ for all). However, trends were noted in which those patients who underwent left-sided ATL and displayed retrieval declines tended to be older (36.4 vs 32.5 years) and tended to have a later age of seizure onset (14.4 vs 10.5 years), a later age at first seizure risk factor (9.7 vs 6.1 years), a higher preoperative retrieval score (8.1 vs 6.9), and a lower rate of seizure-free outcome (71% [20/28] vs 83% [25/30]).

**COMMENT**

The present study examined individual base rate outcome of verbal memory following ATL as a function of severity of HS. Previous research has primarily focused on group-level analysis of cognitive outcome and has not specifically addressed the question of the magnitude of intragroup heterogeneity of cognitive outcome as a function of extent of hippocampal pathological features. The present study was also specifically concerned with what proportion of patients who undergo ATL and who have more severe levels of HS experiences postoperative verbal memory declines and what possible risk factors explained such declines.

Examination of our preoperative data showed that left- and right-sided TLEs were similar across clinical and demographic variables, including verbal IQ. Patients who underwent left-sided ATL tended to perform more poorly than patients who underwent right-sided ATL across all 3 aspects of preoperative verbal memory, although other reports using list-learning tasks have typically found stronger findings indicating left-sided mesial temporal dysfunction negatively impacting verbal memory abilities. Inconsistent with some previously published work, severity of HS was not significantly associated with age at first seizure risk, age at seizure onset, or present age. Further examination of our patient sample revealed that all groups, even those with severe HS, exhibited a range of ages at seizure onset. On average, 30% of each group had seizure onset before the age of 6 years and 50% between the ages of 7 and 25 years. In addition, severity of HS was not statistically associated with the acquisition, retrieval, or recognition aspects of preoperative verbal memory performance in our sample. Others have found similar null findings between hippocampal damage and word list–learning tasks preoperatively, although still others have reported positive associations.

Examination of postoperative verbal memory outcome in a group-level analysis using an SRB method found that patients who underwent left-sided ATL did significantly worse on all 3 CVLT measures compared with patients who underwent right-sided ATL. This finding is well documented in the epilepsy literature and supports notions of the importance of left-sided mesial and cortical temporal lobe structural integrity for adequate verbal memory function. When further examining postoperative group-level memory outcome, we found no statistically significant effects based on HS classification in either the left-sided or the right-sided ATL groups. Although no statistically significant effects were found ($P < .05$), we noted a consistently larger magnitude of decline across all 3 CVLT outcome measures for the left-sided ATL group with mild HS compared with all other groups. Although not as statistically strong, this pattern of outcome is generally consistent with previous studies that have demonstrated positive associations between severity of left-sided HS and verbal memory outcome. The relatively small sample size of our left-sided ATL group with mild HS may have limited these findings.

The central aim of this study was to examine base rates of verbal memory change, at the individual patient level, in patients undergoing ATL with various levels of HS. We wanted to explore outcome beyond group-level analysis and to determine what proportion of patients undergoing ATL were at risk for verbal memory loss. While individual base rate examination of postsurgical cognitive outcome has previously demonstrated considerable within-group outcome heterogeneity, the present study specifically examined individual outcome as a function of level of pathologically verified HS. Previous studies have also found that when examined at a group level, patients with early seizure onset and severe HS are at least risk for verbal memory loss, possibly due to an early developmental lesion of mesial temporal lobe structures resulting in possible functional reorganization of the episodic memory system. Our base rate examination indicated that many patients undergoing left-sided ATL displayed statistically reliable declines in verbal memory.
following surgery. Although base rate differences did not reach statistical significance between the 3 left-sided ATL groups, the patients who underwent left-sided ATL and who had mild HS had consistently more individual cases exhibiting reliable declines. The proportion of individual-level memory change was of much less magnitude across right-sided ATL groups, with most patients showing no reliable changes after surgery. When change was noted for patients undergoing right-sided ATL, it was more often in those with mild HS. Small proportions of patients undergoing right-sided ATL have exhibited some degree of mild verbal memory decline after surgery in previous studies.14,16

While finding postoperative memory declines in patients with mild HS is not surprising,9,20 what has not fully been appreciated by group-level statistics is that many patients with more severe hippocampal pathologic features may also experience statistically reliable memory decline. Interestingly, this was most notable for the CVLT retrieval change score. A question arises as to why retrieval performances would be so negatively affected by resection of severely sclerotic hippocampal tissue. Previous studies10-27 have supported the idea that intrahippocampal acquisition and recognition aspects of verbal episodic memory can be adversely affected following ATL. Our findings demonstrated that many of each left-sided ATL group, regardless of the extent of HS, demonstrated declines on the CVLT retrieval measure. When examining factors potentially associated with verbal memory decline in our patients undergoing left-sided ATL who had severe HS, we found some indication that verbal retrieval decline was mildly associated with older age at seizure onset, first seizure risk, and time of surgery; higher preoperative memory function; and poorer seizure outcome. Although none of these associations were statistically significant, all of them were in a direction found by previous studies.9,12 Thus, patients undergoing left-sided ATL, even in the presence of severe HS, may display verbal retrieval-based memory decline if the previously mentioned risk factors are present.

When examining the results of this study, shortcomings are acknowledged. First, the relatively small sample sizes of the groups with mild HS may have affected the null association found between the degree of HS and memory outcome. Larger samples of patients with mild HS could have produced statistically reliable group differences, especially because qualitative examination of the Figure suggested trends toward worse outcome for the patients undergoing left-sided ATL who had mild HS. In addition, the influence of resection of the temporal neocortex on memory outcome should be considered. Acquisition and recognition aspects of verbal episodic memory can be adversely affected following ATL because of effects of the neocortical resection.30,32 However, resection variables in the present study do not seem substantially different than in those studies that have also examined the relationship between HS and memory outcome. All studies cited indicated that the temporal neocortex resected usually involved inferior and middle temporal gyri. In conclusion, the present study was conducted to demonstrate the range of individual variation found in verbal memory outcome following ATL. Future research should further explore the large amount of within-group heterogeneity, especially in attempting to delineate what specific characteristics are associated with individuals who do not perform as predicted.

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Author contributions: Study concept and design (Drs Martin and Sawrie and Ms Kretzmer); acquisition of data (Drs Martin, Faught, Morawetz, and Kuzniecky and Ms Kretzmer); analysis and interpretation of data (Drs Martin, Palmer, Sawrie, Knowlton, Faught, and Kuzniecky and Ms Kretzmer); drafting of the manuscript (Dr Martin and Ms Kretzmer); critical revision of the manuscript for important intellectual content (Drs Martin, Palmer, Sawrie, Knowlton, Faught, Morawetz, and Kuzniecky); statistical expertise (Drs Martin and Sawrie and Ms Kretzmer); obtained funding (Dr Kuzniecky); administrative, technical, and material support (Drs Palmer, Knowlton, and Morawetz); study supervision (Dr Martin).

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