2006

Evaluating the Contributions of State of the Art Assessment Techniques to Predicting Memory Outcome after Unilateral Anterior Temporal Lobectomy

Tara T. Lineweaver
Butler University, tlinewea@butler.edu

Harold H. Morris

Richard I. Naugle

Imad M. Najm

Beate Diehl

See next page for additional authors

Recommended Citation

Lineweaver, T. T., Morris, H. H., Naugle, R. I., Najm, I. M., Diehl, B. & Bingaman, W (2006). Evaluating the Contributions of State of the Art Assessment Techniques to Predicting Memory Outcome after Unilateral Anterior Temporal Lobectomy. *Epilepsia*, 47, 1895-1903. doi: 10.1111/j.1528-1167.2006.00807.x Available from: digitalcommons.butler.edu/facsch_papers/437/

Authors

Tara T. Lineweaver, Harold H. Morris, Richard I. Naugle, Imad M. Najm, Beate Diehl, and William Bingaman

Evaluating the Contributions of State-of-the-Art Assessment Techniques to Predicting Memory Outcome after Unilateral Anterior Temporal Lobectomy

Tara T. Lineweaver, Harold H. Morris, Richard I. Naugle, Imad M. Najm, Beate Diehl, William Bingaman

Abstract

Summary: Purpose: Although anterior temporal lobectomy (ATL) is an effective treatment for many patients with medically refractory temporal lobe epilepsy (TLE), one risk associated with this procedure is postsurgical decline in memory. A substantial number of past studies examined factors that predict memory decline after surgery, but few have investigated multiple predictors simultaneously or considered measures that are currently in use.

Methods: This study compared the relative contributions made by presurgical neuropsychological test scores, MRI-based hippocampal volumetric analysis, and Wada test results to predicting memory outcome after ATL in a group of 87 patients.

Results: Logistic regression analyses indicated that noninvasive procedures (neuropsychological testing and MRI) made significant contributions to improving the prediction of memory outcome in this sample. The results from the Wada procedure did not significantly improve prediction once these other factors were considered. The only exception was in predicting memory for visual information after a delay, in which Wada results improved prediction accuracy from 78% to 81%.

Conclusions: Current neuropsychological tests and MRI volumetric measures predict changes in verbal and visual memory after ATL. The relatively small change in correct classification rates when Wada memory scores are considered calls into question the benefits of using Wada test results to predict memory outcome when the results of noninvasive procedures are available.

Anterior temporal lobectomy with resection of the mesial structures (ATL) is known to be an effective intervention for patients with temporal lobe epilepsy (TLE). However, one risk associated with this procedure is postoperative decline in cognitive abilities, and particularly in episodic memory (Ivnik et al., 1987; Hermann and Wyler, 1988; Ivnik et al., 1988; Naugle et al., 1993; Martin et al., 1998). Across studies, from 25 to 75% of left ATL (LATL) patients and 22 to 60% of right ATL (RATL) patients experience some degree of decline in their memory abilities after surgery (Ivnik et al., 1988; Chelune et al., 1991; Phillips and McGlone, 1995; Martin et al., 1998). Thus the ability to predict postoperative memory outcome has become a highly relevant issue for patients with medication-resistant TLE who are considering surgical intervention as a treatment option.

Researchers have made considerable strides over the last 20 years in their attempts to delineate individual factors that are associated with memory decline after ATL. One of the most robust findings is that temporal lobe resections involving the speech-dominant left hemisphere are more consistently associated with memory loss than are those confined to the non–speech-dominant right hemisphere (Ivnik et al., 1987; Ivnik et al., 1988; Chelune et al., 1991; Chelune et al., 1993; Naugle et al., 1993; Trenerry et al., 1993; Phillips and McGlone, 1995; Baxendale et al., 1998; Martin et al., 1998). Second, an absence of cell loss in the hippocampus before surgery (hippocampal sclerosis: HS) is associated with a higher incidence of memory decline after surgery, regardless of whether the hippocampal damage is documented histologically (Hermann et al., 1992; Hermann et al., 1994; Seidenberg et al., 1996; Baxendale et al., 1998; Seidenberg et al., 1998) or on presurgical MRI scans (Trenerry et al., 1993). A third factor known to share a strong relation with postoperative changes in memory capacity is preoperative memory ability, with stronger baseline memory abilities predicting greater memory decline after surgery (Ivnik et al., 1988; Chelune et al., 1991; Jokeit et al., 1997; Davies et al., 1998), presumably because removing a functional hippocampus negatively affects memory (Chelune, 1995). Finally, demographic characteristics of epilepsy patients (age, sex, level of general intellectual functioning) and aspects of their seizure disorders (age at seizure onset, age at first risk for developing seizures) also share significant relations with memory outcome after ATL (Jokeit et al., 1997; Davies et al., 1998; Seidenberg et al., 1998; Chelune and Najm, 2000). However, these variables account for little variance in memory change once other predictors are taken into account in multifactorial models (Jokeit et al., 1997; Chelune and Najm, 2000).

In addition to these factors, performance on the Wada test is commonly used in clinical settings to evaluate a patient's risk of memory decline after ATL. The Wada test (Wada, 1960), which was traditionally used to determine speech lateralization in surgical candidates, was later adapted to evaluate the propensity of the nonaffected hemisphere to support memory (Milner et al., 1962) to identify patients at risk for postoperative global amnesia (Scoville and Milner, 1957). Because recent research has called into question the validity of the Wada for this purpose (Loring et al., 1990; Lee et al., 1995; Kubu et al., 2000), attention has shifted to using the Wada test to predict more subtle preoperative-to-postoperative memory changes. Both low memory scores after left injection (i.e., poor right hemisphere–mediated memory) (Davies et al., 1998; Bell et al., 2000) and high memory scores after right injection (i.e., good memory abilities sustained by the to-be-resected left hemisphere) (Kneebone et al., 1995) have been shown to correspond to poor memory outcome after surgery in LATL patients. However, direct comparisons of the relations between absolute and relative memory scores on the Wada and memory outcome suggest that relative memory performances correlate more strongly with postoperative memory decline than with the absolute level of performance achieved by either hemisphere alone (Wyllie et al., 1991; Loring et al., 1995).

The majority of the published studies in the literature have focused on single predictors of memory outcome. The few multifactorial studies that have been published have typically investigated demographic characteristics of patients in combination with preoperative memory performances, with or without taking into consideration Wada memory test scores (Loring et al., 1995; Jokeit et al., 1997; Davies et al., 1998). Two recently published studies have examined more comprehensive multivariate models for predicting memory outcome after ATL (Chelune and Najm, 2000; Stroup et al., 2003). Chelune and Najm (2000) found that a combination of side of surgery, demographic characteristics, baseline memory abilities, presence or absence of hippocampal atrophy, and Wada test scores accounted for 39% of the variance in memory outcome in 72 TLE patients. Side of surgery, hippocampal atrophy, and baseline memory scores were the primary predictors of memory outcome, and other variables (including Wada test scores) did not significantly improve the regression equation. A logistic regression analysis then demonstrated that these three factors correctly classified 71% of the patients as experiencing stable or diminished memory after surgery. Although these results offer some preliminary evidence that Wada test scores do not improve clinicians' ability to predict memory outcome, these scores were considered only at the group, not at the individual, prediction level. Thus the possibility remains that the Wada test contributes to predicting memory outcome for some, but not all, patients.

The second published comprehensive multivariate study was conducted by Stroup and colleagues (2003). This study found that resection of the speech-dominant hemisphere, MRI findings inconsistent with strictly unilateral mesial temporal sclerosis in the resected hemisphere, poor scores on immediate and good scores on delayed memory measures, and good performance on a Wada memory test after contralateral injection were all significant, unique, independent predictors of postsurgical verbal memory decline in a sample of 132 TLE patients. Although scores on the Wada test were significant predictors of outcome, they were relatively weak when compared with side of resection, absence of unilateral mesial temporal sclerosis, and baseline delayed verbal memory.

The previously reviewed studies suggest that side of surgery (speech-dominant vs. nondominant hemisphere), hippocampal atrophy on MRI scans, baseline neuropsychological performance, and (possibly) Wada test results each contributes to predicting memory outcome after surgery. However, none of the multifactorial studies examined memory outcome on visuospatial memory measures. In addition, in all studies to date, both preoperative and postoperative memory abilities were documented by using previous versions of standard neuropsychological tests (Wechsler, 1987) rather than more current measures (Wechsler, 1997).

With this in mind, the current study had two goals: (a) to study the value of new neuropsychological assessment techniques in the prediction and evaluation of memory outcome after ATL in patients with medically refractory TLE, and (b) to compare the relative contributions made by neuropsychological assessment, MRI-based hippocampal volumetric analysis, and Wada test results to the prediction of memory outcome after ATL in patients with TLE. The primary hypothesis of this study was that side of resection, MRI variables, and presurgical memory abilities would be the best predictors of memory decline, with scores derived from the Wada test failing to improve significantly the prediction of outcome once these other factors were taken into account.

METHODS

Participants

During the course of this study, 127 potential participants were identified. Potential participants included patients with medically refractory temporal lobe epilepsy who underwent surgery to treat their seizure disorders. MRI volumetric analysis could not be completed on 24 of these individuals because of missing or inadequate scans, and an additional seven individuals were administered only a unilateral injection during the Wada test. Of the remaining 96 individuals, nine patients were deemed to have speech represented either in the right hemisphere (n = 4) or bilaterally (n = 5), based on the Wada. As these numbers were too small to include as separate groups, only the 87 patients who had full MRI and Wada data and who were left-hemisphere dominant for speech were selected for inclusion. One of these patients was missing data for Visual Delayed Memory at retest, but was retained in all other analyses.

On average, the 87 participants were 33.5 years old (SD, 12.4; range, 16–65) with 12.8 (SD, 2.3; range, 8–20) years of education. Full-Scale IQ scores ranged from 61 to 122 at baseline assessment (mean, 90.3; SD, 13.3). Approximately half of the participants (55%) were male, and 87% were right-handed. Patients had had seizures for ∼19 years (SD, 13.2; range, 1–53) before their surgery. Thirty-seven (43%) patients underwent left hemisphere resections, and 50 (57%) underwent right hemisphere resections; after surgery, 77% were seizure free, with fairly equal distributions of seizure-free LATL (73%) and RATL (80%) patients.

Procedures and materials

The study consisted of a retrospective review and analysis of data collected in the course of routine clinical care and recorded in a registry approved by the Cleveland Clinic Institutional Review Board. All patients underwent an MRI scan, the Wada procedure, and an extensive neuropsychological assessment as part of a comprehensive presurgical evaluation. All patients also underwent repeated neuropsychological assessment as part of their standard postsurgical care.

Baseline memory and memory outcome

Neuropsychological measures used to establish baseline memory functioning and memory outcome after surgery were administered ∼4 months before and 6 months after surgery (mean test–retest interval, 10.2 months; SD, 3.3; range, 6–27 months). Memory abilities were assessed by using the Wechsler Memory Scale–Third Edition (WMS-III; Wechsler, 1997). Among other types of memory, the WMS-III is designed to measure immediate and delayed recall of verbal information presented in an auditory modality [Auditory Immediate (AII) and Auditory Delayed

Index (ADI), respectively], and immediate and delayed recall and recognition of visually presented materials [Visual Immediate (VII) and Visual Delayed Index (VDI), respectively]. Each index score represents an age-corrected standard score with an expected mean value of 100 and a standard deviation of 15 points.

The accurate prediction of memory declines associated with surgical intervention in individual patients with TLE was the primary goal of this study. Although many investigators have used simple difference scores (Hermann et al., 1992; Hermann et al., 1994; Phillips et al., 1995; Seidenberg et al., 1996) or repeated-measures analyses (Ivnik et al., 1988; Chelune et al., 1991; Naugle et al., 1993, Trenerry et al., 1993; Baxendale et al., 1998) to evaluate pre- to postsurgery changes in memory abilities, these methods fail to take into consideration regression to the mean, practice effects, and measurement error, all of which can substantially affect scores in test–retest situations (Lineweaver and Chelune, 2003; Chelune, 2003). Thus consistent with the current standard of practice (McSweeny et al., 1993; Hermann et al., 1996; Sawrie et al., 1996; Martin et al., 1998; Seidenberg et al., 1998), changes in memory ability were assessed by using standardized regression-based norms (Martin et al., 2002). Application of this technique resulted in the calculation of a z-score for each memory index score that reflected the amount by which an individual's postoperative memory score differed from expectations (expressed in standard deviation units) compared with epilepsy patients who took the same test on two occasions without undergoing surgical intervention in the interim (Martin et al., 2002). In essence, the resulting z-scores indicated the effect size associated with undergoing surgical intervention for each patient, assuming his or her memory abilities would have otherwise paralleled those of a medically treated epilepsy control group.

Z-scores less than –1.04 (1.04 SDs below the mean) were used to classify postoperative memory decline (Chelune and Najm, 2000). Scores in this range would be expected to occur at a base rate of 15% in medically treated epilepsy patients in the absence of true underlying change.

Magnetic resonance imaging volumetric analysis

MRI studies were performed preoperatively by using a Siemens 1.5-Tesla scanner. Multiple T_1-weighted coronal images were acquired orthogonal to the main plane of the hippocampal formation by using thin-slice turbo flash sequences (thickness of 2 mm with no interslice gap). For each patient, volumes of right and left hippocampal formations were measured after manual delineation of the hippocampal anatomy on the coronal images (Watson et al., 1992).

Wada test

Transfemoral catheterization of the internal carotid artery was performed under local anesthesia. The majority of patients (n = 77, 43 RATL and 34 LATL) underwent the Wada procedure prior to March 16, 2001, and were administered 100 or 125 mg of amobarbital into each hemisphere, typically beginning with the side of intended resection. While each hemisphere was anesthetized, patients were shown individual cards organized in sets of four, with each set containing one object word (e.g., “river”), one picture (e.g., a line drawing of a tree), one function word (e.g., “though”), and one abstract design (e.g., a picture resembling a Chinese character). Patients were asked to name the object or read the word and to remember the item. Strength and speech were assessed after each set of items was presented. Items presented after return of normal strength and speech were not counted toward the total score in the subsequent memory test. A maximum of four sets of items was presented to each patient for a possible total of 16 to-be-remembered items. After the effects of the anesthetic agent were alleviated, as evidenced by an absence of slowing on EEG, return of normal strength and speech, and at least a 10-min interval after injection, memory for the presented items was tested. Patients were shown a series of 16 cue cards, with each card containing one target item from the memory set and three foils. The percentage of items correctly recognized on this four-choice multiple-choice recognition memory test was recorded after each hemispheric injection. Because the recognition test was conducted as a forced-choice procedure, chance performance was 25%.

Because of a supply shortage of amobarbital, after March 16, 2001, methohexital was used when conducting the Wada procedure with the remaining patients (n = 10; seven RATL and three LATL). Initially, a 3-mg hand injection was administered over 3 to 4 s, and 30 s later, a second hand injection of 2 mg was given. The memory testing procedure remained the same, with the exception that the abstract designs were removed from the stimulus set. Thus patients who underwent the Wada with methohexital were presented cards in sets of three instead of four, resulting in a maximum of 12 possible items to recognize on the memory test. Percentage-correct scores were used in all subsequent analyses to account for possible differences in the number of items presented to each individual patient.

Analyses

Classification of memory outcome

Although the percentage of patients who show memory decline after ATL on older versions of memory tests has been estimated in the literature, information regarding the prevalence of memory decline, as measured by current memory measures, is not readily available. Thus the percentages of patients showing declines on each of the four outcome memory indices were calculated for this sample of patients.

Prediction of memory outcome after ATL

Logistic regression analyses were used to determine the accuracy with which the presence or absence of postsurgical memory decline could be predicted based on side of surgery (SOS), preoperative memory abilities based on neuropsychological tests (NP), MRI volumetric measurements of hippocampal volumes (HVs), and Wada test performances. Change on each of the four memory measures was examined separately.

All analyses were conducted in two stages. During the initial stage, SOS (left vs. right), MRI-determined HV (left and right), and preoperative NP memory scores (auditory and visual memory indices) were entered into each logistic regression analysis. In addition, the interactions of SOS with HV and NP were included because the effects of these variables were expected to differ depending on side of surgery. For example, a large left hippocampus would be expected to predict a positive outcome for a patient undergoing right resection, but a poor outcome for a patient undergoing left resection. This initial stage of the logistic regression analysis allowed patient characteristics derived only from noninvasive techniques to account for as much variance in postoperative memory decline as possible.

In the second stage of the analysis, Wada test scores (i.e., percentage correct after left injection and percentage correct after right injection) were entered into each logistic regression equation. The results of this stage of the analysis determined whether Wada scores significantly improved the prediction of postsurgical memory change. At each stage of the analysis, the percentage of patients correctly classified as having either stable or declining memory abilities based on the logistic regression equation was calculated. This provided an estimate of how accurately the equation predicted outcome.

All of these analyses were then repeated with asymmetry scores, rather than raw scores, entered as predictors. Asymmetry scores could not be included in the same analyses with raw scores because of issues of statistical collinearity. Thus this second group of analyses was designed to determine whether discrepancy scores could do a better job than raw scores at predicting outcome. For this group of analyses, the first stage of analysis included SOS, hippocampal asymmetry scores [right HV/(right HV + left HV)], memory discrepancy scores (VII – AII or VDI – ADI), and interaction terms as predictors. In the second stage of analysis, Wada asymmetry scores (left injection% correct – right injection% correct) and the interaction of SOS with Wada asymmetry were entered as predictors.

RESULTS

Classification of memory outcome

By using regression-based norms with a cutoff set at the 15th percentile ($z < -1.04$), the number of patients showing decline on each memory index was determined. On the AII, 18% of the patient sample evidenced memory decline after surgery. On the ADI, 26% demonstrated memory decline. On the VII and VDI, 20% and 28%, respectively, of the patients declined. Overall, these percentages were lower than expected, given estimates of decline (35–45%) previously documented in the literature.

χ^2 analyses were used to investigate how the likelihood of decline on each memory index was affected by whether the patient underwent left or right ATL. The percentage of LATL patients that demonstrated decline on the AII (32%) and the ADI (38%) was greater than the percentage of RATL patients that demonstrated decline on these two measures (8% and 18%, respectively). These observed differences were statistically significant (AII: $\chi^2 = 8.5$; $p < 0.01$; ADI: $\chi^2 = 4.3$; $p < 0.05$). No significant group differences were found for the VII (19% decline after LATL, 20% decline after RATL) or for the VDI (28% decline after LATL, 28% decline after RATL).

Prediction of memory outcome after ATL

Table 1 shows the overall prediction accuracy, the χ^2 value and significance level of the equations, and the overall Goodness of Fit for the model at each stage of the analysis. These values are represented for both the analyses using baseline scores and those using asymmetry scores as predictors. Using asymmetry scores to predict outcome resulted in lower rates of correct classification for all four memory outcome measures, and the results of these analyses are not discussed further.

Auditory Immediate Index

Because only 18% of the current sample demonstrated postsurgical memory decline on the AII, simply predicting a positive outcome for all patients without taking into account any specific predictors would result in 82% accuracy. During the first stage of analysis, including SOS, baseline NP performance, MRI volumes, and interaction terms (SOS x NP and SOS x HV) in the logistic regression equation improved the correct classification rate to 85%, a statistically significant improvement [$\chi^2(9) = 22.6$; $p < 0.01$]. Together these variables accounted for ~5% of the variance in outcome. Although none of the predictors independently accounted for enough unique variance to reach statistical significance, the SOS x left HV, SOS x right HV, and SOS x baseline VII interaction terms were the strongest predictors of outcome, with each accounting for between 1 and 2% of the variance. Adding Wada variables into the equation did not result in a statistically significant improvement in the prediction of outcome [$\chi^2(4) = 8.5$; NS].

Auditory Delayed Index

Of the patients in the current sample, 26% demonstrated decline on the ADI. In the logistic regression analysis, using SOS, NP, and HV to predict outcome improved the classification rate from 74% to 78%, a result that reached statistical significance [$\chi^2(9) = 32.4$; $p < 0.001$].

Approximately 17% of the variance in outcome was accounted for by the combination of these predictors. The interactions of SOS with left HV and with right HV both reached statistical significance, accounting for 6% and 3% of the variance, respectively. In addition, both raw scores on the VDI and the interaction of scores on this measure with SOS were significant predictors of outcome, accounting for 2% and 4% of the variance, respectively. Finally, SOS accounted for 1.5% of the variance in outcome, although this effect was not statistically significant. Again, adding Wada variables into the equation did not significantly improve the predictability of memory outcome [$\chi^2(4) = 4.8$; NS].

Visual Immediate Index

Twenty percent of the patient sample evidenced memory decline on the VII. Correct classification improved from 80% to 83% on this measure when SOS, NP, and HV were used to predict memory decline. Although the overall model represented a significant improvement relative to using no predictors [$\chi^2(9) = 18.7$; $p < 0.05$], none of the individual variables emerged as significant. As with the auditory memory measures, adding Wada variables into the logistic regression equation did not significantly improve predictive power [$\chi^2(4) = 5.0$; NS].

Visual Delayed Index

The VDI was more sensitive to postsurgical memory decline in this study than the other memory indices, with 28% of patients demonstrating a negative outcome on this measure. SOS, NP, and HV significantly improved the accuracy of classification of patients as showing stable versus declining memory from 72% to 78%[$\chi^2(9) = 30.8$; $p < 0.001$]. Both baseline VDI scores and their interaction with SOS were significant predictors of memory outcome. However, unlike for the other memory indices, adding Wada variables into the prediction equation significantly improved the correct classification rate from 78% to 81%[$\chi^2(4) = 9.6$; $p < 0.05$]. In the final equation, baseline scores on the VDI and the interaction of SOS with baseline VDI scores remained independent unique predictors of outcome, accounting for 11% and 4% of the variance, respectively. The interaction between SOS and memory after left injection during the Wada test significantly accounted for 5% of the variance. Finally, percentage correct after left injection accounted for almost 2% of the variance in outcome, although this effect did not reach statistical significance.

DISCUSSION

Addressing the issue of whether the relative contribution Wada test results make to predicting memory outcome is beneficial enough to justify the risks and costs inherent in the procedure is essential. The possibility of reducing or eliminating reliance on Wada test results when predicting memory outcome is a particularly important consideration due to the invasive nature of the Wada test and the corresponding risk associated with cerebral angiography, including an estimated morbidity of 1 to 3% (Wada et al., 1960; Branch et al., 1964; Serafetinides et al., 1965). As alternative techniques for lateralizing and localizing speech, such as functional MRI of the brain (Binder et al., 1996) and repetitive transcranial magnetic stimulation (Jennum et al., 1994; Epstein et al., 1999), are developed and improved, the necessity of completing a Wada test to document speech dominance may be reduced or eliminated. If new, state-of-the-art, noninvasive techniques are also sufficient to maximize prediction of memory outcome after ATL, routine use of the Wada test for this purpose may be unnecessary. As a result, the risks and costs inherent in evaluating the surgical candidacy of patients with medically refractory temporal lobe epilepsy may be drastically reduced.

Although other studies have suggested that the Wada test contributes only limited information to the prediction of outcome after the results of noninvasive procedures are considered (Chelune and Najm, 2000; Stroup et al., 2003), the current study expands the literature on multivariate prediction of memory outcome after anterior temporal lobectomy by evaluating predictors of both auditory (verbal) and visual memory decline. It also uses the most recent version of commonly used memory measures. Thus these results should apply more directly to current clinical practice than those of previous studies.

Perhaps one of the most surprising findings of this study was that fewer patients than expected demonstrated statistically significant postsurgical memory decline. Whereas prior studies using similar methods (but previous versions of memory tests) reported postsurgical memory decline in 35–45% of ATL patients, in the current sample, estimates of memory decline ranged from merely 18% for auditory immediate memory to 28% for visual delayed memory. Because regression-based z-scores at the 15th percentile were used to define operationally postoperative memory decline, memory decline would be expected to occur at a base rate of 15% in a control group of medically managed epilepsy patients. Thus the portion of this sample that evidenced decline (18–28%) was not that much greater than would be expected in a group of epilepsy patients tested twice without undergoing surgical intervention in the interim.

An important limitation to these results warrants mention. The patients who were selected for this study were a highly screened sample of epilepsy patients. The preoperative tests that were used in this study were also available to and used by the neurologists managing the patient's care when reaching a decision about treatment options and recommendations. Although the data considered in this study may have been more precise than those available to the clinicians working with these patients (e.g., quantitative versus qualitative MRI data), a large amount of overlap existed between the factors used in this study and those used to counsel these patients about surgery. Patients determined to be at high risk for memory decline may have been discouraged from surgery or may have decided against surgery when offered. As a result, a possible explanation for the lower-than-expected incidence of memory decline in this sample is that, as clinicians have gained a better understanding of the variables that affect memory decline after surgery in recent years, patients are being selected more carefully to minimize the negative cognitive outcomes that previously accompanied surgical intervention.

An alternate explanation for this pattern of results may be a lower level of sensitivity on the part of current memory measures to detect changes over time relative to those used in past studies. For example, the WMS-III auditory indices do not require word-list learning and recall, a task commonly thought to be more sensitive to verbal memory decline in epilepsy patients than more context-rich verbal memory measures. Although the patients in this study did complete a word-list learning and memory test, regression-based norms are not currently available to apply to these measures to determine a meaningful change after surgery, rendering them inappropriate for analysis with the techniques used in this study. If test–retest data with nonsurgical epilepsy control patients becomes available for word-list learning tasks, the current techniques and analyses could be applied to investigate empirically the role of the Wada test for predicting outcome on these types of memory measures.

The logistic regression analyses suggested that baseline scores derived from preoperative procedures were better predictors of decline than were asymmetry scores. This result was somewhat surprising, given previous findings in the literature that suggest that asymmetry scores are strong predictors of outcome (Wyllie et al., 1991; Loring et al., 1995). However, this may be due to the inclusion of bilateral indices (e.g., both left and right hippocampal volumes, both auditory and visual memory) in the analyses. Including bilateral indicators allowed the relation between these variables to be considered when the best-fitting logistic regression model was determined. Thus these results do not suggest that unilateral predictors are adequate for assessing risk of memory decline after surgery; instead, they indicate that the relation between ipsilateral and contralateral measures may be more complex than simple difference scores or ratio measures can capture.

In general, side of surgery in and of itself did not significantly predict memory decline, but it did interact with neuropsychological and MRI variables to improve the accurate classification of outcome. Both baseline memory scores and MRI volumes contributed to predicting outcome across the four memory measures, with the nature of their influence dependent on the hemisphere undergoing surgery and the type of memory being considered. Both left and right hippocampal volumes tended to contribute equally to the prediction equations, and MRI results played a role in predicting auditory memory outcome, but not visual memory outcome. Interestingly, only baseline visual memory (not baseline auditory memory) was important to consider when predicting postsurgical memory decline, with its influence being stronger for delayed than for immediate memory measures. The findings that both MRI and neuropsychology make independent contributions to predicting outcome is consistent with other recent findings in the literature that suggest that the functional status of the hippocampus may be somewhat independent of its structural status (LoGalbo et al., 2005).

Consistent with expectations, Wada test results did not typically emerge as significant predictors of outcome in this series of logistic regression analyses once side of surgery, neuropsychological variables, and results from MRI volumetric analysis were taken into account. This appears to support the conclusions of the two earlier studies that addressed this issue with previous versions of verbal memory tests (Chelune and Najm, 2000; Stroup et al., 2003) and different versions of the Wada (Stroup et al., 2003). Perhaps this finding is not surprising, given that the Wada test has not been designed specifically to predict subtle declines in material-specific memory. In addition, it may be unreasonable to expect a brief 12-item or 16-item memory test to demonstrate the equivalent predictive power of a much lengthier standardized neuropsychological test, especially when memory outcome is also being assessed on the standardized measure.

That being said, Wada test results did predict outcome on delayed visual memory measures. One reason Wada test results may have predicted delayed visual memory is that the stimuli used in the Wada procedure were presented visually rather than in an auditory modality, even when they were verbal in nature (i.e., words), making the type of encoding similar for these two types of tests. However, even in this case, the improvement in prediction accuracy was relatively small (78 to 81%), calling into question whether the benefits of considering Wada test results when predicting postsurgical memory outcome outweigh the risks inherent in that procedure.

Of course, the results of this study may or may not generalize to other Wada procedures. Approaches to memory testing during the Wada differ across centers, and other techniques may offer more toward the prediction of outcome. However, the fact that Stroup and colleagues (2003), working at a different epilepsy center, also found little incremental predictive power associated with the Wada after side of surgery, neuropsychological performance, and MRI findings were taken into account, lends support to the recommendation that risks and benefits be carefully considered before administering the Wada test.

Because Wada procedures differ across centers, one question that might arise when interpreting these results is the validity of the Wada procedure used in this study. To assure that the lack of contribution of the Wada test to predicting memory outcome was not due to invalid

Wada memory test scores, additional logistic regression equation analyses were conducted with Wada percentage-correct scores (after left and right injection) and their interaction with side of surgery as the only predictors of memory decline. For both the Auditory Immediate and the Auditory Delayed Index, using Wada memory scores to predict verbal memory outcome resulted in a statistically significant improvement in the logistic regression model. Thus in and of themselves, Wada results did predict postsurgical verbal memory in support of previous findings in the literature (Loring et al., 1990; Wyllie et al., 1991; Kneebone et al., 1995; Loring et al., 1995; Bell et al., 2000). It is only when other noninvasive procedures are considered first and are allowed to account for as much variance in outcome as possible that Wada memory scores do not significantly contribute to prediction equations. This could be explained by a large amount of overlap in the prognostic information contributed by the Wada test and by neuropsychological or neuroimaging techniques. For example, a previous study demonstrated high correlations (r= 0.51) between left hemisphere and right hemisphere Wada memory test scores and ipsilateral hippocampal volumes (Cohen-Gadol et al., 2004). Although both Wada scores and hippocampal volumes showed significant inverse relations with memory outcome when considered separately, the high correlations among these two variables suggest that they may be measuring a common factor ("functional integrity," according to the authors). If this be the case, having two measures of the functional integrity of the to-be-resected hippocampus may not improve the predictability of outcome over having a single measure of this construct, making the Wada a weak predictor once hippocampal volumes have been taken into account.

To assure that the data from the small number of patients evaluated with methohexital (n = 10) did not unduly influence the results of this study, the logistic regression analyses reported in the Results section were rerun for the subset of patients who received amobarbital as the anesthetic agent during the Wada procedure (n = 77). The previously reported results were essentially unchanged in these follow-up analyses. The only exception was that the significant improvement in predicting outcome on the Visual Immediate Memory Index based on neuropsychological and MRI variables no longer reached statistical significance ($p = 0.055$) because of the decrease in statistical power that resulted from the smaller number of participants.

One scenario that often poses difficulty for clinicians involves patients with left TLE whose left hippocampus is similar in volume or larger than the right hippocampus and whose verbal memory abilities appear intact or stronger than visual memory abilities on neuropsychological assessment. This situation would result in a prediction of high risk for memory decline, but whether Wada results might aid decision making in this context is worth exploring. Five patients in the current sample fit this description, and of these, all five did show significant decline on auditory memory tests. In three of these cases, the Wada test results supported the prediction of memory decline or were inconclusive. However, in two cases, the Wada test would have falsely predicted a positive memory outcome because memory performance after left injection (right hemisphere–mediated memory: in both cases, 88% correct) was good and was significantly better than after right injection (left hemisphere–mediated memory: in both cases, 50% correct). Thus in these two patients, Wada test results might have incorrectly led clinicians to conclude a lower risk of memory decline, when in fact memory decline was the final outcome.

Accurately predicting change in memory as measured by psychometric tests does not necessarily reflect the impact this memory change will have on an individual patient. As has been previously demonstrated in the literature, epilepsy patients' self-assessments of changes in their memory from before to after surgery often differ from actual changes documented on standardized memory tests (Vermeulen et al., 1993; McGlone, 1994; Sawrie et al., 1999). However, some recent evidence has suggested that patients are, indeed, sensitive to changes in their memory after surgery (Gleisner et al., 1998; Lineweaver et al., 2004), lending support to the extensive work aimed at predicting psychometric change to provide patients with as much relevant information as possible when they are reaching a decision about whether to pursue surgery as a treatment option.

Acknowledgments

Acknowledgment: Support for this study was provided by a Junior Investigator Award from the Epilepsy Foundation of America.

References

Baxendale SA, VanPaesschen W, Thompson PJ, Duncan JS, Harkness WF, Shorvon SD. (1998) Hippocampal cell loss and gliosis: relationship to preoperative and postoperative memory function. Neuropsychiatry, Neuropsychology, and Behavioral Neurology 11:12–21.

Bell BD, Davies KG, Haltiner AM, Walters GL. (2000) Intracarotid amobarbital procedure and prediction of postoperative memory in patients with left temporal lobe epilepsy and hippocampal sclerosis. Epilepsia 41:992–997.

Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, Benbadis S, Frost BA, Rao SM, Haughton VM. (1996) Determination of language dominance using functional MRI: a comparison with the Wada test. Neurology 46:978–984.

Branch JW, Milner B, Rasmussen T. (1964) Intracarotid sodium amytal for the lateralization of cerebral speech dominance: observations in 123 patients. Journal of Neurosurgery 21:399–405.

Chelune GJ. (1995) Hippocampal adequacy versus functional reserve: predicting memory functions following temporal lobectomy. Archives of Clinical Neuropsychology 10:413–432.

Chelune GJ. (2003) Assessing reliable neuropsychological change. In FranklinRD (Ed). Prediction in forensics and neuropsychology: sound statistic practices pp. 223–247. Erlbaum, Mahwah , NJ .

Chelune GJ, Najm I. (2000) Risk factors associated with postsurgical decrements in memory. In LüdersHO, ComairY (Eds), Epilepsy surgery. 2nd ed. Lippincott, Philadelphia , pp. 497–504.

Chelune GJ, Naugle RI, Lüders H, Awad IA. (1991) Prediction of cognitive change as a function of preoperative ability status among temporal lobectomy patients seen at 6-month follow-up. Neurology 41:399–404.

Chelune GJ, Naugle RI, Lüders H, Sedlak J, Awad IA. (1993) Individual change after epilepsy surgery: practice effects and base-rate information. Neuropsychology 7:41–52.

Cohen-Gadol AA, Westerveld M, Alvarez-Carilles J, Spencer DD. (2004) Intracarotid amytal memory test and hippocampal magnetic resonance imaging volumetry: validity of the Wada test as an indicator of hippocampal integrity among candidates for epilepsy surgery. Journal of Neurosurgery 101:926–931.

Davies KG, Bell BD, Bush AJ, Wyler AR. (1998) Prediction of verbal memory loss in individuals after anterior temporal lobectomy. Epilepsia 39:820–828.

Epstein CM, Meador KJ, Loring DW, Wright RJ, Weissman JD, Sheppard S, Lah JJ, Puhalovich F, Gaitan L, Davey KR. (1999) Localization and characterization of speech arrest during transcranial magnetic stimulation. Clinical Neurophysiology 10:1073–1079.

Gleisner U, Helmstaedter C, Quiske A, Elger CE. (1998) The performance-complaint relationship in patients with epilepsy: a matter of daily demands? Epilepsy Research 32:401–409.

Hermann BP, Seidenberg M, Schoenfeld J, Peterson J, Leveroni C, Wyler AR. (1996) Empirical techniques for determining the reliability, magnitude, and pattern of neuropsychological change after epilepsy surgery. Epilepsia 37:942–950.

Hermann BP, Wyler AR. (1988) Neuropsychological outcome of anterior temporal lobectomy. Journal of Epilepsy 1:35–45.

Hermann BP, Wyler AR, Somes G, Berry ADIII, Dohan FC. (1992) Pathological status of the mesial temporal lobe predicts memory outcome from left anterior temporal lobectomy. Neurosurgery 31:652–657.

Hermann BP, Wyler AR, Somes G, Dohan FC, Berry ADIII, Clement L. (1994) Declarative memory following anterior temporal lobectomy in humans. Behavioral Neuroscience 108:3–10.

Ivnik RJ, Sharbrough FW, Laws ER Jr. (1987) Effects of anterior temporal lobectomy on cognitive function. Journal of Clinical Psychology 43:128–137.

Ivnik RJ, Sharbrough FW, Laws ER Jr. (1988) Anterior temporal lobectomy for the control of partial complex seizures: information for counseling patients. Mayo Clinic Proceedings 63:783–793.

Jennum P, Friberg L, Fuglsang-Frederiksen A, Dam M. (1994) Speech localization using repetitive transcranial magnetic stimulation. Neurology 44:269–273.

Jokeit H, Ebner A, Holthausen H, Markowitsch JH, Moch A, Pannek H, Schulz R, Tuxhorn I. (1997) Individual prediction of change in delayed recall of prose passages after left-sided anterior temporal lobectomy. Neurology 49:481–487.

Kneebone AC, Chelune GJ, Dinner DS, Naugle RI, Awad IA. (1995) Intracarotid amobarbital procedure as a predictor of material-specific memory change after anterior temporal lobectomy. Epilepsia 36:857–865.

Kubu CS, Girvin JP, McLachlan RS, Pavol M, Harnadek MCS. (2000) Does the intracarotid amobarbital procedure predict global amnesia after temporal lobectomy? Epilepsia 41:1321–1329.

Lee GP, Loring DW, Smith JR, Flanigin HF. (1995) Intraoperative hippocampal cooling and Wada memory testing in the evaluation of amnesia risk following anterior temporal lobectomy. Archives of Neurology 52:857–861.

Lineweaver TT, Chelune GJ. (2003) Use of the WAIS-III and WMS-III in the context of serial assessments: interpreting reliable and meaningful change. In TulskyD, SaklofskeD (Eds) Interpretation of the WAIS-III and WMS-III. Academic Press, San Diego , pp 303–337.

Lineweaver TT, Naugle RI, Cafaro AM, Bingaman W, Lüders HO. (2004) Patients' perceptions of memory functioning before and after surgical intervention to treat medically refractory epilepsy. Epilepsia 45:1604–1612.

LoGalbo A, Sawrie S, Roth DL, Kuzniecky R, Knowlton R, Faught E, Martin R. (2005) Verbal memory outcome in patients with normal preoperative verbal memory and left mesial temporal sclerosis. Epilepsy and Behavior 6:337–341.

Loring DW, Lee GP, Meador KJ, Flanigin HF, Smith JR, Figueroa RE, Martin RC. (1990) The intracarotid amobarbital procedure as a predictor of memory failure following unilateral temporal lobectomy. Neurology 40:605–610.

Loring DW, Meador KJ, Lee GP, King DW, Nichols ME, Park YD, Murro AM, Gallagher BB, Smith JR. (1995) Wada memory asymmetries predict verbal memory decline after anterior temporal lobectomy. Neurology 45:1329–1333.

Martin R, Sawrie S, Gilliam F, Mackey M, Faught E, Knowlton R, Kuzniecky R. (2002) Determining reliable cognitive change after epilepsy surgery: development of reliable change indices and standardized regression-based change norms for the WMS-III and WAIS-III. Epilepsia 43:1551–1558.

Martin RC, Sawrie SM, Roth DL, Gilliam FG, Faught E, Morawetz RB, Kuzniecky R. (1998) Individual memory change after anterior temporal lobectomy: a base rate analysis using regression-based outcome methodology. Epilepsia 39:1075–1082.

McGlone J. (1994) Memory complaints before and after temporal lobectomy: do they predict memory performance or lesion laterality? Epilepsia 35:529–539.

McSweeny J, Naugle RI, Chelune GJ, Lüders H. (1993) “T-scores for change”: an illustration of a regression approach to depicting change in clinical neuropsychology. Clinical Neuropsychology 7:300–312.

Milner B, Branch C, Rasmussen T. (1962) Study of short term memory after intracarotid injections of sodium amytal. Transactions of the American Neurological Association 87:224–226.

Naugle RI, Chelune GJ, Cheek R., Lüders H, Awad IA. (1993) Detection of changes in material-specific memory following temporal lobectomy using the Wechsler Memory Scale-Revised. Archives of Clinical Neuropsychology 8:381–395.

Phillips NA, McGlone J. (1995) Grouped data do not tell the whole story: individual analysis of cognitive change after temporal lobectomy. Journal of Clinical and Experimental Neuropsychology 17:713–724.

Sawrie SM, Chelune GJ, Naugle RI, Lüders H. (1996) Empirical methods for assessing meaningful change following epilepsy surgery. Journal of the International Neuropsychological Society 2:556–564.

Sawrie SM, Martin RC, Kuzniecky R, Faught E, Morawetz R, Jamil F, Viikinsalo M, Gillam F. (1999) Subjective versus objective memory change after temporal lobe epilepsy surgery. Neurology 53:1511–1517.

Scoville WB, Milner B. (1957) Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery, and Psychiatry 20:11–21.

Seidenberg M, Hermann BP, Dohan FC, Wyler AR, Perrine A, Schoenfeld J. (1996) Hippocampal sclerosis and verbal encoding ability following anterior temporal lobectomy. Neuropsychologia 34:699–708.

Seidenberg M, Hermann BP, Wyler AR, Davies K, Dohan FC, Leveroni C. (1998) Neuropsychological outcome following anterior temporal lobectomy in patients with and without the syndrome of mesial temporal lobe epilepsy. Neuropsychology 12:303–316.

Serafetinides EA, Hoare RB, Driver MV. (1965) Intracarotid sodium amylobarbitone and cerebral dominance for speech and consciousness. Brain 88:107–130.

Stroup E, Langfitt J, Berg M, McDermott M, Pilcher W, Como P. (2003) Predicting verbal memory decline following anterior temporal lobectomy (ATL). Neurology 60:1266–1273.

Trenerry MR, Jack CR Jr, Ivnik RJ, Sharbrough RW, Cascino GD, Hirschorn KA, Marsh WR, Kelly PJ, Meyer FB. (1993) MRI hippocampal volumes and memory function before and after temporal lobectomy. Neurology 43:1800–1805.

Vermeulen J, Aldenkamp AP, Alpherts WCJ. (1993) Memory complaints in epilepsy: correlations with cognitive performance and neuroticism. Epilepsy Research 15:157–170.

Wada J. (1960) A new method for the determination of the side of cerebral speech dominance: a preliminary report on the intracarotid injection of sodium amytal in man. Igaku to Seibutsugaki (Medical Biology) 14:221–222. [In Japanese.

Wada J, Rasmussen T. (1960) Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance: experimental and clinical observations. Journal of Neurosurgery 17:266–282.

Watson C, Andermann F, Gloor P, Jones-Gotman M, Peters T, Evans A, Olivier A, Melanson D, Leroux G. (1992) Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 42:1743–1750.

Wechsler D. (1987) Wechsler Memory Scale–Revised: manual. The Psychological Corporation, San Antonio .

Wechsler D. (1997) WMS-III test administration and scoring manual. The Psychological Corporation, San Antonio.

Wyllie E, Naugle R, Awad I, Chelune G, Luders H, Dinner D, Skibinski C, Ahl J. (1991) Intracarotid amobarbital procedure, I: prediction of decreased modality-specific memory scores after temporal lobectomy. Epilepsia 32:857–864.

TABLE 1. *General summary of logistic regression analysis: prediction accuracy, statistical significance, and goodness of fit (GoF) at each stage of the analysis when considering either baseline score predictors or asymmetry score predictors*

	No predictors	Block 1				Block 2			
	Prediction accuracy	Prediction accuracy	χ^2	p	GoF	Prediction of accuracy	χ^2	p	GoF
		Baseline score predictors							
AI	82%	85%	22.63	<0.01	78.88	87%	8.49	NS	65.25
AD	74%	78%	32.40	<0.001	113.94	80%	4.79	NS	119.27
VI	80%	83%	18.69	<0.05	69.37	82%	5.01	NS	74.75
VD	72%	78%	30.82	<0.001	82.01	81%	9.59	<0.05	71.57
		Asymmetry score predictors							
AI	82%	82%	14.91	<0.05	79.60	82%	3.95	NS	72.55
AD	74%	77%	20.82	<0.001	105.08	78%	3.10	NS	102.24
VI	80%	80%	3.36	NS	83.69	80%	4.15	NS	76.11
VD	72%	73%	10.77	NS	82.52	73%	2.38	NS	81.79

AI, auditory immediate; AD, auditory delayed; VI, visual immediate; VD, visual delayed; GoF, goodness-of-fit index.