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Diagnostic Utility of Wada Memory Asymmetries: Sensitivity, Specificity, and Likelihood Ratio Characterization

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The authors used logistic regression, dichotomous and multiple level likelihood ratios, and receiver operating characteristic (ROC) analyses to examine Wada Memory Asymmetries (WMAs) in 324 patients who subsequently underwent temporal lobe (TL) surgery (left TL surgery = 172; right TL surgery = 152) using the Medical College of Georgia Wada protocol. Logistic regression correctly classified 84% of left TL patients and 77% of right TL patients using WMA. Corresponding dichotomous likelihood ratios (LRs) were: LR+ = 3.64; LR− = 0.21. The area under the curve using ROC was similarly highly significant (.886, standard error = .018, $p < .001$). When classifying patients using multiple level LRs, 40 left TL patients (23.3%) obtained asymmetry scores greater than +4, whereas no right TL patients obtained asymmetry scores in this range. No left TL patients obtained a WMA of -8 or less, although 12 right TL patients (7.9%) obtained a difference score of -8. Multiple level LRs indicate impressive diagnostic sensitivity for certain WMA ranges, greatly increasing the probability of undergoing either left or right TL surgery depending on WMA magnitude.

The Wada test is an essential component of the preoperative evaluation for anterior temporal lobectomy at most epilepsy surgery centers. In addition to establishing cerebral language representation preoperatively, the Wada memory component is used to both estimate risk for postoperative memory decline and to assist in identification of focal functional deficits associated with a unilateral seizure focus (Cohen-Gadol, Westerveld, Alvarez-Carilles, & Spencer, 2004; Loring & Meador, 2009 in press; Sabsevitz, Swanson, Morris, Mueller, & Seidenberg, 2001; Stroup et al., 2003).

The routine use of invasive Wada testing has been questioned due to the rapid development of functional magnetic resonance imaging (fMRI) to establish cerebral language representation, as well as other methods to establish risk of postoperative decline following anterior temporal lobectomy such as structural MRI, MR T2 relaxation time, and preoperative neuropsychological testing (Baxendale, Thompson, Harkness, & Duncan, 2007; Baxendale, Thompson, & Duncan, 2008). fMRI can reliably establish cerebral language representation in many epilepsy surgery candidates (Gaillard et al., 2004; Sabsevitz et al., 2003), and also holds the potential to functionally image mesial temporal lobe structures noninvasively (Binder, Bellgowan, Hammeke, Possing, & Frost, 2005; Detre et al., 1998; Richardson, Strange, Duncan, & Dolan, 2006). The application of fMRI memory paradigms, however, has lagged behind the development of fMRI language procedures (Loring & Meador, 2009 in press). Further, once reliable fMRI memory protocols have been established and are implemented in more routine clinical evaluation, there will continue to be a need for Wada testing for patients in whom a structural lesion cannot be readily identified (Cohen-Gadol et al., 2005) or reliable fMRIs cannot be obtained, either for technical or behavioral reasons (Loring & Meador, 2009, in press).

The evaluation for anterior temporal lobectomy is based upon a comprehensive evaluation that includes patient history, clinical semiology, and both structural and functional diagnostic evaluations. Wada memory results are an important functional measure that are often considered when establishing surgical candidacy in patients with complex partial seizures that are presumed to be temporal lobe in origin. Patients in whom there is convergence of findings to suggest unilateral temporal lobe seizure onset are generally considered to be better surgical candidates, both with respect to postsurgical seizure outcomes and postoperative cognitive morbidity, than patients in whom less consistent lateralized findings are obtained (Labiner et al., 2002). Noncongruent Wada findings (i.e., interhemispheric memory difference scores that suggest relative temporal lobe dysfunction in the hemisphere contralateral to the side of seizure onset) are often interpreted to indicate increased postsurgical cognitive risk (Sabsevitz et al., 2001).

Wada protocols are not standardized, however, making it difficult to estimate to what degree variations in procedure contribute to the reported ability to lateralize temporal lobe dysfunction. Factors such as stimulus type (pictures vs. real objects) (Loring, Hermann et al., 1997), timing of stimulus presentation (Loring et al., 1994; Loring, Meador et al., 1997), verbal versus dually encodable stimuli (Vingerhoets, Miatton, Vonck, Seurinck, & Boon, 2006), and amobarbital dose (Loring, Meador, & Lee, 1992) will influence Wada memory correlations with seizure onset laterality. The effects of aphasia on certain verbal memory stimuli is

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well recognized (Kirsch et al., 2005), decreasing the sensitivity of verbal memory stimuli for evaluations of both left and right temporal memory function (Vingerhoets et al., 2006). Because of significant method variance effects on Wada memory results (Lee, Park, Westerveld, Hempel, & Loring, 2002), generalizations of protocol specific results to other Wada memory paradigms necessarily must be made cautiously (Meador & Loring, 2005).

In addition to Wada protocol heterogeneity, universally agreed-upon pass/fail criteria do not exist, and different cutpoints for establishing meaningful Wada memory asymmetries (WMAs) or hemispheric pass/fail performances have been used to evaluate the clinical utility of Wada memory testing (Alpherts, Vermeulen, & van Veelen, 2000; Hamberger & Hirsch, 1999; G. P. Lee, Park, Hempel, Westerveld, & Loring, 2002; Loring et al., 1995; Mani et al., 2008; Perrine et al., 1995; Sabsevitz et al., 2001). Regardless of what approach is used to classify Wada memory outcomes, a single cutpoint criterion is generally reported rather than examining Wada memory results across a range of possible scores. Using a single cutpoint, however, discards potentially relevant information from interval measurement scaling by using cutpoints to create a dichotomous outcome. Multiple-level likelihood ratios (LRs) avoid artificial classification dichotomies by examining classification rates across a range of scores (Grimes & Schulz, 2005; Hosmer & Lemeshaw, 2000; Strauss, Richardson, Glasziou, & Haynes, 2005). Despite the many advantages of multiple-level LRs, which have been advocated for continuous variables when evaluating evidence-based practice, this approach has been underutilized in neuropsychological diagnosis (Ivnik et al., 2001). In the present study, we report the lateralizing value of Wada memory score asymmetries in lateralizing temporal lobe dysfunction in ATL candidates using logistic regression, dichotomous LRs, and multiple-level LRs to compare and contrast these approaches to individual patient classification.

Method

Patients

Participants were retrospectively identified from the Medical College of Georgia Neuropsychology Epilepsy Database. This is identified archival database in which clinical variables were entered for internal tracking purposes, quality control, and clinical reports which was subsequently de-identified for research purposes.

The sample consisted of 324 patients with complex partial epilepsy who were being evaluated for anterior temporal lobectomy (ATL). Patients with space occupying lesions on MRI were excluded, and no patients had evidence of any structural abnormality other than medial temporal lobe sclerosis. The majority of patients underwent ATL although some patients underwent less extensive temporal lobe (TL) resection. Less than 1% of surgical candidates were excluded based solely upon Wada test findings suggesting significant postoperative risk. Patients with invalid Wada test findings due to negative behavioral reactions (e.g., agitation, excessive sedation) underwent repeat Wada testing at lower dose, and the number of patients in who behavioral reactions to amobarbital administration prevented us from obtaining clinically useful test results at a lower dose is estimated retrospectively to be 1–2%.

Of the 172 patients undergoing left TL resection, there were 14 patients in whom the hippocampus was spared, 3 patients underwent selective amydalohippocampectomy, and 2 patients underwent a temporal lobe disconnection procedure. Based upon Wada language testing, 119/172 (69%) left TL patients and 145/152 (95%) right TL patients demonstrated exclusive left cerebral language dominance.

All patients were evaluated at the Medical College of Georgia. In addition to history, surgical candidacy was based upon multiple ictal and interictal video electroencephalography (EEG) recordings, MRI, neuropsychological testing including Wada testing, and when available, interictal and ictal SPECT scans. Of the 152 patients undergoing right TL resection, there were 5 in whom hippocampus was spared and 5 underwent selective amydalohippocampectomy. Additional information on the sample characterization is presented in Table 1.

Wada Memory Protocol

Our Wada protocol has been previously described in detail (Loring, Meador, Lee, & King, 1992), and as is the case at most epilepsy centers, was modified over the course of time with increasing experience with the procedure. In most patients, Wada memory testing was performed following injection of 100 mg amobarbital. However, patients tested earlier in this series had doses greater than 100 mg ($n = 45$) and there were 19 patients with amobarbital doses smaller than 100 mg due to either small body size, or previous amobarbital exposure in which results were confounded with behavioral complications including agitation or significant sedation. The average dose between left and right hemisphere injections were comparable (left dose = 106 mg, sd = 25.5 mg; right dose = 105.5, sd = 24.5 mg).

The side of presumed seizure onset was not routinely injected first, and according to our protocol, the order of injection was alternated across patients to avoid the potential confound of medication carryover effects on the second Wada study. Approximately 30–45 seconds following injection and following a very brief language and motor examination, 8 common objects were presented for 4–8 seconds each, and the object names are repeated twice to the patient. The objects were presented in the visual field ipsilateral to the side of injection, and the patient's eyes were held open if necessary. Return to baseline was inferred based upon complete return of contralateral motor strength, absence of asterixis, and normal language function assessed using a modified

Table 1
Demographics: Means (SDs) for Left and Right Temporal Lobe (TL) Surgery Groups

	Left TL ($N = 172$)	Right TL ($N = 152$)
Age (years)	31.7 (10.3)	33.4 (11.4)
Education	11.9 (2.5)	12.6 (2.4)
Sex	88 F, 81 M	76 F, 75 M
FSIQ	84.4 (13.7)	89.0 (13.1)
BNT	41.2 (11.9)	46.9 (10.4)
CLTR-6	19.7 (16.6)	25.8 (16.6)

Note. Scores based upon all available data; some data not entered into database at time of patient evaluation. BNT = Boston Naming Test; CLTR-6 = Continuous Long-Term Retrieval-6 Trial Version.

token test. Recognition memory was assessed following return to baseline, with a minimum of 10 minutes between injection and memory testing, with the 8 target objects individually presented randomly interspersed with 16 foils. When unsure of an object had been previously seen, the patient was encouraged to guess. One-half the number of false positive responses is subtracted from the number of objects correctly recognized.

To assess lateralized Wada Memory Asymmetries (WMAs), interhemispheric Wada memory difference scores (i.e., [left injection] − [right injection]) derived from corrected memory performances were computed. Positive scores suggest left temporal lobe dysfunction and negative scores suggest right temporal lobe impairment.

Results

A frequency histogram for WMAs as a function of seizure onset laterality is presented in Figure 1. As illustrated, there is a prominent difference in the frequency distribution of WMAs for the left and right TL patients.

Logistic Regression

Principal component analysis of left and right Wada memory scores was performed (SPSS 14.0) using default parameters. The exception to default settings was that two factors were specified for extraction to determine the dimensionality of the left and right Wada memory scores. The resulting 2-factor solution explained 100% of the variance: left—right WMA (53% of variance), and the left + right sum of both hemispheric Wada memory score (47% of variance). Consequently, these two simple algebraeic combinations of bilateral Wada memory scores were used in subsequent analysis.

When both Wada memory score combinations were entered into the logistic regression with seizure onset laterality as the dependent variable, only WMA entered into the equation and accounted for substantial variance in predicting seizure laterality (Cox and Snell $R^2 = .42$, and Nagelkerke $R^2 = .55$). The sum of left + right Wada memory scores was not related to seizure laterality ($p = .95$) and was excluded from the final regression equation. Similarly, age, education (years completed), sex, injection order, and Wada language lateralization were not significant (all $p > .10$). Thus, WMA was the only variable remaining in the final regression equation and was a highly significant predictor temporal lobe seizure onset laterality (logistic regression coefficient = −.511, standard error = .055, Wald statistic = 87.585, $df = 1$, $p < .001$). A nonsignificant Hosmer and Lemeshow statistic was associated with this final model [Hosmer & Lemeshow $\chi^2(N = 334, df = 7) = 1.25$, $p = .99$], indicating no significant lack of fit (Hosmer & Lemeshaw, 2000).

Sensitivity, Specificity and Dichotomous Likelihood Ratios

Logistic regression indicated a WMA greater than −2.0 was the best cutpoint to maximize laterality classification, and classification rates are presented in Table 2. The percentage of left TL patients correctly classified by regression (Sensitivity, Se) was 84%, and the percentage of right TL patients correctly classified (Specificity, Sp) was 77%. The positive likelihood ratio (LR+) was 3.64 (95% CI = 2.70 to 4.90), and the negative likelihood ratio (LR−) was 0.21 (95% CI = 0.15 to 0.30). These LRs, based on dichotomous classification, indicate that WMA is only moderately diagnostically useful in lateralizing lateralized temporal lobe impairment (Strauss et al., 2005).

For comparative purposes, an ROC curve analysis of the WMA data is shown in Figure 2 (analysis performed with SPSS 14.0). The area under the curve (AUC) is highly significant (AUC = .886, standard error = .018, $p < .001$). The AUC statistic indicates that a randomly chosen person from the left seizure focus group has a larger (positive) WMA value 89% of the time, approxi-

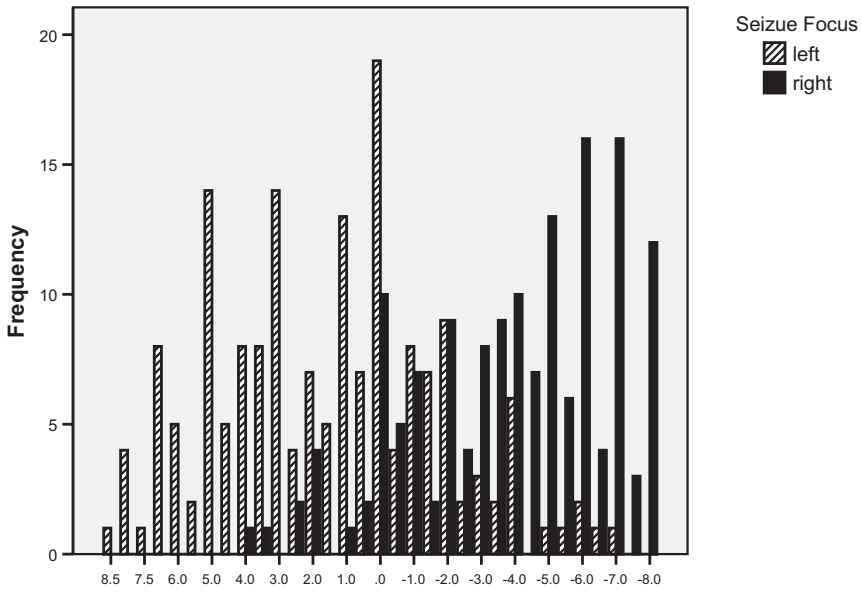

Figure 1. Frequency histogram of L-R WMAs.

Table 2
Correct Classification Table Resulting from Logistic Regression Analysis Predicting Seizure Focus from WMA

	Left TL (N = 172)	Right TL (N = 152)	
	Freq (column %)	Freq (column %)	LRs (95% CI)
WMA			
>−2.0	144 (83.7%)	35/(23.0%)	3.6 (2.7, 4.9)
≤−2.0	28/(16.3%)	117 (77%)	0.2 (0.2, 0.3)

Note. Left − Right WMA scores ranges from −8.0 to +8.5. Higher score indicates better performance following left hemisphere injection. LR = Likelihood Ratio; WMA = Wada memory asymmetries; TL = temporal lobe.

mately, when compared to a randomly chosen person from the right focus group (Zweig & Campbell, 1993). Assuming equal prevalence of left and right seizure focus in the target population and assuming equal costs associated with false-positive and false-negative diagnoses, the point at which the ROC curve touches a line with slope equal to unity shows the optimal trade-off between Se and Sp (Zweig & Campbell, 1993). This graphical analysis would lead to the same conclusion as the logistic regression analysis above, specifically the point of touching the ROC curve is associated with Se = 84% and Sp = 77% approximately. Overall, the ROC provides little additional information of practical value other than to show that there is always a trade-off when choosing Se versus Sp. That is, limiting validity interpretation to the dichotomous Se and Sp information will always lead to loss of Sp when increasing Se, or vice versa.

Multiple Level Likelihood Ratios

We next cross-tabulated seizure focus with WMA at various asymmetry cutpoints (see Table 3). Detailed explanation of multiple level LRs, with worked examples, are presented in Bowden and Loring (submitted). Further detailed examples are provided by Grimes and Schulz (2005). Unlike the calculation of dichotomous LR+ and LR−, multiple-level LRs can be interpreted as a sequence of LRs reflecting the likelihood of the left TL surgery after the patient obtains any particular WMA score, ranging from highest likelihood of left focus through to lowest likelihood. For the WMA data plotted in Figure 1, these data can be tabulated as in Table 3 where cell size was established using uniform intervals expanding from the central cut-score, and collapsed over both extremes containing few entries. Forty left TL patients (23.3%) obtained asymmetry scores greater than +4, whereas no right TL patients obtained asymmetry scores in this range. At the other extreme, no left TL patients obtained a difference score of −8.0 or less. In contrast, 12 right TL patients (7.9%) obtained a difference score of −8.0. Less extreme asymmetry scores included a greater number of patients from both left and right TL groups.

When tabulated in this way whether a test score is "positive" or "negative" becomes unimportant, and instead the validity information is communicated in terms of the change in likelihood of the target condition (left focus) after a given patient is observed to have a particular WMA score or score range. If column percentages are calculated for the observed frequencies as shown in Table 3, then multiple-level LRs can be calculated simply by taking the ratio of the cell percentages in each row (Grimes & Schulz, 2005; Strauss et al., 2005). The resulting multiple level LRs are shown in the right hand column of Table 3.

Multiple-level LRs, reflecting the likelihood of left or right TL surgery across a range of WMAs, yielded a LR of positive infinity (42%/0%) for WMAs that were at least +4 in size. In contrast, WMAs ranging from +2.5 to 4 increases the likelihood of left TL surgery by a factor of 7.62 (19.8%/2.6%). A WMA between −7.5 to −6 decreases the likelihood of left TLE by a factor of .09 (2.3%/25.7%). A LR <0.1 is regarded as highly useful (Grimes & Schulz, 2005; Strauss et al., 2005). At the lowest extreme, a difference score −8.0 decreases the likelihood of left TL surgery from the base rate by an infinitely small factor (0%/7.9%).

Discussion

This report indicates that WMAs are a reliable marker of lateralized temporal lobe dysfunction associated with a unilateral temporal lobe seizure onset in patients undergoing temporal lobe resections. A WMA score of −2.0 was identified using logistic regression as the optimal single cutpoint for group classification (L TL = 83.7%, R TL = 77.0%). The optimal cutpoint of −2.0, rather than a value closer to zero, is empirically derived from the observed score distributions and likely reflects the negative effects of aphasia on memory performance following left hemisphere injection.

Despite the high level of statistical significance for a single cutpoint classification, however, the LRs derived from this analysis indicate only moderately useful diagnostic information (Strauss et al., 2005). LRs have a variety of advantages when compared to sensitivity and specificity classification including making full use

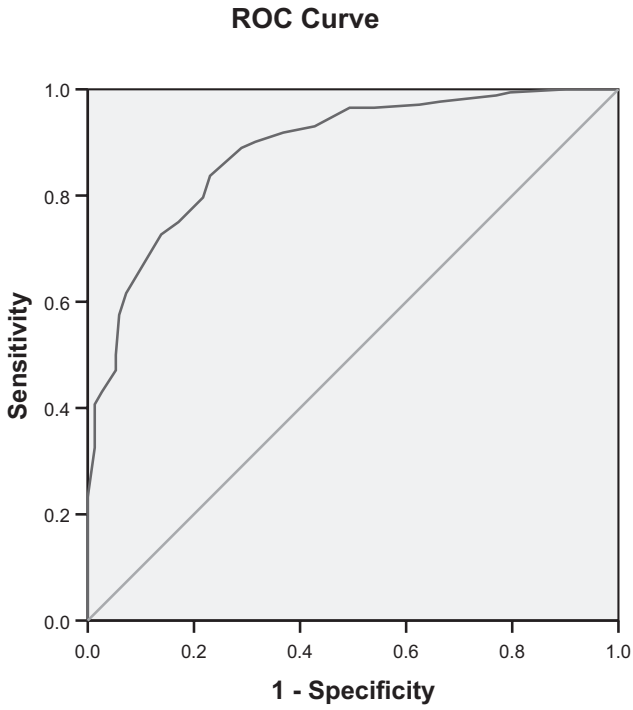

Figure 2. ROC curve of WMA scores for Left TL surgery patients.

Table 3
Multiple Level Likelihood Ratios

	Left TL (N = 172)	Right TL (N = 152)	
	Freq (column %)	Freq (column %)	LRs
WMAs			
>4.0	40 (23.3%)	0 (0.0%)	Infinitively large
2.5 to 4.0	34 (19.8%)	4 (2.6%)	7.6
0.5 to 2.0	32 (18.6%)	7 (4.6%)	4.0
−1.5 to −0.0	38 (22.1%)	24 (15.7%)	1.4
−3.5 to −2.0	16 (9.3%)	30 (19.7%)	0.47
−5.5 to −4.0	8 (4.7%)	36 (23.7%)	0.20
−7.5 to −6.0	4 (2.3%)	39 (25.7%)	0.089
−8.0	0 (0.0%)	12 (7.9%)	Infinitely small

Note. LR = Likelihood Ratio; WMA = Wada memory asymmetries; TL = temporal lobe.

of the information in a 2x2 validity summary table, providing a single metric to interpret the diagnostic validity of a test and forcing explicit reliance on pretest probability whenever posttest probability is calculated (Bowden & Loring, submitted; Grimes & Schulz, 2005; Strauss et al., 2005). Nevertheless, when posttest probability is calculated from LR+ and the corresponding pretest probability, the posttest probability for a positive test result will be the same as the positive predictive power value. Similarly, when posttest probability is calculated from LR- and the corresponding pretest probability, the posttest probability for a negative test result will be the same as 1 - negative predictive power (Bowden & Loring, submitted; Grimes & Schulz, 2005; Strauss et al., 2005).

The ROC analysis (see Figure 2), while indicating that the WMA score was highly statistically significant, nevertheless failed to offer any additional diagnostic validity information over and above the simple Se and Sp analysis derived from logistic regression. In contrast to the sensitivity, specificity and dichotomous LRs, multiple-level LRs based upon WMA of differing magnitudes markedly improved the overall diagnostic information. Specifically, WMAs that were greater than 4.0 points (out of a possible 8 objects) indicate left TL100% of the time; no patients with right TL obtained WMA in this range. Thus, a WMA cutpoint of +4 or more correctly classifies all of the patients scoring in this range as left TL patients. At the opposite extreme, a WMA of −8 was associated with an infinitely small LR. Independent of base rates, a difference score of −8 gives rise to a post test probability of being left TL close to 0.

Intermediate LRs were present for less extreme WMAs. The LRs for the score ranges −5.5 through 0 are close to 1, and therefore have relatively less impact on the likelihood of left TL surgery. However, WMAs ranging from −7.5 to −6.0 are associated with LR = .09, which reduces the likelihood of left TLE by approximately one-tenth. A difference score in the range 0.5 to 2.0 will increase the likelihood of left TL surgery by a factor of 4.

Large LRs increase the posttest probability of the target condition to a number close to 1, irrespective of pretest probability. In this sample, the LR associated with a WMA >4 is so large because there were no patients with right seizure focus with this range of difference scores. In other words, if the distribution of left-right difference scores had been cut at greater then +4, then Sp = 100%. An infinitely large (or small) LR will only be observed when there nonoverlapping segments of the respective sample distributions. When tabulated this will appear as empty cells in one of the columns as in Table 3. Confidence in the accuracy of observed cell frequencies will depend on the quality of representative sampling. A large LR produces a substantial, and diagnostically useful increase in posttest probability, even for low values of pretest probability. Conversely a very small LR will result in substantial reduction in posttest probability, even as values of pretest probability higher than are likely to be encountered in clinical practice. The important implication of the multiple level LR analysis is to show that when a patient obtains a score associated with a very large LR, then this information has the effect of dramatically *increasing* the posttest probability of the diagnosis. Conversely, when a patient obtains a score associated with a very small LR, then this information has the effect of dramatically *decreasing* the posttest probability of the diagnosis.

The overall agreement using logistic regression derived single cutpoint of −2.0 yielded correct group classification of 80% of the sample, which compares favorably with other functional methods to identify seizure onset laterality. These results indicate that the clinical utility of WMA depends in part of the magnitude of the WMA.

WMAs have typically been considered lateralizing if based solely on the direction of simple interhemispheric difference scores (Cohen-Gadol et al., 2004; Lee, Westerveld, Blackburn, Park, & Loring, 2005; Sabsevitz et al., 2001). Other reports have required a larger discrepancy to be considered lateralizing (Perrine et al., 1995; Sperling et al., 1994), or have determined WMAs based on the pattern of Wada memory failure between both hemispheres (Alpherts et al., 2000).

WMAs are considered a useful adjunct to identifying temporal lobe dysfunction associated with a lateralized unilateral temporal lobe seizure focus, although the degree to which different epilepsy centers rely on this information varies. In our experience, WMAs assist in identifying laterality in patients in whom their seizure workup is suggestive of lateralized dysfunction but not conclusive. In these contexts, WMAs provide additional information that may permit these patients to proceed to surgery without the need for invasive EEG monitoring.

The other major use of WMAs is the identification of patients thought to be at elevated risk for memory decline following surgery. Although with baseline NP testing that deviates from expected patterns, patients with WMAs that are inconsistent with established seizure onset laterality are considered to be at greater cognitive risk

than those in which there is either no WMA or an "incorrect" WMA (Loring et al., 1995; Sabsevitz et al., 2001). Follow-up neuropsychological evaluation in the patient series is not routinely obtained unless clear clinical indication exist, however, preventing us from exploring the degree to which WMAs deviate from expected patterns predict neuropsychological outcome following surgery.

It is possible that different findings might emerge had our sample been restricted only to patients with good surgical outcomes. By doing so, there is greater confidence that the WMAs reflect isolated temporal impairment. However, there is no universally agreed upon approach to identifying good surgical outcomes, with some centers classifying patients as having good outcomes if the are seizure free or have only a rare seizure (Engel Class I or II; e.g., Jutila et al., 2002), whereas other centers subdivide seizure free patients into those with auras only (simple sensory seizures) from those who are completely seizure free (e.g., Markand et al., 2000). This sample also include patients who were less than ideal candidates for surgery, but in whom surgery was performed because it was considered to nevertheless provide patients with a good possibility of being rendered seizure free, and if not reaching this goal, would decrease seizure frequency sufficiently to improve a patients quality of life. Although not available for this patient series, postoperative surgical outcome at the Medical College of Georgia for nonlesional ATL cases for a comparable patient cohort was 67% (Smith et al., 1999).

In conclusion, we demonstrate that in contrast to traditional sensitivity and specificity classification using either dichotomous LR or logistic regression on WMAs, the multiple level LRs indicate impressive diagnostic sensitivity for certain WMA ranges, greatly increasing the probability of either left or right TLE depending on the respective score. We encourage greater use of multiple-level LRs with neuropsychological test findings when dichotomous outcomes such as determining presence or absence of specific diagnoses is inferred.

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