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Naming Outcome Prediction in Patients with Discordant Wada and fMRI Language Lateralization

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Abstract

Objective—Investigations of the validity of fMRI as an alternative to Wada language testing have yielded Wada/fMRI discordance rates of approximately 15%, but almost nothing is known regarding the relative accuracy of Wada and fMRI in discordant cases. The objective of this study was to determine whether the Wada test or language fMRI is more predictive of postoperative naming outcome following left anterior temporal lobectomy in discordant cases.

Methods—Among 229 epilepsy patients who prospectively underwent Wada and fMRI language testing, ten had discordant language lateralization results, underwent left anterior temporal lobectomy, and returned for postoperative language testing. The relative accuracy of Wada and fMRI for predicting language outcome was examined in these cases.

Results—FMRI provided the more accurate prediction of language outcome in seven patients, Wada was more accurate in two patients, and the two tests were equally accurate in one patient.

Conclusions—In cases of discordance, fMRI predicted post-surgical naming outcome with relatively better accuracy compared to the Wada test.

Keywords

fMRI; Wada test; epilepsy surgery; outcome research; language lateralization

Anterior temporal lobectomy (ATL) is an effective treatment for intractable temporal lobe epilepsy (TLE) [1, 2]. However, naming decline is a potential complication after left ATL surgery [3–5]. Wada testing has been used for many years to assess pre-operative language lateralization and to predict post-operative language outcome [6, 7]. Investigations of the validity of fMRI as an alternative to Wada testing have yielded numerous comparison studies, with overall discordance rates of approximately 15% [8, 9], but very little outcome data. In the few reports that included outcome data, the number of discordant cases was

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negligible, or the outcomes were reported as uniformly good (“no post-operative aphasia”) even when surgery was done in the language-dominant hemisphere [10, 11]. In the only study that systematically examined the relationship between language lateralization and naming outcome using standardized language testing, Sabsevitz and colleagues [12] reported that both Wada and fMRI lateralization indices (LIs) were predictive of post-operative naming decline, though regression analyses showed that the fMRI LI was a stronger predictor than the Wada LI. The objective of this study was to determine whether the Wada test or fMRI is more predictive of naming outcome after left ATL resection in patients with discordant Wada and fMRI language lateralization. The low incidence of discordance, the focus on left (as opposed to right) ATL surgery, and practical difficulties in obtaining systematic neuropsychological outcome data make such patients relatively rare. This is the first study to provide data on language outcome after left ATL in a group of patients who had discordant Wada and fMRI language lateralization scores.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

All procedures were approved by the Medical College of Wisconsin institutional review board, and written informed consent was obtained from all patients participating in the study.

Participants

A consecutive series of 229 adults (ages ≥ 18) underwent standardized outpatient Wada testing, standardized fMRI language mapping, and pre-operative neuropsychological assessment at the Medical College of Wisconsin Comprehensive Epilepsy Program between 1993 and 2009. This sample has been described in more detail elsewhere [9]. FMRI studies were done for research purposes only, and results were not available to the clinical team. Of these patients, 32 patients were determined to have discordant Wada and fMRI results (see definition below). No significant differences were found between concordant and discordant patients with regard to subject variables, Wada quality variables, or fMRI quality variables [9]. Of these discordant patients, 10 underwent left ATL surgery and had both pre-operative and 6-month post-operative neuropsychological testing. All patients underwent tailored ATL with electrocorticography and intra- or extraoperative stimulation mapping of language cortex [13]. The remaining 22 patients were excluded because they had a right temporal seizure focus (n= 10), or extratemporal seizure focus (n= 7), had a left temporal seizure focus but did not have surgery (n= 2), or had left ATL but no post-operative neuropsychological testing (n= 3). We limited the sample to left ATL patients because no relationships were observed between naming outcome and either fMRI LIs ($r = .12$, $p = .38$) or Wada LIs ($r = -.02$, $p = .89$) in the right ATL patients. Clinical data for the sample are presented in Table 1.

Wada testing

Wada testing was always performed blind to the fMRI results. The Wada test was modeled after the procedure developed at the Medical College of Georgia [6]. Baseline testing was performed 2 hours before the procedure. Amobarbital (75–125 mg) was injected into the internal carotid artery ipsilateral to the seizure focus, and language functions of the contralateral cerebral hemisphere were tested. All patients were initially given 75 mg of amobarbital followed by a saline flush. If they did not develop hemiplegia and delta slowing on EEG they were administered 1–2 additional 25-mg boluses until hemiplegia was obtained and delta slowing occurred. The procedure was then repeated on the hemisphere contralateral to the seizure focus. Counting disruption was numerically rated, as well as ability to follow two simple midline commands just after injection. Language was assessed using measures of counting, comprehension of commands, object naming, phrase repetition, and sentence reading during the period of hemianesthesia. Return of motor function and cessation of delta slowing on EEG were used to determine the duration of anesthesia. Only language trials obtained during the period prior to any motor return in the contralateral upper extremity or resolution of delta on EEG (whichever occurred first) were included in the language lateralization score. The scores for each language task ranged from 0–3, with lower scores indicating a greater degree of impairment. LIs were calculated as the difference between the percent of maximal obtainable score in the inject right/test left condition and the percent of maximal obtainable score in the inject left/test right condition. LIs ranged from +100 (indicating complete left hemisphere dominance) to −100 (indicating complete right hemisphere dominance).

Functional magnetic resonance imaging

The language activation protocol was a semantic decision/tone decision contrast developed by Binder et al [14]. During the semantic decision task, individuals listened to animal names and were instructed to press a button if the animal was both found in the United States and used by humans. During the tone decision task, individuals listened to brief sequences of high (750 Hz) and low (500 Hz) tones and were instructed to press a button if they heard a sequence containing two high tones. Tasks were alternated in a block design. The contrast of the semantic decision task with the tone decision task isolates speech perception and semantic language processes while controlling for attention, working memory, auditory, and motor processes. This contrast produces left-lateralized language activation in frontal, temporal, and parietal areas in healthy right-handed controls [15, 16].

As described elsewhere [15, 16], imaging was conducted on commercial 1.5T and 3T scanners (General Electric Medical Systems, Milwaukee, WI). High-resolution, T1-weighted anatomic reference images were obtained using a three-dimensional spoiled-gradient-echo sequence. Functional imaging used a gradient-echo T2*-weighted echoplanar sequence. Echoplanar image volumes were acquired as contiguous sagittal or axial slices covering the whole brain.

Image processing and statistical analyses were performed using AFNI software. All analyses were performed at the individual subject level. Volumetric image registration was used to reduce the effects of head movement. Task-related changes in MRI signal were identified using a multivariable general linear model. The predicted task effect was modeled by convolving a gamma function with a time series of impulses representing each task trial. Movement vectors (computed during image registration) and a second-order linear trend were included as covariates of no interest. ROIs used for automated measurement of language lateralization were based on activated regions in the left hemisphere in 100 healthy right-handed adults [16, 17]. A “lateral” ROI was created by combining temporal, frontal, and parietal activations in the lateral two-thirds of the hemisphere, excluding medial regions because they tend to be more bilaterally activated and can include midline voxels containing tissue from both hemispheres [18]. Corresponding right hemisphere ROIs were created by reflecting the left hemisphere ROIs symmetrically across the midline. Voxels passing an uncorrected activation threshold of $p < 0.001$ were counted for each patient. LIs reflecting the interhemispheric difference between voxel counts in the left and right homologous ROIs were calculated using the following formula: LI = 100 * (L−R)/(L+R), where L equals the number of activated voxels in the left hemisphere and R equals the number of activated voxels in the right hemisphere. These LIs range from +100 (complete left hemisphere dominance) to −100 (complete right hemisphere dominance). All fMRI analyses were fully automated and performed by a technician without knowledge of the Wada test results.

Neuropsychological testing

Language was assessed using the Boston Naming Test (BNT), a standardized measure of visual confrontation naming [19] commonly used to assess language function and outcome in individuals with intractable epilepsy [12, 20]. The test consists of 60 black and white line drawings of objects.

Operational definition of discordance

There is no standard, validated definition of Wada/fMRI language lateralization discordance. Clinical judgment is often used to determine left, right, or bilateral language dominance, and arbitrary cut-offs are frequently applied in studies investigating discordance. We defined concordance conservatively, using a method that accounts for the inherent differences in the distributions of Wada and fMRI LIs. Detailed descriptions and rationale for these criteria were provided previously [9]. In brief, we chose an fMRI LI cut score of 25: left (LI ≥ 25), right (LI ≤ −25), and bilateral (LI between −25 and 25), consistent with previously published studies [22, 24]. Using this cut score, 80% of the current sample was left language dominant, consistent with left language dominance rates (67–81%) reported in other epilepsy samples [21–23]. As Wada language lateralization estimates are not available for neurologically normal individuals, we set the Wada cut score to yield similar proportions of left, bilateral, and right dominant cases as fMRI. Accordingly, Wada language dominance was categorized using a cut score of 50: left (LI ≥ 50), right (LI ≤ −50), and bilateral (LI between −50 and 50). To avoid the possibility that similar LIs on either side of the arbitrary cut scores could be categorized as discordant (e.g., an fMRI LI of 40 and a Wada LI of 40 being defined as discordant), we also required that discordant cases have Wada and fMRI LI values differing by more than 50 units (i.e., |Wada LI - fMRI LI|) > 50). "Discordance" was thus defined as follows: the Wada and fMRI LIs must 1) be in different categories as defined above, and 2) differ by more than 50 units.

Prediction of individual language outcomes

To quantify the predictive accuracy of each test, we updated linear regression models [12] in which the fMRI LI and Wada LI were used to predict change on the BNT from pre- to post-operative evaluation. From our total sample ($N = 229$), we examined the subset of patients who underwent left ATL surgery, Wada testing, fMRI, and pre- and post-operative neuropsychological assessment. This yielded a subset of 65 participants. Of these, we removed the 10 cases with discordant fMRI and Wada LIs to avoid biasing the regression models in favor of one test over the other.

Following the methods reported previously [12], we computed two regression equations, one using the Wada LI and pre-operative BNT score to predict post-operative BNT change score (i.e., post-operative BNT score minus pre-operative BNT score) and the other using the fMRI LI and pre-operative BNT score to predict post-operative BNT change score. The pre-operative BNT score was included because it is a known predictor of post-operative language change [12, 25, 26] and was correlated with BNT change in our sample ($r = -.234$, $p < .05$). The overall fMRI regression model was significant ($R^2 = .19$, $F(2, 52) = 6.04$, $p < .01$), and the fMRI LI accounted for a significant portion of the variance in BNT change ($R^2 change = .134$, $p < .01$) above and beyond pre-operative BNT score. The overall Wada regression model was also significant ($R^2 = .16$, $F(2, 52) = 4.81$, $p = .01$), and the Wada LI also accounted for a significant portion of the variance in BNT change ($R^2 change = .10$, $p = .02$) above and beyond pre-operative BNT score. The fMRI regression equation was: BNT change = 8.894 + (−.234 × preop BNT) + (−.090 × fMRI LI). The Wada regression equation was: BNT change = 10.239 + (−.260 × preop BNT) + (−.071 × Wada LI). These models, which provide optimal predictions of BNT change, were then used to obtain the change scores (Y_p) predicted by fMRI LI and Wada LI in each discordant case. The difference between the predicted (Y_p) and observed change (Y_o) score for each method was then examined in each case.

Results

Based on Wada testing, 5 patients had left language dominance, 4 had bilateral language, and one had right language dominance. Based on fMRI, 4 patients had left language dominance, 6 had bilateral language and none had right language dominance. Accuracy of outcome prediction was assessed by comparing the difference between predicted BNT change score and actual, observed BNT change score (i.e., $Y_o - Y_p$) for each test. Accuracy was better using fMRI in seven cases, better using the Wada test in two cases, and equivalent for fMRI and Wada in one case. Table 2 shows the actual pre- and post-operative BNT scores, Wada LI, fMRI LI, predicted BNT change scores for each lateralization method, and the actual BNT change score for each patient. In the first patient (case 2385), Wada and fMRI were equally “accurate” with regard to the prediction of post-operative BNT change, although in different directions: Wada predicted an increase of 4.5 raw score points on the BNT, whereas fMRI predicted a 4.5 point decrease. In actuality, there was no change in BNT score for this patient. Outcomes in the next two patients (639 and 1737) were better predicted by Wada, which classified both patients as bilateral, than by fMRI, which classified both as left dominant. The next two patients (551 and 597) were also bilateral on Wada and left dominant on fMRI, yet fMRI provided a more accurate outcome prediction in these cases. The remaining five patients were left dominant on Wada and bilateral on fMRI, with fMRI providing a more accurate outcome prediction in all five.

Notably, most of the patients had small changes in BNT performance, therefore the test with the more atypical language LI, and thus the test that predicted the smaller decline, tended to be more accurate. The two exceptions were cases 551 and 597, whose large declines were better predicted by fMRI, which showed left dominance, than by Wada, which showed bilateral language.

Discussion

This is the first study to provide comparative evidence concerning language outcome in left ATL surgery patients with discordant Wada and fMRI language lateralization. We used a sensitive, widely used, standardized test of picture naming to measure change in language function, and an objective, quantitative method for comparing the accuracy of the Wada and fMRI tests. Among the 10 discordant cases with post-operative data after left ATL surgery, fMRI predicted post-surgical language outcome with relatively better accuracy than the Wada test. This pattern is consistent with a previous study [12], which showed that across all left ATL surgery patients (regardless of test concordance) the fMRI LI was somewhat more strongly correlated with naming change scores than the Wada LI.

Although the relative accuracy of prediction values is important, their clinical significance should also be considered. This was of particular importance for two patients (2385 and 1539). Patient 2385 had numerically equal post-operative predictions of language outcome (+/− 4.5 raw score points on the BNT). However, from a clinical standpoint, the Wada test could be viewed as more accurate because fMRI predicted a small decline, whereas the Wada test predicted improvement or essentially no decline, which is consistent with the actual postoperative change. This is one limitation of using regression equations, as improved scores are predicted by the regression equation at the outer limits of a distribution. In actuality, significant cognitive improvements are not expected after surgery. Similarly, patient 1539 was predicted to have a very minimal decline (1.1 BNT points) by fMRI and a more significant decline by the Wada test (8.3 BNT points). In actuality, this patient showed a small (4 BNT points) decline post-operatively. In this case, although the fMRI prediction was numerically closer to the actual outcome, this may not be a clinically meaningful difference.

In the majority of these discordant cases (9/10), one test classified the patient as having bilateral language and the other classified the patient as left dominant. In all but two of these patients, the method that best predicted language outcome was the one that classified the discordant case as bilateral. In one exception to this rule (patient 551: Wada bilateral, fMRI left), close examination of the Wada test record did not clarify the cause of the inaccurate Wada result. In the other exception (patient 597: Wada bilateral, fMRI left), methodological problems with the Wada administration may have caused an erroneous bilateral pattern. Although the patient's Wada test was judged to be clinically valid at the time it was administered, the report summary included caveats about the interpretation of the results due to obtundation in the inject right/test left hemisphere condition, indicating that the language capacity of the left hemisphere likely had been underestimated. However, the finding of paraphasic errors after both injections led to the ultimate conclusion that language was bilaterally represented. This case, however, does not fit any of the four main patterns of bilateral language described in a previous large Wada series by Risse and colleagues [27]. These patterns include: 1) automatic speech only in the right hemisphere, 2) duplication of auditory language comprehension in the right hemisphere, 3) superior language capacity in the right hemisphere for every language modality except reading, and 4) nearly perfect language with both injections. Patient 597 demonstrated almost no language capacity with either hemisphere, a pattern that would have been considered "unclassified" by Risse and coauthors. In hindsight, the finding of almost no language capacity in either hemisphere likely indicates an invalid Wada.

Several hypotheses can be offered as to why a bilateral result, which was more frequently obtained by fMRI, is more accurate in discordant cases. When fMRI suggests bilateral language and Wada suggests left dominance, it may be that there is some degree of right hemisphere language representation that is nevertheless not detected when the left hemisphere is anesthetized. In such cases the left hemisphere may be the locus of language control processes, whereas the subsidiary system located in the right hemisphere is unable to function when these control processes are anesthetized. Although the right hemisphere may not be able to perform independently during the Wada test, some less critical aspects of language function that are subserved by the right hemisphere nevertheless enhance recovery after left hemisphere surgery and thus have an effect on outcome. The reverse scenario, in which Wada indicates bilateral language dominance and fMRI shows left language, is more difficult to explain. One of these patients (patient 639) had a rare interhemispheric dissociation of language processes on Wada testing, with comprehension ability in the left hemisphere and production ability in the right hemisphere, as reported previously [subject S1 in reference 28]. This case is therefore explained by the hypothesis, suggested by Lee et al. [28], that the semantic decision fMRI protocol detects mainly lexical-semantic comprehension processes, which in this patient are located in the left hemisphere. Indeed, when a subset of the Wada language subtests that focus on comprehension abilities is used to compute the Wada LI, the Wada LI for this patient is 80, which agrees closely with the fMRI LI. The explanation for the remaining two patients (551 and 1737) with left dominance on fMRI and bilateral language on Wada is unclear. Given the small number of cases in question, these are problems that will require further investigation with still larger patient samples.

Limitations

Although the sample size is small, this study drew from the largest published sample (N = 229) of patients tested with both Wada and fMRI [9] and is the only study to prospectively follow a subset of patients with discordant language results who then underwent left ATL. Collecting such evidence is difficult for many reasons. Given the relatively low incidence of language discordance (14% in our sample of 229), a large number of patients must first be studied using standard fMRI and Wada tests. Of the discordant cases, only a subset will go on to ATL surgery, and only about half of these will have surgery on the left side. Finally, such patients must be willing to undergo post-operative neuropsychological testing, and resources must be committed to make this testing possible. These facts create difficult logistical challenges for the prospects of collecting a larger sample in the near future.

Finally, this study does not address verbal memory, which has also been shown to decline in some patients after left ATL. Although fMRI has not yet been shown to be predictive of global amnesia, one previous study found that fMRI language LIs were more predictive of postoperative verbal memory outcome than Wada language LIs or Wada memory asymmetry indices [18]. While these data suggest that fMRI may be a useful alternative to Wada testing for both language and memory, there are situations where Wada testing may be necessary or recommended. If a patient has an implanted metal device or cognitive dysfunction that precludes fMRI task compliance, the patient should be referred for Wada testing. If a patient has evidence of pathology contralateral to a left-sided seizure focus, such as hippocampal sclerosis, contralateral epileptiform activity, temporal lesion or atrophy (thereby increasing risk for amnesia after left ATL), a Wada test should be considered to assess the functional reserve of the right hemisphere memory system. A Wada test should also be considered in the rare circumstance in which fMRI shows right language dominance in a patient with a right seizure focus and contralateral (left) pathology.

Conclusion

Among ten patients with discordant Wada/fMRI language lateralization who underwent left ATL surgery, fMRI was more accurate in predicting outcome in seven patients, Wada was more accurate in two patients, and the tests were equally accurate in one patient. These findings suggest that pre-surgical epilepsy patients who successfully complete a standardized and validated fMRI test for language lateralization do not require Wada testing for language dominance, as the two methods are generally concordant, and in cases of discordance, fMRI predicts post-operative naming outcome with relatively better accuracy than Wada testing.

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Table 1

Pre-operative Clinical Data and Seizure Outcome

ID	Sex	Age, y	Onset, y	Hand	MTS/ Atrophy	Precipitating Event	Ed, y	FSIQ	Seizure Outcome
2385	F	39	0.3	Left	Yes	Perinatal stroke	16	85	Seizure-free
639	F	46	9	Right	No	None known	17	116	Seizure-free
1737	M	38	14	Left	Yes	None known	15	98	Seizure-free
551	M	42	20	Right	No	None known	18	113	<75% seizure reduction
597	F	26	23	Right	No	None known	12	80	Seizure-free
706	F	56	10	Left	Yes	None known	11	95	Seizure-free
574	M	32	0.3	Right	No	None known	12	97	Seizure-free
1539	M	42	17	Left	Yes	None known	12	95	Seizure-free
633	M	37	7	Right	Yes	None known	14	102	Seizure-free
638	M	35	10	Right	No	Left temporal grade 1 astrocytoma	16	109	<75% seizure reduction

y, years; F, female; M, male; hand, handedness; MTS, mesial temporal sclerosis; Ed, education; FSIQ, full scale intelligence quotient

Table 2

Predicted and Observed Post-operative BNT scores using Wada and fMRI Language Laterality Indices

	Pre-op	Post-op			Predicted BNT Change (Y_p)		Observed BNT
ID	BNT	BNT	Wada LI	fMRI LI	Wada Y_p	fMRI Y_p	Change (Y_o)
2385^	49	49	−98	21	4.5	−4.5	0
639*	54	50	−16	77	−2.7	−10.7	−4
1737*	51	47	2	71	−3.2	−9.4	−4
551	52	44	−29	63	−1.2	−8.9	−8
597	54	32	16	92	−4.9	−12.0	−22
706	49	53	50	−24	−6.1	−0.4	+4
574	49	51	67	14	−7.3	−3.8	+2
1539	53	49	67	−24	−8.3	−1.1	−4
633	59	60	87	13	−11.3	−6.1	+1
638	53	53	90	−1	−9.9	−3.4	0

^ BNT change predicted with equal accuracy by Wada and fMRI

* BNT change predicted with greater accuracy by the Wada test than by fMRI

BNT, Boston Naming Test; fMRI, functional magnetic resonance imaging