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FMRI and Wada Studies in Patients with Interhemispheric Dissociation of Language Functions

Dongwook Lee^{*}, Sara J. Swanson, David S. Sabsevitz, Thomas A. Hammeke, F. Scott Winstanley, Edward T. Possing, and Jeffrey R. Binder

Department of Neurology and the Comprehensive Epilepsy Center Medical College of Wisconsin, Milwaukee, Wisconsin

Abstract

Rare patients with chronic epilepsy show interhemispheric dissociation of language functions on intracarotid amobarbital (Wada) testing. We encountered four patients with interhemispheric dissociation in 490 consecutive Wada language tests. In all cases, performance on overt speech production tasks was supported by the hemisphere contralateral to the seizure focus, while performance on comprehension tasks was served by the hemisphere with the seizure focus. These data suggest that speech production capacity is more likely to shift hemispheres than is language comprehension. Wada and fMRI language lateralization scores were discordant in three of the four patients. However, the two methods aligned more closely when Wada measures loading on comprehension were used for calculating lateralization scores. Thus, interhemispheric dissociation of language functions could explain some cases of discordance on Wada/fMRI language comparisons, particularly when the fMRI measure used is not sensitive to speech production processes.

Keywords

language dissociation; language mapping; fMRI; Wada test; intracarotid amobarbital test; epilepsy; interhemispheric dissociation; discordance

Measurement of language lateralization, using either the intracarotid amobarbital (Wada) test or functional magnetic resonance imaging (fMRI), is a routine part of the presurgical evaluation of patients with intractable epilepsy. Knowledge about language dominance can be useful for predicting cognitive morbidity from surgery. Patients with epilepsy have a higher incidence of atypical language representation than the healthy population [1–3]. Many factors are known to influence language lateralization. The role of early brain injury in language reorganization is well documented [1–6]. The location of the seizure focus, seizure frequency, size of brain lesion, and handedness also influence language reorganization and shifting of language abilities [7–11].

Although atypical language representation is not uncommon among patients with chronic epilepsy, a strong difference in lateralization between different language skills is rare. Kurthen

^{*} Corresponding author Phone: 414.805.5660, Fax: 414.259.9012, E-mail address: dolee@mcw.edu.
Address: Medical College of Wisconsin, Department of Neurology, 9200 W. Wisconsin Ave., Milwaukee, WI 53226

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at al. [12] reported four cases of dissociation of language functions during Wada testing among 144 patients. These authors considered counting backward, speech production on tasks of naming, repetition, and reading, and dysphasic errors (paraphasias and perseveration) to reflect “expressive” linguistic capacities, while comprehension of spoken commands and questions was used to assess “receptive” language functions. Their findings demonstrated that in rare cases the expressive language system can be located in one hemisphere and receptive language ability in the other. In a study examining bilateral language representation among epilepsy patients, Risse and coauthors [2] mentioned that they found only two patients among over 500 Wada studies whose results suggested interhemispheric dissociation of language skills. The Wada test used by these authors assessed automatic speech, naming, reading, and auditory comprehension. Dissociations in their two patients reportedly reflected differential lateralization on comprehension and overt speech production tasks. No further information is available about these patients because neither met criteria for inclusion in the study.

Although the Wada test has been the gold standard for many years for assessing language dominance, fMRI has recently emerged as a viable non-invasive alternative to the Wada. Many studies have examined the degree of concordance between these methods. Although several initial studies with small patient samples reported 100% concordance [13–20], more recent, larger series show discordance rates in the range of 5–25% [21–24]. The degree of discordance varies depending on region of interest (e.g., frontal vs. temporal) over which the lateralization measure is computed, the methods used to determine laterality (e.g., placement of cutoff scores), seizure location (e.g., temporal vs. extra-temporal), the language (e.g., semantic judgment vs. fluency) and control/contrast tasks (perceptual controls vs. rest) employed during fMRI, and the Wada language tasks used.

Discrepancies between Wada and fMRI could arise from several factors, as each test has potential methodological limitations. The validity of the Wada test can be compromised by obtundation, insufficient anesthetization, interhemispheric arterial crossflow, and the relatively brief period available for testing. FMRI results can be affected by head motion, insufficient statistical power due to inadequate number of trials or image volumes [25], and poor task compliance. FMRI procedures also must be carefully designed to activate a wide range of language processes yet avoid activation of non-language systems (e.g., attention, low-level audition, or vision) engaged by the language task(s). FMRI and Wada are fundamentally different in that one is an activation method and the other is a transient “lesion” paradigm. Discrepancies could thus arise when the fMRI lateralization score reflects activation that is not essential for performance.

Discordance might also arise when the fMRI protocol does not examine the same set of language processes assessed during Wada testing. During the Wada procedure, each hemisphere is tested on multiple language tasks (i.e., comprehension, naming, repetition, and reading), whereas fMRI protocols often use a single task or task contrast. FMRI protocols may thus be more sensitive to some language processes than others. Given this difference between the two techniques, discordance could arise in some cases due to differential lateralization of certain language capacities (e.g., speech production) relative to others (e.g., language comprehension). In such cases, the Wada lateralization score would be more likely to show bilateral language representation, whereas fMRI might suggest a more lateralized language system due to inability to detect particular language components.

We present four patients who showed clear interhemispheric dissociation of language functions on Wada testing. For these patients, one type of language task (either production or comprehension) was supported exclusively by one hemisphere, while the other type was supported by the opposite hemisphere. All four patients underwent fMRI language mapping to determine if patients with this pattern of bilateral language would show discordance between

Wada and fMRI and to examine several hypotheses about the underlying reason for this discordance. This study provides the first fMRI data on patients with clear signs of interhemispheric dissociations in language functions.

Methods

Patient Selection and Wada Testing

The patients were selected from 490 consecutive adults who underwent comprehensive evaluation for surgical treatment of medically intractable epilepsy. Of this sample, 269 patients underwent both Wada and fMRI tests, including all four of the patients described in the present report. In addition to fMRI, the presurgical evaluation for epilepsy included long-term video-EEG monitoring, neuropsychological testing, structural brain MRI, and a standardized Wada test. The Wada procedure was similar to that described by Loring et al. [5] and was described in detail elsewhere [14,16]. Baseline testing of memory and language was conducted two hours before the Wada test. Internal carotid artery angiograms were obtained and inspected for any vascular abnormalities prior to Wada testing. With the patient in a supine position with arms outstretched, 75 to 100 mg of sodium amobarbital were injected by hand over a 4 to 5 second interval into the internal carotid artery while the patient counted aloud by ones. The side of suspected seizure focus was injected first. Simultaneous EEG recording was conducted during the procedure to monitor the onset and cessation of slowing in the injected hemisphere. If contralateral flaccid hemiplegia was not present, an additional 25 mg bolus of amobarbital was injected. Counting, comprehension, naming, repetition, and reading were scored based on the number of correct responses. Counting scores were based on a rating of counting disruption at the initiation of the Wada test. Comprehension was assessed using a modified token task and the ability to follow two simple midline commands (“Touch your nose” and “Stick out your tongue”). Naming was assessed by having the patient name objects and portions of objects pictured in line drawings. Repetition was assessed by asking the patient to repeat three phrases of varying difficulty. Patients were asked to read two sentences aloud for assessment of reading. These tasks were then repeated during the period of hemianesthesia until the patient performed at baseline level. Only trials presented prior to return of motor function in the contralateral upper extremity were scored. A rating of paraphasic errors was also included in the scoring, based on the total number of semantic or phonemic paraphasic errors that occurred during the language assessment. Approximately 30 minutes after the first injection, the identical procedure was repeated on the contralateral hemisphere. A Wada laterality index (Wada LI) was calculated for each patient as the difference between the percentage of correct responses during anesthetization of the right hemisphere (W_L , test left condition) and the percentage of correct responses during anesthetization of the left hemisphere (W_R , test right condition). This approach yields LIs ranging between +100 (strong left hemisphere dominance) and -100 (strong right hemisphere dominance). Wada LI calculations were performed by a neuropsychologist blind to the fMRI results.

In addition to an overall Wada LI, separate lateralization indexes were calculated using tasks that load heavily on either speech production (LI_{sp}) or comprehension (LI_c). The speech production LI was computed using performances on counting, naming, and repetition. Reading was not included because motor return often occurred before reading was assessed. The LI_c was computed based on performance of midline commands and the modified token test. While all of these tasks make demands on a variety of language-specific processes (e.g., lexical, semantic, and phonological) as well as on various general-purpose processes (e.g., sensory, attention, working memory, response selection), this grouping provides a relatively clear separation between tasks that make strong demands on overt speech production without strong demands on comprehension, and vice versa. Additionally, the grouping was chosen because this is the only type of interhemispheric dissociation that was observed in our sample. Patients

with clear signs of interhemispheric dissociation between these factors were then selected based on the LIsp and LIc measures. Four patients out of the 490 studied showed a clear dissociation, with intact comprehension and impaired speech production during one injection and the opposite pattern during the other injection.

FMRI image acquisition

MRI studies were conducted on a 1.5 Tesla GE Signa scanner (GE Medical, Milwaukee, WI, USA) using a three-axis local gradient coil and insertable transmit/receive RF coil (Medical Advances, Milwaukee, WI, USA). FMRI used a gradient echo, echo-planar sequence (TE 40 ms, TR 3000–4000 ms, field of view 24 cm, matrix 64×64 , and slice thickness 7–8 mm). Functional slices were acquired in the sagittal plane with 14 to 21 contiguous slices covering the whole brain. High-resolution, T₁-weighted anatomical reference images were obtained as a set of 124 contiguous sagittal slices using a 3D spoiled-gradient-echo sequence.

FMRI activation tasks

Stimuli used for the fMRI protocol were tones and auditory words presented binaurally using a computer playback system. The protocol used a block design with alternation between a semantic decision task and a tone decision task, details of which were described previously [14,26]. Briefly, patients heard trains of 3–7 tones in the tone decision (control) task. Each tone had a frequency of either 500 Hz or 750 Hz. Patients were instructed to press a button for any train containing two high-pitch (750 Hz) tones. In the semantic decision task, patients heard spoken English nouns designating animals (e.g., “chicken”) and responded according to specified semantic criteria. Target words were animals that are both “found in the United States” and “used by humans.” The two tasks were matched for stimulus intensity, average stimulus duration, average trial duration, and frequency of positive targets. The semantic decision - tone decision contrast is thought to highlight activation in speech perception, phonological word-form, semantic memory, and lexical-semantic retrieval systems, as well as language-specific working memory components. This fMRI protocol produces strongly left-lateralized frontal, temporal, and parietal lobe activation in most right-handed [3] and non-right-handed [27] people. The degree of lateralization is highly correlated with Wada language lateralization [14] and predicts language outcome in patients undergoing left temporal lobe resection [28].

FMRI data analysis

All analyses were performed at the individual subject level. Image volumes were registered to minimize effects of head motion. Identification of event-related MRI signal changes was performed using multiple regression implemented in AFNI [29]. Task regressors were derived by convolving a boxcar function representing the task block alternation with a canonical hemodynamic response function. Other regressors modeled head motion and linear and second-order trends. Correlation maps were thresholded at voxel-wise $p < 0.001$ and a minimum cluster size of 200 μl to give a whole-brain corrected $p < .05$ as determined by Monte Carlo simulation (AlphaSim in AFNI). The same thresholding was applied to each patient. Activation volumes were determined in each patient by counting the voxels in each hemisphere that passed the threshold. Region-of-interest (ROI) volumes were defined based on the average left hemisphere activation map from 80 normal, right-handed subjects [27,30]. Mirror-image right hemisphere ROIs were created by reflecting these volumes symmetrically across midline. The following ROIs were created: frontal (lateral and medial frontal areas), temporoparietal (lateral and medial temporal areas and parietal areas, mainly angular gyrus), and whole hemisphere (combining all individual ROIs). FMRI LIs were calculated for each patient for each of these three ROIs, using the formula $([V_L - V_R]/[V_L + V_R]) \times 100$, where V_L and V_R are activation volumes for the homologous left and right ROIs. This approach yields fMRI LIs ranging

between +100 (strong left hemisphere dominance) and −100 (strong right hemisphere dominance). Following previous precedent [3,27], LI values > 20 were considered left hemisphere language dominant, LIs between −20 and +20 were considered bilateral/symmetric, and LIs < −20 were considered right hemisphere dominant. fMRI LIs were calculated using automated scripts by an investigator blinded to the Wada results. Reliability of the fMRI protocol has been previously explored [26,49–50]. Test-retest comparisons (within and across-sessions) showed good reproducibility of both activation patterns and laterality indexes.

Results

Demographic and relevant epilepsy-related information for the four patients is summarized in Table 1. The differences between Wada LIs and fMRI LIs (absolute values) were relatively large for three patients (discordant cases: S1 = 93, S2 = 43, and S3 = 113), while the difference in the remaining patient was relatively small (concordant case: S4 = 14). Both S1 and S2 had Wada LIs showing relatively symmetric language representation (S1: −16, S2: +10) and had fMRI LIs showing clear left dominance (S1: +77, S2: +53). S3 showed a different pattern of discordance, with weak left dominance on Wada (+49) and strong right dominance on fMRI (−64) (See Figure 1).

Among the discordant patients, S1 and S2 had seizures originating in the left hemisphere, and language comprehension was clearly represented in the left hemisphere on Wada testing; whereas S3 had right hemisphere seizures, and language comprehension was strongly represented in the right hemisphere (Table 2). When only comprehension components of the Wada test were considered, language dominance on Wada testing more closely aligned with the lateralization based on whole hemisphere fMRI in all three discordant patients (Figure 1). For S4, the comprehension component of the Wada test was less concordant with fMRI than the full Wada test.

To further examine the possible relationship between regional fMRI activation patterns in anterior and posterior language areas and interhemispheric dissociation in language functions on Wada testing, two ROI-based fMRI LIs (frontal and temporoparietal) were also calculated. It was hypothesized that fMRI activation in the temporoparietal region might be closely associated with the hemisphere serving language comprehension on Wada testing and that fMRI activation in the frontal lobe might be associated with the hemisphere serving speech production. As seen in Table 2, the fMRI LIs based on activation of the whole hemisphere, frontal, and temporoparietal regions were all similar to each other. For all of the discordant patients, the fMRI LIs agreed with Wada language lateralization based on language comprehension rather than language production, regardless of the region on which the fMRI LI was based.

Discussion

Epilepsy surgery candidates provide a unique opportunity to examine the effects of a chronic focal abnormality on the cerebral organization of language. It is well documented that patients with early left hemisphere lesions, particularly non-right-handed patients, have a higher incidence of atypical (right or bilateral) representation of language functions. Atypical language representation is estimated to occur in 5% to 53% of right-handed epilepsy patients [1–3,7,31], while the incidence of atypical language representation in the healthy right-handed population is approximately 4–6% [3,11,32–33]. Prior reports of Wada language testing in large patient cohorts have noted rare cases with qualitatively different language abilities in the left and right hemispheres. Following the traditional distinction between “expressive” and “receptive” language abilities, most of these patients have been described as having

interhemispheric dissociation between speech production and comprehension abilities [2,12]. The most common pattern involves arrest of speech output on a variety of tasks (e.g., counting, naming, reading aloud, and repetition) with relatively preserved ability to follow commands after injection of one hemisphere, and the opposite pattern on injection of the other hemisphere. We observed this pattern in only 4 of 490 patients, consistent with two prior reports showing a combined incidence of 6 in over 644 cases [2,12]. Although relatively rare, these patients provide an opportunity to understand factors that influence language reorganization in chronic brain disease.

Our patients showed several notable features that may offer preliminary clues to the presumed reorganization in language functions that occurred. First, all had had seizures for more than 20 years prior to Wada testing (average duration of 28 years). Although epilepsy of long duration is common among patients in surgical programs (the average duration in our entire sample is approximately 20 years), the fact that interhemispheric dissociation of speech production and comprehension networks was not observed in patients with shorter duration epilepsy suggests that it may be more likely in patients with longstanding epilepsy. Second, three of the four patients had seizures begin relatively late in development (ages 9, 14 and 25), suggesting that interhemispheric separation of production and comprehension processes may be more likely to occur after language lateralization has been established in earlier years. Third, the three patients whose language comprehension was represented in the left hemisphere (S1, S2, and S4) were all right-handed and had seizure foci in the left hemisphere. Evidently, the presence of seizures in the temporal lobe resulted in a rightward shift of speech production processes, while language comprehension processes remained in the left hemisphere. In contrast, S3 showed right dominance for language comprehension, was left-handed (with a left-handed father), and had a right hemisphere seizure focus. We speculate that S3 was originally right-dominant for language and, analogous to the other three patients, experienced a shift of speech production processes to the hemisphere opposite from the seizure focus. Thus, interhemispheric dissociation of language functions in all four patients was likely due to a shift of speech production capacities to the hemisphere contralateral to the seizure focus. In contrast, language comprehension processes appear not to have shifted to the hemisphere opposite from the seizure focus, despite many years of recurring seizures.

We can only speculate on possible reasons why speech production capabilities in our patients showed greater capacity for interhemispheric reorganization than comprehension processes. One possibility is that the articulatory skills indexed by speech production tasks emphasize motor, sensory, and motor planning processes that have a relatively symmetric representation in the normal brain [34–39]. Thus, the non-dominant hemisphere may possess an innate ability to support speech production after chronic damage to the dominant hemisphere [4–43]. Another likely factor is the relatively more distributed anatomical representation of brain regions involved in comprehension, which include large regions of the dominant temporal, parietal, and frontal cortex [44], compared to the more focal representation for speech articulation mechanisms in sensorimotor, premotor, and inferior prefrontal cortex [36,45–46]. As a result of this difference, language comprehension processes may be better able to reorganize *intra*hemispherically, whereas damage to the dominant hemisphere articulatory system is, at least in some patients, more easily compensated by a shift of control to the opposite hemisphere. Janszky et al. [47] showed that higher interictal spike frequency is associated with a shift (left to right) of word production ability in temporal lobe epilepsy patients. Votes et al. [43] presented a patient who showed increased fMRI activation in the right inferior frontal gyrus on verbal fluency tasks following a left hemispherectomy. While all our cases suggest shifting of speech production, one of Kurthen et al.'s [12] cases indicates shifting of language comprehension, but not speech production. This patient had a left temporo-parietal seizure focus without evidence of frontal damage and left parieto-occipital hypoperfusion on interictal SPECT. Wada testing suggested better comprehension ability in the right and expressive

speech in the left hemisphere. This patient underwent left anterior two-thirds temporal lobectomy and showed intact language abilities three months after surgery on neuropsychological assessment. Although Kurthen et al. [12] acknowledge that determination of language dissociation in this patient was complicated by persistent perseveration during Wada testing, this case raises the possibility of the shifting of language comprehension by focal epileptic activities in temporoparietal areas.

Interhemispheric dissociation of language capabilities could explain some cases of discordance between Wada and fMRI language lateralization. Using a Wada lateralization index calculated over all language subtests, the Wada and fMRI results were markedly discordant in two of our four patients and moderately discordant in another. Concordance was also poor using a Wada index based on speech production tasks, but was much better overall when using only the comprehension components of the Wada. These results are consistent with a previous report showing that this fMRI protocol gives different lateralization results than a Wada test based only on side of speech arrest [48]. These patterns can be explained by the fact that the fMRI task contrast used here emphasizes speech perception and lexical-semantic retrieval processes and is not designed to activate speech articulation systems.

According to the traditional neuroanatomical view of language, which localizes speech production to Broca's area in the frontal lobe and speech comprehension to Wernicke's area in the temporal lobe, different patterns of lateralization in the frontal and temporal lobes would be predicted in patients with interhemispheric dissociation of these functions. Specifically, fMRI activation in the temporal lobe and other posterior heteromodal regions is predicted to be associated with the hemisphere serving language comprehension in the Wada test. Similarly, frontal lobe activation is expected to correlate with the hemisphere of speech production based on Wada testing. In contrast to these predictions, we observed no differences in lateralization of activation in frontal and temporoparietal ROIs, both of which were similar to the whole hemisphere lateralization pattern. The fMRI task contrast used in the present study activates not only temporal and parietal regions but also frontal regions supporting language comprehension [49]. This result is consistent with a large body of neuroimaging evidence indicating involvement of the prefrontal cortex in a variety of language processes, including lexical-semantic retrieval and selection [44,51–55]. Because the frontal lobe supports a variety of linguistic processes, it is overly simplistic to equate the frontal lobe with speech production. In our patients, the motor control processes necessary for speech production appear to have shifted to the hemisphere contralateral to the seizure focus, while other frontal lobe language processes did not shift away from the seizure focus.

Given its rare occurrence, dissociation of language functions could not explain all cases of discordant Wada and fMRI tests, but it provides a potential explanation for some of these cases. Multiple language tasks assessing comprehension as well as speech articulation might, in combination, yield more concordant results between the Wada test and fMRI mapping. Several groups of researchers have advocated such a "language panel" approach and reported that agreement between the Wada test and fMRI increased when multiple language tasks were incorporated in the fMRI studies [22,56–58]. On the other hand, this improvement in concordance may have occurred simply because the combination of several fMRI data sets enhances statistical power and reliability in areas where overlapping activation occurs across tasks [25]. Other studies have shown that some tasks are better than others for the purpose of determining language lateralization. For example, listening to sentences, single-word reading, and object naming tasks, when compared to resting or passive baseline states, produced lateralization results that were not well correlated with Wada lateralization [17,18,22,58]. Thus, simply combining a number of tasks may be ineffective if these tasks and their controls are not suitably designed to target language processes of interest. In addition to the multiple task approach, multiple neuroimaging modalities, including activation and deactivation methods

such as magnetoencephalography and transcranial magnetic stimulation, might be necessary to optimize the localization of component language functions.

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Figure 1. Concordance and discordance between Wada and fMRI LI indices

LI: Total Wada Lateralization Index

LIc: Wada Lateralization Index – comprehension

LIsp: Wada Lateralization Index – speech production

Figure 2. FMRI activation map for each patient. Symmetric, sequential sagittal slices are shown Activation maps were thresholded at uncorrected $p < 0.001$ and a minimum cluster size of 200 μl to give a whole-brain corrected $p < .05$. The images are presented as sequential sagittal slices from lateral to medial at regular 10-mm intervals. For each patient, the upper row shows left hemisphere sections, and the bottom row shows mirror-symmetric right hemisphere sections.

Table 1

Demographic and epilepsy-related information

Patient	Etiology	Onset of Epilepsy	Epilepsy Duration	Seizure Focus	Dom. Hand	MRI	FSIQ
S1	Idiopathic	9	37	L TLE	R	L HA	116
S2	Idiopathic	Birth	31	Left	R	L HA	80
S3	Encephalitis	25	27	R TLE	L	R Par-Occip	109
S4	Idiopathic	14	20	L TLE	R	Normal	87

Abbreviations: TLE = temporal lobe epilepsy, HA = hippocampal atrophy, Par-Occip = parietal-occipital encephalomalacia, FSIQ = Full Scale IQ. Handedness was determined using the Edinburgh Handedness Inventory (right-handed: laterality quotient > 50) (Oldfield, 1971) [59].

Table 2

Wada and fMRI lateralization indices

Patient	Wada LI	Wada LIc	Wada LIsp	fMRI LI(whole)	fMRI LI(frontal)	fMRI LI (temporo-parietal)	Wada LI- fMRI LI (absolute value)
S1	-16	80	-66	77	84	67	93
S2	10	80	-35	53	56	43	43
S3	49	-100	88	-64	-79	-24	113
S4	-33	80	-70	-19	-21	-40	14

LI: Total Laterality Index

LIc: Laterality Index – comprehension

LIsp: Laterality Index – speech production