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Threshold-independent fMRI determination of language dominance: A validation study against clinical gold-standards

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Abstract

Functional MRI (fMRI) is often used for presurgical language lateralization. The most common approach calculates a laterality index (LI) based on suprathreshold voxels. However, strong dependencies between LI and threshold can diminish the effectiveness of this technique; in this study we investigated an original methodology that is independent of threshold. We compared this threshold-independent method against the common threshold-dependent method in 14 epilepsy patients who underwent Wada testing. In addition, clinical results from electrocortical language mapping and post-operative language findings were used to assess the validity of the fMRI laterality method. The threshold-dependent methodology yielded ambiguous or incongruent lateralization outcomes in 4 of 14 patients in the inferior frontal gyrus (IFG), and in 6 of 14 patients in the supramarginal gyrus (SMG). Conversely, the threshold-independent method yielded unambiguous lateralization in all the patients tested, and demonstrated lateralization outcomes incongruent with clinical standards in 2 of 14 patients in IFG, and in 1 of 14 patients in SMG. This validation study demonstrates that the threshold-dependent LI calculation is prone to significant within-patient variability that could render results unreliable; the threshold-independent method can generate distinct LIs that are more concordant with gold-standard clinical findings.

Keywords

language laterality index (LI); language dominance; presurgical planning; fMRI threshold; Wada test; postsurgical language; noninvasive language

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INTRODUCTION

Brain surgery in regions within or adjacent to essential language areas may result in permanent postsurgical language impairment. Therefore, determining whether the planned resection is in the language dominant hemisphere can aid in risk determination, change the course of treatment, or preclude the surgical intervention entirely. In addition, it has been observed that patients harboring mass lesions or epileptogenic foci have an increased likelihood of atypical language lateralization [1,2]. For these reasons, the determination of language dominance is an important preoperative step that is generally taken for at-risk surgical candidates.

The preoperative clinical standard to determine cerebral language dominance is the intracarotid amytal test, also known as the Wada test [3]. While the Wada test is generally reliable, there are disadvantages to the technique: it is invasive, costly, time-consuming, and carries a risk of stroke [4]. There may also be cerebral vascular perfusion effects, such as cross-filling, that cannot be controlled for and which may confound the Wada results. Moreover, because the anesthetic acts on volumes encompassing both the anterior and posterior language centers, it is not possible to examine how individual cerebral lobes or the cortical structures within them are affected; therefore, no inference can be made about the level of language-specific participation by specific brain structures. This is particularly problematic in patients who may have lesion-induced cerebral reorganization, as in such cases, mixed language dominance may result [5–10]. It would therefore be beneficial if presurgical planning were to reliably assess language laterality with a higher spatial resolution than is feasible by Wada testing alone.

Intra-operative testing using electro-cortical stimulation (ECS) is a method for localizing essential language during resection surgery by application of electrical currents directly on the surface of the cortex in order to induce temporary language deactivation [11,12]. For the purpose of identifying language dominance, positive ECS sites confirm the location of critical language regions within a given hemisphere, although, it cannot exclude other essential language areas outside the tested area or in the opposite hemisphere. ECS testing therefore is also useful for language lateralization; however, the technique is restricted to the region of the craniotomy electrode strip placement and is limited by its invasiveness.

Functional magnetic resonance imaging (fMRI) offers an alternative technique for the assessment of language dominance that is non-invasive, available preoperatively, safer, more cost effective, and provides full-brain coverage at higher spatial resolution than the current clinical standards. While presently fMRI cannot replace the clinical standards, numerous methods are currently under development which aim at improving the reliability of fMRI as a tool for clinical assessment of language dominance [13–16]. In the majority of these techniques fMRI activation asymmetry is used as the determining factor for inferring functional lateralization. The most commonly used method relies on counting activated voxels above a particular statistical threshold cutoff and from this calculating a laterality index (LI) [17–27]. Implicit in the application of this approach is the assumption that the choice of cutoff threshold does not significantly affect the LI outcome. However, it has been shown that LI values have a strong dependency on the statistical threshold that is used [28,29]; this threshold dependency can make the LI procedure prone to subjective manipulation. In a previous report we demonstrated in healthy volunteers that threshold dependencies can lead to highly variable and often ambiguous language lateralization outcomes [16]. Moreover, recent studies have demonstrated that in patients with brain tumors, these threshold dependencies often lead to significantly higher within-patient LI variability than in healthy controls [15]; and similarly, high within-patient variability in language LI have been demonstrated in epilepsy patients [29]. Other than relying on statistical significance, currently there is no a priori method for objectively picking the most appropriate statistical threshold value for use in standard threshold-dependent LI calculations. Furthermore, it is not clear if the statistical threshold

chosen should remain constant, or if it should change, depending upon the task, the fMRI stimulus paradigm, the MRI scanner, or the specific patient.

In the present study, we apply our previously described threshold-independent method [16, 30] for the presurgical determination of language lateralization in 14 clinical cases, and validate the method by way of Wada testing, ECS findings, and postsurgical language outcome. Participating in the study are patients with and without structurally noticeable abnormalities, with and without tumor, one with a prior surgery, and three with atypical language dominance, as determined by the Wada test. The objective of this work is to examine fMRI language laterality using the threshold-independent method and the more common threshold-dependent method, for their comparison against clinical standards.

METHODS

Participants

We enrolled 14 presurgical patients, four females and ten males, with an average age of 41.9 years (SD, 12.7 years). For this study we included all recent Wada tested patients at our institution who also had presurgical fMRI using our custom language mapping paradigm [16]. Of the four female patients, one was left-handed and the other three were right-handed. Two of the male patients were left handed, the other eight were right-handed. Patient handedness was determined by the Edinburgh Handedness Inventory [31]. One patient had a Grade II left anterior temporal lobe ganglioglioma and a history of complex partial seizures (patient ep13). The other thirteen patients were diagnosed with epilepsy, one of whom had prior surgery to remove a low grade left frontal lobe tumor, approximately 16 years prior to this study (patient ep14). Of the fourteen patients studied, ten underwent resection surgery and intra-operative ECS mapping, five of whom demonstrated observable language function alterations in the perioperative period. See Table 1 for patient codes and patient demographics. Written informed consent was obtained from each participant, and the study was approved by the Partners' Institutional Review Board.

FMRI behavioral paradigm

Patients performed a visually presented antonym-generation task with vocalized responses. When presented an antonym cue word, patients were instructed to vocalize a word having the opposite meaning. This behavioral task was selected in an effort to activate all major aspects of language: receptive decoding, expressive encoding, and vocalization. We chose an overt language task as opposed to a covert one in order to improve localization precision, robustness of activation, degree of volumetric involvement by associated functional cortex, and achieve high ECS congruence [32–38]. Stimulus presentation consisted of a rapid, event-related paradigm with a pseudorandom inter-stimulus-interval of 8.5 sec mean duration (SD, 5.1 sec). Antonym cue words were presented for 2 sec each, a fixation point was shown between word presentations. Two versions of this task were used differing only in the total number of trials: initially we presented 50 antonym cue words, resulting in a total acquisition time of 7 min (used with patients ep1, ep2, ep3, and ep4). In order to minimize the scanning time burden on our patients, we later implemented a shorter version of the same paradigm which presented only 35 cue words and resulted in a shortened acquisition time of 5 min, this version was used for all other patients.

Visual stimuli were presented through MRI-compatible video goggles (Resonance Technology, Los Angeles, CA, USA). Stimulus paradigms were controlled by a laptop computer (Dell Inc., Round Rock, TX, USA) running the Presentation software package, version 9.70 (Neurobehavioral Systems Inc., Davis, CA, USA).

Image acquisition

Magnetic resonance images were acquired at 3T using a GE Signa system (General Electric, Milwaukee, WI, USA). Blood-oxygen-dependent (BOLD) functional imaging was performed with a quadrature head coil using echo-planar imaging (EPI) acquired in spatially contiguous and temporally interleaved axial slices.

For patients ep1–ep6, contiguous slices of 5 mm thickness were used. In plane resolution was $3.75 \times 3.75 \text{ mm}^2$; TR = 2 sec; TE = 29 msec; flip angle = 68-degrees; field-of-view = 24 cm; matrix acquisition at 64×64 . These patients received volumetric T1-weighted Magnetization Prepared RAPid Gradient Echo (MPRAGE) acquisition using a quadrature head coil, acquired to provide an anatomic reference frame with 256×256 matrix dimensions. Due to hardware and software upgrades at our institution, these imaging parameters were changed during the course of the study, which spanned approximately 2.5 years. For patients ep7–ep14, contiguous slices of 4 mm thickness were used. In plane resolution was $2 \times 2 \text{ mm}^2$; TR = 2 sec; TE = 40 msec; flip angle = 90-degrees; field-of-view = 25.6 cm; matrix acquisition at 128×128 . These patients received volumetric T1-weighted axial SPoiled Gradient Recalled echo (3D-SPGR) using an eight-channel head coil, with a 256×256 matrix acquisition for the overlay of functional activation maps. No across scanner parameters, or across patient, comparisons are done in this study. To help minimize head motion, foam padding was placed around the head of each patient; strips of tape were adhered across the video goggles and the patient table.

Data analysis

Following functional image reconstruction, motion correction was performed using the SPM2 (Statistical Parametric Mapping) software package (Wellcome Department of Imaging Neuroscience, London, UK). For region-of-interest (ROI) analysis, structural and functional images were initially coregistered, and then spatially normalized into Montreal Neurological Institute (MNI) space. Spatial normalization of both structural and functional volumes was based on normalization of the T1-weighted gray matter segmentation volume as derived by the SPM2 software package. The transformation matrix calculated during normalization of each patient's gray matter, to the standard gray matter brain volume, was then applied to the functional volumes. An 8 mm Gaussian kernel was applied for functional image smoothing. Following slice timing correction, run-specific responses were modeled in an event-related design [40,41] by convolving a series of Dirac's delta function, each representing a stimulus event onset, with the canonical hemodynamic response function (HRF), including standard linear summation effects and time derivatives. Statistical parametric maps based on the T-score correlation between HRF and voxel-by-voxel BOLD signal response were generated for each run and overlaid onto high-resolution patient anatomic images.

Using the Talairach Daemon [42], Human Atlas ROI volumes were identified in MNI normalized anatomies and ROI mask volumes generated using WFU PickAtlas software (Department of Radiologic Sciences, Wake Forest University, Winston-Salem, NC, USA). Coordinate transformations and corrections were done by the WFU PickAtlas software using the methods outlined by Maldjian et al. [43,44] and Lancaster et al. [45,46].

We focused the language lateralization analysis on the two putative language regions, in the inferior frontal gyrus and the supramarginal gyrus. We defined specific ROIs for LI analysis initially by standard Human Atlas segmentations of the inferior frontal gyrus and supramarginal gyrus; we further limited these structural volumes to include only portions which overlapped with cortical functional regions as defined by Brodmann Areas (BA). These volumes were symmetric across the cerebral hemispheres with respect to size, shape, and number of voxels. For the assessment of language-specific laterality, two ROIs were empirically chosen based on across patient consistency in fMRI language lateralizations in healthy subjects [16]:

1. IFG—the portion of the inferior frontal gyrus encompassing BA 44 and 45
2. SMG—the portion of the supramarginal gyrus encompassing BA 40

These ROIs are illustrated in Figure 1 and Figure 2 for patients ep13 and ep14, respectively.

Threshold-dependent LI calculations

Threshold-dependent LIs were evaluated using the standard ratio: $LI = (LH - RH)/(LH + RH)$, where LI represents the laterality index, and LH and RH represent the number of suprathreshold voxels, in the left and right cerebral hemispheres respectively. This formula renders positive LI values for left-dominance and negative values for right-dominance; bilateral activation distributions are defined as LI values between -0.1 and $+0.1$ [23–27].

In order to observe the influence of fMRI threshold on LI, we plotted LI value as a function of threshold over the entire range of positive T-scores (ranging approximately from 0 to 15) [29]. We examined laterality ambiguity using the threshold-dependent method by noting instances in which the LI outcome changed asymmetry determination as a function of threshold. If within the statistically significant range of possible thresholds an LI vs. threshold curve varied between positive values greater than 0.1 and negative values less than -0.1 , language laterality in that patient could potentially be called leftward, bilateral, or rightward, depending on the threshold used. When occurring within the statistically significant threshold range of T-scores denoting $p < 0.05$, (uncorrected, with no cluster analysis) we classified this undesirable behavior in the LI curves as demonstrating ambiguous lateralization outcome.

Threshold-independent LI calculation

Threshold-independent LIs were determined by comparing the integrated T-score weighted distributions of all the positively correlated voxels, between the left and right hemisphere ROIs [16,30]. Initially for each hemisphere, histograms were generated that tabulate the total number of voxels having positive T-scores within the full range (T-score range = $0 - 15$, bin increment = 0.25). These histogram distributions were then multiplied by a weighting function, defined as: $\text{weighting} = (T\text{-score})^2$. After applying this weighting function to each bin, a numerical integration of the areas under the entire weighted distributions was done. Integrated areas were then compared across the left and right cerebral hemispheres by applying the ratio: $LI = (LHA - RHA)/(LHA + RHA)$, where LHA represents the area under the weighted distribution curve for the left hemisphere and RHA represents the area under the weighted distribution curve for the right hemisphere. This formula renders positive LI values for left-dominance and negative values for right-dominance; bilateral activation distributions are defined as LI values between -0.1 and $+0.1$. See Figure 3 for an illustration of this procedure in a representative patient.

Wada testing procedure

Each hemisphere was injected with 112.5 mg sodium amobarbital. Determination of adequate drug effect was based on neurological response (contralateral hemiparesis) and lateralized electroencephalographic (EEG) effect. If the effect was deemed to be inadequate, additional boluses of 25 mg drug were injected until an adequate effect was obtained. Language function under hemispheric anesthesia was tested in a multimodal fashion including appraisal of spontaneous speech in discourse, ability to follow simple praxis commands, orientation questions, visual confrontation naming using items from the Boston Naming Test [47], and repetition of standard words and phrases. Observation of paraphasic errors was regarded as particularly compelling evidence of hemispheric language involvement whereas simple speech arrest, in the absence of other language abnormalities, was considered a non-specific finding. Neuropsychologists blinded to the fMRI results classified language lateralization using results from both hemisphere tests (when available) as exclusively left, predominantly left, bilateral,

predominantly right, or exclusively right—13 of 14 patients had bilateral Wada testing done, except for ep14 who only had the left hemisphere tested.

Comparisons of fMRI laterality and Wada results

Wada test results from all fourteen patients were compared against non-invasive LIs determined using the threshold-independent and threshold-dependent methods. Whenever the threshold-dependent method yielded ambiguous laterality determinations in a particular patient, all the possible outcomes were deliberately included in the comparison to demonstrate lateralization indetermination. If any of these threshold-dependent lateralization outcomes differed from the Wada test findings, they were classified as potentially incongruent. The distinct LIs calculated for each patient by the threshold-independent method were compared against Wada findings. All of these comparisons were independently made for the IFG and SMG regions in each patient.

Additional validations

If any of the patients demonstrated confirmed positive ECS language sites, those mapping results served as compelling evidence that dominant language function resided within the tested region; 10 of 14 patients underwent intra-operative ECS: ep1, ep2, ep4, ep5, ep6, ep7, ep8, ep9, ep10, and ep13. Of the 10 patients tested, 4 demonstrated confirmed positive sites: ep1, ep5, ep6, and ep8.

Based on pre-operative and post-operative neurological exams, patients with any observable language changes were noted. Word finding difficulties, as often reported by patients undergoing temporal lobe resection in the dominant hemisphere, or language improvement, were both considered to corroborate ipsilateral language support; 4 patients were observed to exhibit this type of perioperative language alterations (Table 1).

Experimental weighting functions

In order to evaluate the impact that weighting functions have on the resulting threshold-independent LI values, we compared alternative weightings. We chose five basic mathematical functions, and focused the analysis exclusively on IFG activation in all 14 patients. The five weighting functions tested are defined as:

1. Linear (T-score).
2. Quadratic (T-score²)
3. Cubic (T-score³)
4. Fourth power (T-score⁴)
5. Exponential (e^{T-score})

Using each of these functions separately, we calculated the average LI value in our patient group and performed a repeated-measure ANOVA on these means in order to detect any significant changes of that would depend on the weighting used. Statistical analysis was done using SPSS for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

FMRI activation patterns

All patients demonstrated robust bilateral activations consistent with vocalization-specific motor activation in superior precentral gyri and midline supplementary motor cortices (threshold for visualization of activation patterns set at $p < 10^{-4}$, uncorrected). All patients also

demonstrated robust sensory-specific activations bilaterally in middle occipital gyri. Local activation maxima were seen for all patients in language-specific ROIs, IFG and SMG.

IFG lateralization

Threshold-dependent results—Using the threshold-dependent method we calculated LI over the full range of positive thresholds and generated curves of IFG LI vs. threshold for each patient (Figure 4). These curves were examined to evaluate the degree of within-patient variability in LI values. Ambiguous lateralization outcomes of IFG were noticed in 4 of 14 patients. IFG lateralization outcomes that alternated between leftward, bilateral, and rightward asymmetry were observed in patient ep2. IFG outcomes that alternated between bilaterality and rightward asymmetry were observed in patient ep12; outcomes that alternated between bilaterality and leftward asymmetry were observed in 2 patients, ep3 and ep5. Nine patients consistently demonstrated left lateralization of IFG: ep1, ep4, ep6, ep7, ep8, ep9, ep10, ep11, and ep13. Patient ep14 consistently demonstrated right lateralization of IFG.

Threshold-independent results—Distinct IFG LIs by the threshold-independent method were calculated for each patient and plotted in Figure 4. Left lateralization of IFG was observed in 11 of 14 patients: ep1, ep3, ep4, ep5, ep6, ep7, ep8, ep9, ep10, ep11, and ep13. Two patients yielded a bilateral IFG outcome, ep2 and ep12. Patient ep14 demonstrated right lateralization of IFG.

SMG lateralization

Threshold-dependent results—Curves of SMG LI vs. threshold were assessed for degree of within-patient variability (Figure 5). Ambiguous SMG lateralization was noticed in 4 of 14 patients. SMG Lateralization outcomes that alternated between leftward, bilateral, and rightward asymmetry were observed in two patients, ep2 and ep3; outcomes that alternated between bilaterality and leftward asymmetry were observed in two patients, ep10 and ep13. Ten patients consistently demonstrated left lateralization of SMG: ep1, ep4, ep5, ep6, ep7, ep8, ep9, ep11, ep12, and ep14.

Threshold-independent results—Threshold-independent LIs revealed left lateralization of SMG in 12 of 14 patients: ep1, ep4, ep5, ep6, ep7, ep8, ep9, ep10, ep11, ep12, ep13 and ep14 (Figure 5). Patient ep2 demonstrated right lateralization of SMG; patient ep3 yielded a bilateral outcome.

Comparison of LIs with Wada, ECS, and postsurgical findings

IFG lateralization—Threshold-dependent IFG LIs yielded lateralization outcomes that were potentially incongruent with Wada results in 4 of 14 patients. Threshold-independent lateralization outcomes were incongruent with Wada results in 2 of 14 patients. Positive ECS sites were confirmed within or in close proximity to left IFG of patients ep6 and ep8, confirming congruency with the lateralizations that were determined by the threshold-dependent and threshold-independent methods for both patients. No patients in the series underwent surgical resections within the frontal lobes, therefore, no postsurgical data are available for IFG. Comparisons of fMRI-derived IFG lateralization with Wada findings, and ECS testing outcomes are summarized in Table 2.

SMG lateralization—Threshold-dependent SMG LIs yielded lateralization outcomes that were potentially incongruent with Wada findings in 6 of 14 patients. Threshold-independent lateralization outcomes were incongruent with the Wada results in 1 of 14 patients. Positive ECS sites were found within or in close proximity to left SMG of patients ep1, ep5, and ep8, confirming the lateralizations that were determined by the threshold-dependent and threshold-

independent methods in these three patients. Perioperative language function changes after temporal lobectomy in the dominant hemisphere was observed in patients ep4, ep5, ep6, ep8, and ep13 (patient ep13 demonstrated improved language function). Postsurgical findings confirmed the SMG LIs determined by the threshold-dependent and threshold-independent methods in patients ep4, ep5, ep6, and ep8; perioperative language findings of patient ep13 supported leftward lateralization determined by the threshold-independent method. Comparisons for fMRI-derived SMG lateralization against Wada test, ECS, and postsurgical language results are summarized in Table 3.

Influence of weighting function

We noted no significant difference in the average threshold-independent IFG LI values measured in our patient group when any of the high-order weighting functions were tested—quadratic, cubic, fourth power, or exponential; the lateralization classification remained unchanged in 13 of 14 patients for all of these weighting functions, patient ep2's classification changed from bilateral to rightward when exponential weighting was used.

ANOVA findings demonstrated no significant difference in mean LI values derived by all of the weighting functions we tested: $F = 0.34$, and $p = 0.80$. However, paired t-test on the mean LI values determined using linear weighting and mean LI determined using all of the higher order weighting functions revealed a significant difference: $t = -3.08$, $p = 0.004$ (one-tail), or $p = 0.009$ (two-tail), indicating less asymmetric LIs were determined for linear weighting compared to the higher order functions.

DISCUSSION

In prior studies we introduced a novel method for assessment of functional LI that is applied without the necessity of an fMRI statistical threshold. We have previously demonstrated this technique to be effective for the lateralization of memory function in both healthy subjects and presurgical patients [30], and for language function in healthy volunteers [16]. The main objective of the present work was to validate our methodology for the lateralization of language by direct comparison against clinical gold-standards in surgical patients. We performed a comparative analysis exploring a variety of weighting functions and found that all of the high-order weighting functions we tested resulted in no significant changes to the average LI values of our patient group, however, linear weighting on average resulted in less asymmetric LIs. We illustrated in our patient population that using the common threshold-dependent method to determine language laterality can lead to LI values that are unstable as they depend upon the statistical threshold used, confirming similar observations previously reported by others [29,39,48,49,50].

Using the threshold-independent method we observed concurrence with Wada test results in 12 of 14 patients in the IFG region, and in 13 of 14 patients in the SMG region. However, a completely parallel assessment of Wada test congruency by the threshold-dependent method was complicated by the indistinctness we observed in the lateralization outcomes. For example, when evaluating IFG LI we observed indistinct lateralization in 4 of 14 patients, similar uncertainty was observed for SMG in which 4 of 14 patients yielded indistinct outcomes. Therefore, while the threshold-dependent analysis shown in Table 2 and Table 3 often included LIs that were congruent with a particular patient's Wada result, they also included incongruent outcomes. The difficulty in resolving these ambiguities arises from having no clear methodology for uniquely selecting a statistically significant threshold, or spectrum of thresholds. Therefore, since multiple LI results were possible in a given patient, we included all of them in order to demonstrate the concern.

In a recent article Wilke et al., (2007) reported their development of a software toolbox that provides users choices from a battery of previously described LI methodologies [39]. While these authors do not recommend a specific methodology in order to address the thresholding issue, the proposed toolbox provides investigators with a more informed decision which can be subjectively reevaluated on a case-by-case basis. In this work, the authors present a comprehensive discussion that outlines the major issues currently involved in the determination of LI, including: voxel score versus suprathreshold voxel count, LI dependence on threshold, data exclusion and sparsity, and influence of LI outcome by outliers.

Alternative lateralization approaches

Strategies to determine functional lateralization have been proposed that do not rely directly on activation threshold. Such strategies have instead either evaluated specific characteristics of the fMRI signal, or assessed asymmetries in task-induced mean signal changes [48,51], or mean signal intensities [52]. However, relying on average quantities for lateralization assessment invariably requires voxel sampling schemes for the calculation of the means. Benson et al. (1999) sampled every voxel in the left and right cerebral hemispheres, selecting for laterality assessment only those voxels with task-induced correlations above a certain threshold [51]. This methodology therefore requires the use of a cutoff threshold, and has a potential of assigning equal importance to voxels that may only weakly participate in the language-specific aspects of the task—as opposed to sensory- or motor-specific participation similarly elicited by the task. Adcock et al. (2003) sampled only the signal fluctuations from voxels deemed significantly activated, and having achieved a given cluster significance, therefore relying on somewhat arbitrary thresholds [48]. Similarly, Baciú et al. (2005) calculated mean signal intensities based exclusively on voxels achieving a threshold activation of $p < 0.05$ [52]. Generally, it can be reasoned that if an optimal cutoff threshold exists for a given task, it will likely vary depending upon numerous fMRI variables. For instance, the number of activated voxels that characterize most LI approaches has been shown to be strikingly unstable across subjects, acquisition trials, and MR scanners [53].

Voxel value versus voxel count, outliers, and data sparsity

The advantage of using a standard suprathreshold voxel count as the determining factor for LI is in transforming the voxel inclusion criteria into a binary decision based exclusively on exceeding the threshold; since actual voxel values are not entered into the calculation, this procedure makes the LI resistant to statistical outliers. However subsequent to voxel selection, this technique disregards the correlation intensity of the surviving voxels, and therefore neglects relative voxel strength—for example, an LI value indicating symmetry could be generated from an equal number of activated voxels in each hemisphere even if one hemisphere's voxels are more highly correlated than the other [50]. An alternative approach instead uses voxel T-score sums as the measure for LI calculations [54,55]. However, such summing schemes render the LI outcome particularly susceptible to artifactual influence by statistical outliers [50]. Our proposed methodology simultaneously addresses these two issues by sorting voxel values into a T-score histogram and weighting the resulting frequency distributions by statistical correlation—accordingly, making the LI calculation resistant to outliers while still taking the voxel correlation strength into account.

In addition to the issues that result from LI threshold-dependency, which include the indeterminacy of LI outcome, within subject variability, and threshold choice subjectivity, calculating LIs based exclusively on a suprathreshold voxel count invariably leads to data exclusion. For example, in an effort to increase LI magnitude there may be a tendency to apply increasingly conservative thresholds (see Figure 4 and Figure 5); however, stricter thresholds invariably exclude more data. As such, the use of excessively strict thresholds could potentially determine an LI based on only a few surviving voxels, rendering the outcome biologically and

computationally less plausible [39]. By using the entire positively correlated voxel distribution without thresholding, our proposed method calculates LI without excluding any correlated voxels, effectively addressing the issue of data sparsity that is encountered by standard threshold-based methods.

Whole voxel distributions in LI assessment

Perhaps the earliest attempt to extract language LIs from activation score distributions was carried out by Nagata et al. (2001) [49]. In this work, it was found that an empirically-derived reference function was highly correlated with the number of activated voxels above each Z-score histogram bin, and therefore useful as a basis for comparing ROIs across the left and right hemispheres. One of the drawbacks to this approach, however, lies in the need for an empirically derived reference function. In order to make such a procedure more universally applicable, the reference function chosen would need to be independently validated for specific clinical cases, different tasks, different ROIs, and alternative paradigms. By contrast, the method we recommend does not rely on fitting data to estimated curves, being concerned only with comparing weighted voxel distributions from both sides of the brain. Nevertheless, Nagata et al. were able to demonstrate that calculating the LIs based on voxel distributions is a reasonable approach to produce more robust and consistent lateralizations, as the outcome does not vary with any threshold, and therefore is less variable across multiple trials [49]. These are important characteristics for applications in clinical decision-making.

Potential for resolving atypical lateralization

Atypical language dominance in lesion patients presents important challenges for the validation of fMRI lateralization methods. The incidence of atypical dominance is quite low in the healthy population (4–6%); however, it is known to be significantly higher in lesion patients suffering from long-term seizures or structural lesions (10–53%) [20,25]. This implies that the higher incidence of atypical dominance seen in patients results from lesion-induced reorganization of language functions over long periods of time [5–10]. It has been suggested that frontal language function is more likely to migrate to the contralateral hemisphere following long-term insult [25,58], although, analogous migration of temporoparietal language has also been documented [25,59]. The higher incidence of mixed dominance seen in atypically dominant patients implies that reorganization does not necessarily need to include both language centers of the brain, but may instead exclusively involve the affected region. This presents a specific challenge to validation studies that rely on comparing ROI lateralization methods against whole-hemispheric evaluations such as Wada testing. Lesion-induced mixed language dominance cannot be conclusively ruled out by standard methods; therefore in such cases, accurate identification by non-invasive, region-specific methodologies could appear incorrect or discordant with the gold-standard.

Although in our study the threshold-independent method yielded non-ambiguous lateralization outcomes that agreed with the Wada test results in more patients than the threshold-dependent method, there were three cases in which the results were at variance with Wada findings. We note however that most of these discrepancies can be interpreted in the context of mixed language laterality, specifically in patients ep2 and ep12. This interpretation is supported by the finding that fMRI-determined lateralization by our proposed methods was found to differ between the IFG and SMG regions, and by the existence of long-term seizures in both of these patients—ep2 in left temporal lobe for over 20 years, and ep12 in right temporoparietal since early childhood—allowing for the possibility of lesion-induced reorganization of language in both of these cases.

Patient ep2 was found right language dominant by Wada testing, while threshold-independent LIs showed bilateral language in IFG and right lateralized language in SMG, and consequently

was classified as having an incongruent lateralization of IFG, but congruent lateralization of SMG (Table 2 and Table 3). This case however raises the possibility that an epileptic lesion in the left temporal lobe may have induced reorganization of temporoparietal language function towards the right hemisphere more robustly than in the frontal region, as has been previously documented in other epilepsy patients [59].

Threshold-independent LI results observed in patient ep12—bilateral IFG, congruent with Wada findings, and incongruent left-lateralized SMG—can similarly be interpreted in the context of mixed laterality [6,9,10]. It is plausible that ep12's, who is a strong left-hander, may have begun as right-dominant for language, however, following a longstanding epileptic lesion in right temporoparietal regions reorganized SMG processing to the left hemisphere more completely than for the IFG regions. The Wada test findings in this patient, predominantly right-sided language function with some left hemisphere support, may support this hypothesis.

Other studies have evaluated atypical language laterality using threshold-dependent fMRI for LI calculation and using similar ROIs as were used in our study. Benke et al., (2006) noted incongruencies in 2 of 6 Wada-determined right-dominant cases [60]. While these results may suggest a higher success rate in identifying right-dominant language than our proposed approach, we note that of these 6 cases, only 2 demonstrated different fMRI lateralization outcomes between the two ROIs—implying that mixed language dominance can be suspected in perhaps only 2 of the cases. As such, a different interpretation of the results could therefore imply incongruency in 2 out of 2 cases with suspected mixed language. Rutten et al., (2002) noted incongruency in only 1 out of 3 Wada-determined right-dominant cases; we note however that none of these 3 cases demonstrated different fMRI lateralization outcomes between the two ROIs (implying low suspicion of mixed dominance) [61]. Conversely, Lee et al., (2008) specifically targeted patients with mixed language dominance and noted incongruencies in 3 of 4 cases when the comparison was done against a standard Wada test [25].

Based on prior literature and the findings of our study, we note that validation of our proposed methodology in cases of suspected mixed language dominance would require region-specific, dominance determination as ascertained by bilateral electrocortical stimulation testing or by surgical findings. In the absence of these data in our atypical patients, we must conclude that this represents an important limitation of our study that needs to be addressed in future research, including a higher number of right-dominant cases than are presented here. However the results presented provide preliminary evidence that the threshold-independent approach can serve as an important adjunct to help interpret atypical Wada findings, especially for the purpose of surgical-planning in these patients.

Limitations

While the threshold-independent LI method effectively eliminates the arbitrariness of threshold setting and lateralization ambiguity, it nonetheless introduces a degree of subjectivity with regards to the selection of the weighting function. Our weighting scheme is designed to reduce the contributions to LI from voxels with low T-scores, while more heavily emphasizing the contributions from voxels that are more robustly scored. Given that large volumes tend to inadvertently include many weakly scored voxels, we chose the quadratic weighting function for the relatively large ROIs necessary in language assessment, as opposed to a more straightforward linear weighting. This was noted in our exploration of five different weighting functions as we observed significantly less asymmetric LIs when using linear weighting. Our results additionally demonstrated that higher order weighting functions result in average LI outcomes that do not differ significantly from those derived using T-score² weighting. Although encouraging, this comparative analysis explored five simple mathematical functions which did not take into consideration complex issues such as biological factors, the behavioral task used, the cerebral region of interest, or the clinical pathology of the given patients,

therefore, it is not clear if more complex weighting functions may be more appropriate. These issues pose important questions regarding the choice of weighting function that necessitate further study.

In our study we held whole-hemispheric Wada testing results as ground-truth, however, the non-invasive fMRI LIs used in the comparison were determined exclusively in the IFG and SMG regions, not whole hemispheres. The ROIs chosen are useful for excluding non-language-specific bilateral activation and focusing the analysis on clinically-relevant sites, they also allow assessment of mixed laterality, and similar ROIs have been used by others [23,25,29, 39,48,50,56,57]. Nevertheless while of important clinical utility, the use of different ROIs makes the validation procedure complex and renders comparison against whole-brain Wada testing more difficult to interpret.

CONCLUSIONS

This validation study illustrates that the most common method for fMRI determination of language lateralization—choosing a threshold based on statistical significance and calculating a suprathreshold-based voxel count—is prone to significant within-patient variability. This indeterminacy often renders the fMRI lateralization outcome ambiguous, or even erroneous, and can ultimately reduce its reliability in the clinic. The threshold-independent method we recommend generates a single, unambiguous lateralization, is free of subjective statistical threshold cutoffs, has been shown to generate lateralization outcomes that are stable across a variety of weighting functions, can be applied with most BOLD fMRI activation paradigms (such as event-related or boxcar designs), and yields outcomes with high congruency to gold-standards. As such, the methods recommend here hold promise for increasing the ease and reliability of fMRI-based language dominance evaluation in clinical settings.

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The authors would like to dedicate this article in loving memory of our respected colleague and dear friend, Dr. Edward Bromfield

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Figure 1.

T1-weighted structural images for patient ep13, note lesion (Grade II ganglioglioma) in the left anterior temporal lobe. *Left panel:* structural MRI scan showing the patient anatomy before spatial normalization. *Right panel:* the same patient anatomy after spatial normalization into standard coordinates; white regions illustrate location of the frontal (IFG) region-of-interest (*top*), and the supramarginal (SMG) region (*bottom*).

Figure 2.

T1-weighted structural images for patient ep14, note large postsurgical lesion encompassing the left frontal lobe region. *Left panel:* structural MRI scan showing the patient anatomy before spatial normalization. *Right panel:* the same patient anatomy after spatial normalization into standard coordinates; white regions illustrate location of the frontal (IFG) region-of-interest (*top*), and the supramarginal (SMG) region (*bottom*).

Figure 3.

A graphical illustration of the threshold-independent method used for laterality index (LI) calculation in the frontal region (IFG) of patient ep3. *Top panel:* the un-weighted histograms representing voxel frequency at each T-score bin (increment = 0.25) for the left and right inferior frontal gyri. *Middle panel:* the weighting function applied to the un-weighted voxel histograms. *Lower panel:* the resulting weighted distributions. LH indicates the left hemisphere and RH indicates the right hemisphere. Laterality indices were calculated by comparing the integrated areas, LHA and RHA, underneath the resulting distribution curves after weighting. This patient demonstrated activation asymmetry favoring the left IFG (LI = 0.41).

Figure 4.

Comparison of frontal (IFG) language lateralization using the threshold-dependent and threshold-independent methods. Gray data markers represent the three patients with atypical Wada results (ep2, ep3, and ep12). Positive laterality indices (LIs) indicate left lateralization, negative LIs indicate right lateralization; values of magnitudes lower than 0.1 indicate bilateral activation. *Left panel:* LI as a function of threshold using the threshold-dependent method; shown are the curves for each of the 14 patients. The region of the graph outlined by a gray vertical bar represents the range of thresholds that are not statistically significant ($p > 0.05$). The LI values bounded by a gray horizontal bar represent bilateral outcomes. *Right panel:* Threshold-independent LIs of each patient.

Figure 5.

Comparison of supramarginal (SMG) language lateralization using the threshold-dependent and threshold-independent methods. Gray data markers represent the three patients with atypical Wada results (ep2, ep3, and ep12). Positive laterality indices (LIs) indicate left lateralization, negative LIs indicate right lateralization; values with magnitudes lower than 0.1 indicate bilateral activation. *Left panel:* LI as a function of threshold using the threshold-dependent method. The region of the graph outlined by a gray vertical bar represents the range of thresholds that are not statistically significant ($p > 0.05$). The LI values bounded by a gray horizontal bar represent bilateral outcomes. *Right panel:* Threshold-independent LIs of each patient.

Table 1

Patient identification codes, demographics, and clinical characteristics.

Patient ID	Age (yrs)	Sex	Handedness (EHI Score)	Etiology	Presurgical WFD	Postsurgical WFD
ep1	39	M	R (+90)	left temporal lobe epilepsy	-	-
ep2	51	M	R (+70)	left temporal lobe epilepsy	-	-
ep3	49	F	L (-85)	left temporal lobe epilepsy	-	n/a
ep4	27	M	R (+95)	left temporal lobe epilepsy	-	+
ep5	42	M	L (-90)	left temporal lobe epilepsy	-	+
ep6	68	F	R (+100)	left temporal lobe epilepsy	-	+
ep7	50	F	R (+100)	right temporal lobe epilepsy	-	-
ep8	23	F	R (+95)	left temporal lobe epilepsy	-	+
ep9	31	M	R (+60)	right temporal lobe epilepsy	-	-
ep10	34	M	R (+100)	left temporal lobe epilepsy	-	-
ep11	39	M	R (+100)	right frontotemporal lobe epilepsy	-	n/a
ep12	31	M	L (-100)	right temporoparietal epilepsy	-	n/a
ep13	43	M	R (+65)	epilepsy, left temporal lobe ganglioglioma, Grade II	+	-
ep14	60	M	R (+100)	epilepsy, left frontal lobe surgery 16 years prior	-	n/a

EHI Score--Edinburgh Handedness Inventory score; WFD--word finding difficulties; n/a--surgery was not yet performed by the time of this study.

Table 2

Comparison of patient Wada findings, positive ECS sites, and postsurgical language observations, against frontal (IFG) language lateralization as determined using the threshold-dependent and threshold-independent methodologies.*denotes patients with atypical language lateralization by Wada testing (those not exclusively left-dominant); underlined entries denote instances in which fMRI-derived language laterality was classified as incongruent with that patient's clinical standards

Patient ID	Wada Result	ECS	post-surgery	Threshold-dependent LI (all possible outcomes)	Threshold-Independent LI
ep1	exclusively left	-	-	leftward	leftward
ep2*	exclusively right	-	-	leftward, bilateral, rightward	bilateral
ep3*	predominantly left w/ right support	-	-	leftward, bilateral	leftward
ep4	exclusively left	-	-	leftward	leftward
ep5	exclusively left	-	-	leftward, bilateral	leftward
ep6	exclusively left	left	-	leftward	leftward
ep7	exclusively left	-	-	leftward	leftward
ep8	exclusively left	left	-	leftward	leftward
ep9	exclusively left	-	-	leftward	leftward
ep10	exclusively left	-	-	leftward	leftward
ep11	exclusively left	-	-	leftward	leftward
ep12*	predominantly right w/ left support	-	-	leftward	leftward
ep13	exclusively left	-	-	bilateral, rightward	bilateral
ep14	eft predominantly left (right not tested)	-	-	leftward	leftward
				rightward	rightward
cases potentially incongruent with clinical standards:				4	2

Table 3

Comparison of patient Wada findings, positive ECS sites, and postsurgical language observations, against supramarginal (SMG) language lateralization as determined using the threshold-dependent and threshold-independent methodologies.*denotes patients with atypical language lateralization by Wada testing (those not exclusively left-dominant); listed under post-surgery are regions in which resection surgery resulted in perioperative language function alterations in patient; underlined entries denote instances in which fMRI-derived language laterality was classified as incongruent with that patient's clinical standards

Patient ID	Wada Result	ECS	post-surgery	Threshold-dependent LI (all possible outcomes)	Threshold-Independent LI
ep1	exclusively left	left	-	leftward	leftward
ep2*	exclusively right	-	-	leftward, bilateral, rightward	rightward
ep3*	predominantly left w/ right support	-	-	leftward, bilateral, rightward	bilateral
ep4	exclusively left	-	left	leftward	leftward
ep5	exclusively left	left	left	leftward	leftward
ep6	exclusively left	-	left	leftward	leftward
ep7	exclusively left	-	-	leftward	leftward
ep8	exclusively left	left	left	leftward	leftward
ep9	exclusively left	-	-	leftward	leftward
ep10	exclusively left	-	-	leftward, bilateral	leftward
ep11	exclusively left	-	-	leftward	leftward
ep12*	predominantly right w/ left support	-	-	leftward	leftward
ep13	exclusively left	-	left	leftward, bilateral	leftward
ep14	left predominantly left (right not tested)	-	-	leftward	leftward
cases potentially incongruent with clinical standards:				6	1