Accuracy of Resting Functional MRI for Language Lateralization in Temporal Lobe Epilepsy

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BRIEF. Method development for language lateralization using resting-state fMRI scans in temporal lobe epilepsy patients.

ABSTRACT. For a third of patients with temporal lobe epilepsy (TLE), medication is an ineffective treatment, and surgery is the only option to reduce or eliminate seizures. Surgical intervention may interfere with nearby regions of the brain, including regions associated with language use. Determining language hemispheric dominance through language lateralization is required to predict damage to these areas. Currently, task-based functional magnetic resonance imaging (fMRI) is the non-invasive standard. However, the tasks introduce error through patient noncompliance. By applying resting state functional connectivity, fMRI scans can be conducted without a task; however, there is currently no standard to use resting scans to replace task scans. Two methods were developed in this research to determine language lateralization using resting-based scans. Task- and resting-based methods were compared using a lateralization index, which quantifies right and left side dominance. No significant linear relationships were established between the developed rest-based methods and the task-based standard. However, the percentage chance for the rest methods to falsely predict language dominance was under 15% for patients and controls. While the methods here are not clinically applicable, this work provides the foundation for future development of resting-state methods.

INTRODUCTION.

Epilepsy is a neurological condition associated with otherwise unexplainable seizures. The most common form is temporal lobe epilepsy (TLE), as 60% of patients have seizures that originate in the temporal lobe [1]. Treatment for this condition begins with anti-epileptic medications; however, in one third of patients this is ineffective [2]. Surgical intervention, typically involving the removal of the origin of seizures, is used to reduce or eliminate seizures [3]. Surgery requires the localization and/or lateralization of important brain functions to prevent damage to these areas and preserve functioning. For presurgical TLE patients, it is crucial to identify the language network in the temporal lobe to establish language hemispheric dominance. The results of lateralization inform both the surgeon and patient of the risk to benefit ratio for surgery. It will affect both party's decision of whether to perform surgery at all, or just a limited resection to avoid language areas, despite the fact that the chance for seizure remission is lessened. Epilepsy patients have previously shown atypical language organization compared to the general population, which further emphasizes the need for lateralization [4]. The intracarotid amobarbital procedure (IAP) is commonly conducted on patients to determine the lateralization of language function; however, this method is invasive and may not be reproducible. Functional magnetic resonance imaging (fMRI) is currently being implemented clinically and in research to replace IAPs and their aforementioned limitations [5].

In an fMRI scan, the blood oxygen-level dependent (BOLD) signals are acquired during the performance of a task in a block format [6]. The signal from each voxel of an image is then correlated with a block-design paradigm to produce a parametric map of activated regions. A more active voxel will follow the paradigm more closely than a less active voxel. Most tasks require concentration and effort from subjects. Failure to adequately perform a task may skew the results of the fMRI. Therefore, any conclusions made about the activation level are potentially invalid.

In the past two decades, resting-based scans have become prominent in research. Resting-based scans provide an alternative to the limitations of task-based fMRI by eliminating the need for a task altogether. Spontaneous low-frequency oscillations (~0.01-0.1 Hz) of blood oxygenation detected in the BOLD signal from a "resting" brain have been shown to significantly correlate be-tween regions with similar functions [7, 8]. Instead of using a task paradigm, a time series from a region of interest (seed region) is compared with every voxel in a subject's brain, to find regions with similar functions. There is currently no standard to replace task fMRI with resting-state fMRI for localization of function. The goal of this research was to develop and evaluate methods to lateralize language in TLE patients using resting fMRI data.

MATERIALS AND METHODS.

Subjects.

Twenty-one unilateral TLE patients were recruited (2 left handed, 7 left TLE, 14 right TLE, 10F/11M, age = 38.2 ± 14.3 years). Inclusion criteria were standard presurgical evaluation diagnosis of unilateral TLE based on structural imaging with MRI, ictal and interictal EEG, analysis of seizure semiology, and functional imaging with positron emission tomography (PET). Exclusion criteria included structural abnormalities other than hippocampal sclerosis. In addition, healthy controls (4 left handed, 19F/14M, age = 39.5 ± 13.8 years) with no history of head trauma or neurological or neuropsychological disease were also enrolled.

MR Image Acquisition.

The imaging was performed with a Philips Achieva 3T MRI scanner (Philips Healthcare, Best, Netherlands). The MRI protocol during the language tasks was as follows: fMRI BOLD imaging (matrix = 80 x 80 voxels, field of view = 240 mm, 30 axial slices, temporal resolution = 2 sec, slice thickness = 3.5 mm/ 0.5 mm gap, 100 volumes, 200 seconds). The same MRI protocol was used to acquire images at rest with eyes closed, with 300 volumes over 600 seconds. Informed consent was obtained prior to scanning each subject per Vanderbilt University Institutional Review Board guidelines.

Laterality Index Calculation.

To be able to efficiently compare the lateralization of language between resting scans and task scans we used the laterality index (LI) (Equation 1.),

$$LI=\frac{L-R}{L+R} \quad \textbf{(1)}$$

where L and R are the numbers of voxels in the left and right hemispheric regions above a certain activation level, respectively. The LI result is a number between -1 and 1. An LI less than -0.2 indicates right dominance, one above 0.2 indicates left dominance, and between -0.2 to 0.2 may indicate bilaterality [11].

The LIs from task-based and resting-based scans are assumed to follow a linear relationship. A significant correlation would confirm that the resting laterality value can predict the task laterality value, and therefore become an accurate replacement. In this work, two novel methods using resting-state fMRI to lateralize language were evaluated.

fMRI Task-Based Analysis.

To map the regions of the brain that are activated during language, task-based fMRI scans were conducted. Two tasks were used, category word generation (CWG) and reading descriptions of nouns (READ) [10, 11]. Word generation targets Broca's area, which is responsible for speech production, and the reading task activates Wernicke's area, responsible for the comprehension of speech and language.

One activation map is produced for each task scan for each subject. For each map, masks for Broca's and Wernicke's area are used to identify each region separately. The numbers of voxels above a threshold in both the left and right hemispheres of a certain region can be computed. From these values the laterality indices (LIs) are calculated, based on Equation 1, using a bootstrap thresholding method employed by an adapted version of the LI toolbox [12]. The bootstrap method computes an automatic threshold for the LI equation. The LI toolbox produced four LI values for each subject when used with task data: one for each region for each task scan.

fMRI Resting-State Analysis.

Two novel methods to determine language laterality from resting-state fMRI scans were developed and implemented. The methods (Supplemental Figure 1) are as follows:

A. Fisher Z (zLI): The average time series from the two ROIs were correlated. Coefficient values were associated with the "L" and "R" of the LI equation, and the resulting number was the LI value for that subject. For this method, the L value was the correlation coefficient between the averaged time series in BRO(Left) and WER(L), while the R value was BRO(Right) and WER(R). Correlation values were converted to a Fisher Z-statistic to ensure normal distribution [13], and one LI value per subject was computed.

B. SMA as a seed region (SMA LI): Instead of using correlation coefficients, this method involved computing parametric maps, similar to maps produced from the original task method. A single parametric map was made for each subject by using the SMA as a seed region, instead of a comparison with the task paradigm. The map was produced with the bootstrap threshold method with the same LI toolbox used in the task method. Two LI values were produced per subject, one for each Broca's and Wernicke's area, and are referred to as "rest BRO" and "rest WER." As the most robust task LI was determined to be for Wernicke's area, the LI value for rest WER was used when comparing task LI to the rest SMA LI method.

RESULTS.

Regions of Interest (ROIs).

The regions studied here were Broca's area (BRO), Wernicke's area (WER), and the Supplementary Motor Area (SMA). Both Broca's and Wernicke's area contribute to the language network, while the SMA activates along with language activation. The reading fMRI scan of 25 controls of this study indicates the areas of the three ROIs (Figure 1A). Regions masks, which were used to discern the ROIs, were taken from a brain imaging atlas in FreeSurfer [14]. The subject's brain was co-registered to the atlas and the regions were then identified (Figure 1B).

Task LI.

The task LIs were compared for each region as shown in Figure 2. The significance of the correlations was calculated and was the deciding factor in determining the most robust task LI value. In controls, the comparison between READ/WER and CWG/BRO) yielded a significant correlation [$r = 0.52$, $p < 0.01$], however the comparison between READ/WER and READ/BRO did not [$p > 0.01$] (Figure 2A). For patients, the comparison between READ/WER and CWG/BRO did not produce a significant correlation [$p > 0.01$], however the comparison between READ/WER and READ/BRO (Figure 2D) did [$r = 0.82$, $p < 0.01$] (Figure 2B). Across subjects, all correlations using the LI values for CWG/WER were not significant [$P > 0.01$] (Figure 2).

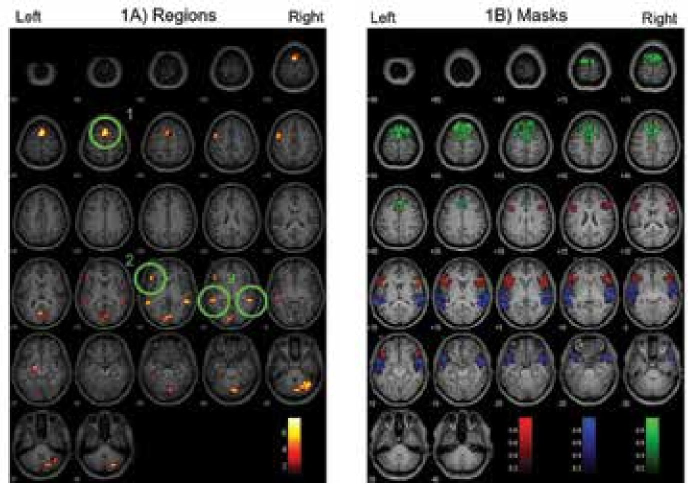

Figure 1. A) Composite activation map image of 25 healthy controls from the reading task. $P < 0.0001$, cluster size 10. ROIs are circled: 1) Supplementary motor area 2) Broca's area, in the frontal lobe. 3) Wernicke's area, in the temporal lobe. B) shows the masks used for the ROIs. The red mask fits Broca's area, the blue fits Wernicke's, and green the SMA.

A) Controls Task LIs		
	READ/WER	CWG/WER
READ/BRO	p < 0.01	p < 0.01
CWG/BRO	p > 0.01 r = 0.52	p < 0.01

B) Patients Task LIs		
	READ/WER	CWG/WER
READ/BRO	p > 0.01 r = 0.82	p < 0.01
CWG/BRO	p < 0.01	p < 0.01

Figure 2. Results from the comparison between task LIs A) In controls, READ/WER was significantly linearly correlated with CWG/BRO [$r = 0.52$, $P < 0.01$]. No other comparisons across task LIs were significant [$p > 0.01$]. B) In patients, READ/BRO and READ/WER were significantly correlated [$r = 0.82$, $p < 0.01$]. No other comparisons across task LIs were significant [$p > 0.01$].

The correlations for controls and patients were observed to determine the most robust set of task LI values. The values for READ/WER persisted in two significant correlations across all subjects, and were thus chosen as the most robust. Therefore, they were compared to the two resting LI values.

Rest LI.

The two resting methods, zLI and SMA LI, were used to produce LI values for subjects. The resulting values were individually compared against the most robust task LI, READ/WER. These correlations can be observed in Figure 3A-B. None of the comparisons produced significant correlations [$p > 0.01$].

Clinically, laterality is categorized as "left," "right," or "bilateral," rather than specifically quantified with the LI. By categorizing the results from resting data, it is shown that the resting LI methods from this research disagree with their task LI counterparts in no more than 15% of the subjects (Figure 3C-F). This is compared to the percentage that task and rest LIs agree, between 36% and 43% across subjects. The majority of comparisons are uncertain (48%), where either the task or rest LIs result in a bilateral value. Rest LIs for the zLI and SMA methods are bilateral values 51% and 67% of the time for controls, respectively, while both methods result in bilateral values 38% of the time for patients.

A) Controls Task LIs	
	READ/WER
READ/BRO	p < 0.01
CWG/BRO	p < 0.01

B) Patients Task LIs	
	READ/WER
zLI	p < 0.01
SMA LI	p < 0.01

C) Task vs. Rest Outcomes for Controls zLI Method					
	Rest Left	Rest Bilateral	Rest Right		
Task Left	6	11	5	Agreeing:	36%
Task Bilateral	2	4	1	Disagreeing:	15%
Task Right	0	2	2	Uncertain:	48%

D) Task vs. Rest Outcomes for Controls SMA Method					
	Rest Left	Rest Bilateral	Rest Right		
Task Left	4	14	3	Agreeing:	39%
Task Bilateral	0	7	1	Disagreeing:	12%
Task Right	1	1	2	Uncertain:	48%

E) Task vs. Rest Outcomes for Patients zLI Method					
	Rest Left	Rest Bilateral	Rest Right		
Task Left	3	3	3	Agreeing:	38%
Task Bilateral	1	3	4	Disagreeing:	14%
Task Right	0	2	2	Uncertain:	48%

F) Task vs. Rest Outcomes for Patients SMA Method					
	Rest Left	Rest Bilateral	Rest Right		
Task Left	6	3	0	Agreeing:	43%
Task Bilateral	4	3	1	Disagreeing:	10%
Task Right	2	2	0	Uncertain:	48%

Figure 3. Results from the comparison between READ/WER and the rest LI methods are shown in Figures 3A-B. For both controls (A) and patients (B), READ/WER and both rest LIs were insignificantly correlated [p > 0.01]. Results from the categorization of these same comparisons are shown in Figures 3C-F. The task LI values from READ/WER were compared with the rest LI values through categorization from zLI (C) and SMA LI (D) in controls, and from zLI (E) and SMA LI (F) in patients.

DISCUSSION.

This study aimed to develop methods to determine language lateralization from resting-state fMRI scans, to replace the current standard of using task-based fMRI scans in presurgical TLE patients. This replacement would address inherent limitations with task fMRI, including patient noncompliance and task variability. Two methods were developed to calculate the LI from resting-state scans, and interpreted in both patients and controls.

The task LI values were compared within the group to determine which LI value was the most robust. The category word generation task was expected to activate Broca's region more consistently over Wernicke's, while the reading task was expected to preferentially activate Wernicke's area [9]. This was illustrated in the initial results (Figure 2), where CWG/BRO and READ/WER were the most significant comparisons between task LIs for controls. However, in patients, READ/WER significantly correlated with READ/BRO. This was unexpected but not unusual, as the reading task has been shown to activate all ROIs (Figure 1A). READ/WER was chosen as the most robust LI because it persisted in the most significant correlations, and then was used to compare to the rest LIs.

The Fisher Z LI method was developed to produce resting LI values using the averaged time series in Broca's and Wernicke's areas. The results suggest that the LIs produced from this method were inaccurate, because the correlation between the zLI and the task LI was insignificant (Figure 3A-B). Furthermore, many of the LI values did not exceed the threshold of bilaterality, indicating little hemispheric dominance. This may indicate that averaging time series of entire regions will not yield notable differences in regions, because the differences between regions are averaged out.

The SMA LI method was developed to mimic the method of producing laterality values from task data. This involved producing a voxel-wise activation map of values, and executing the LI toolbox to calculate the LI values. The supplementary motor area was used as a seed region instead of the task paradigm. Because the SMA region activates in the reading task along with the task associated ROIs, the SMA region was predicted to be able to replace the task paradigm. The LI values from this method did not significantly correlate with the LIs from the task method in controls and in patients (Figure 3A-B). In future research, the SMA could be divided into a left and a right side and form independent seed regions to be used with the left or right Broca's and Wernicke's area. The results from categorization from both methods illustrate how the majority of the comparisons were uncertain because either the task or rest LI value was deemed bilateral (Figure 3C-F).

Replacing the standard of using task-based data to determine language laterality with resting-based data is a query that other studies have attempted to answer. Doucet *et al*. researched three seeds in the inferior frontal cortex to calculate a laterality index value [15]. This study used only a verb generation task, like the category word generation task. In research conducted by DeSalvo *et al*., the results from resting-state fMRI were compared to results from IAP testing [16]. Laterality was calculated in subjects through determining a laterality index as well using spatial maps of the language regions identified from independent-component analysis (ICA). The results from these studies were mixed and not conclusive enough to be applicable in a clinical setting.

CONCLUSION.

Due to subject noncompliance, the data acquired from task-based fMRI scans may not be reliable. The basis of the present study, as well as the Doucet study, involve the comparison between results from task fMRI and rest fMRI. This comparison may not yield valid results if the task fMRI is inherently untrustworthy. DeSalvo's research used IAP results instead of a task scan; however, IAP testing brings its own limitations. Future studies to measure language laterality of TLE patients may include a greater patient population. Comparing to other measures of laterality other than task fMRI, such as neuropsychological tests or electrophysiological testing, may also help to develop the resting methods. This study has not disproved using rest fMRI to replace task fMRI. The methods developed here set the foundation for future studies.

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