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Advantages of sentence-level fMRI language tasks in presurgical language mapping for temporal lobe epilepsy

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ABSTRACT

fMRI language mapping has become increasingly utilized for determining language dominance before surgical intervention for temporal lobe epilepsy (TLE). This study aimed to examine the differences between two classes of fMRI word generation tasks used in our clinic: tasks using a single word cue, referred to as simple generative tasks (SGTs), and tasks also involving sentence-level processing, referred to as sentence-level language tasks (SLTs). Specifically, we aimed to investigate the extent and laterality of activation and frontal–temporal connectivity during these language tasks and their relationship to clinical language measures. Thirty-one patients with TLE (18 patients with left TLE and 13 patients with right TLE) performed four language tasks during an fMRI scan, two SGTs and two SLTs. We found significantly greater activity for SLTs over SGTs in bilateral inferior frontal and middle temporal gyri and the left temporal pole. Sentence-level language tasks also showed greater lateralization compared with SGTs. Finally, we found that while activation extent did not correlate with clinical language tests, the degree of left frontal–temporal connectivity was significantly correlated with naming and semantic fluency performance. These correlations also were more robust for SLTs than for SGTs. Taken together, these results provide a compelling argument for including some form of SLTs in fMRI language lateralization protocols for TLE as they allow for better characterization of language networks, particularly in the temporal lobes which are at risk in surgery.

1. Introduction

Removal of the anterior and mesial temporal lobe that is an epileptic focus is well established to be highly successful in reducing or eliminating seizures in patients with temporal lobe epilepsy (TLE) [1]. It is, however, typically associated with a mild to moderate decline in language abilities, particularly naming and fluency, when the surgery involves the language-dominant hemisphere [2–4]; for a recent review, see Ref. [5]. Thus, determining language dominance has long been a key consideration in epilepsy surgery programs. Over the past 15 years, there has been tremendous advancement in developing fMRI for lateralizing and localizing language functions. There are now dozens of papers comparing fMRI measures such as focal activation in specific regions or hemispheric asymmetry with 'gold standards' of language lateralization and localization such as electrical stimulation mapping and the intracarotid amytal procedure (IAP); for reviews, see Refs. [6,7]. The largest series involve IAP comparison, and these generally demonstrate high correspondence with respect to hemispheric dominance in 'typical' cases; for factors associated with discordance, see Ref. [8].

There are fewer studies that aimed at identifying activation parameters or patterns that correlate with performance on clinical language tasks (typically confrontation naming and verbal fluency) conducted during presurgical assessment of patients with TLE or that are correlated with the degree of change on these tasks following anterior temporal lobe (ATL) resection in the dominant hemisphere. Here, too, there are some promising findings [7]. With respect to preoperative language performance in patients with left TLE, Bonelli and colleagues found that activation in the left inferior and middle frontal gyri was positively correlated with naming performance [9,10], whereas another study using similar activation and clinical measures reported that smaller left frontal activity compared with right frontal activity was correlated with verbal fluency [11]. An even scarcer literature is available regarding the prediction of language decline following surgery on the basis of presurgical fMRI. In one study, the degree to which activation was left lateralized during a semantic decision task was strongly predictive of postoperative naming decline in patients with left TLE [12]. Of interest, asymmetry of activation in the temporal lobe showed a higher association with postoperative language change than asymmetry in the frontal lobe (r values of −0.64 and −0.47, respectively), underscoring the importance of focusing on the area of the brain at surgical risk. Other investigators have also found that greater left lateralization in the frontal regions at baseline, in this case with word generation activation tasks, is associated with greater postoperative decline in naming

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[9,11]. Given these positive findings, there has been a strong trend in epilepsy surgery centers to incorporate fMRI paradigms into their standard of practice for presurgical investigations in TLE.

Another avenue for exploring language networks is to examine connectivity between regions rather than extent of activation. Clearly, focal damage in the temporal lobe disrupts processing not only within this area but also more widespread in functional networks in which temporal lobe structures participate [13]. Furthermore, connectivity may offer a more informative view of the relationship between the language task and language performance, given that magnitude of activation in compromised tissue is somewhat ambiguous. That is, increased activation could indicate an area working effectively (i.e., more activation with better performance), or it could indicate that a patient is having difficulty performing a task and, therefore, needs to recruit more resources to compensate for deficits. Several studies have found subtle differences in both resting state and task-related connectivity in language networks between patients with epilepsy and controls [14,15]. Further, there is evidence that these alterations in connectivity correlate with clinical measures, such as naming to confrontation and verbal IQ, in patients with TLE [16,17]. In the current study, we were interested in whether connectivity between the frontal and temporal language areas during task performance would correlate with performance on clinical language tests and how connectivity might compare with focal activation in correspondence with behavioral measures.

A strong argument has been made that the identification of language regions and lateralization, as well as concordance with IAP, is aided by using a panel or combination of tasks rather than a single one [18,19]. Here, we were particularly interested in both the individual merits of four fMRI language tasks as well as any reliable differences brought out by a combined analysis of tasks that involved sentence-level processing versus those that did not. Two of the tasks, verb generation and category fluency, are referred to as simple generative tasks (SGTs) in which participants covertly produce responses to single lexical cues (e.g., 'glass' and 'flowers', respectively). The other two, sentence completion and naming to description, are sentence-level language tasks (SLTs) that involve both word generation and sentence-level comprehension (e.g., 'he wore red?' and 'furniture you sleep on', respectively). We primarily aimed at (1) assessing each task and the two-task combinations in terms of their ability to produce robust and strongly lateralized activation and (2) determining how activation and connectivity between the frontal and temporal regions correlate with clinical measures of language ability (Boston Naming Test, phonemic fluency, and semantic fluency). To address these aims, we examined 31 patients with unilateral TLE (18 patients with left TLE and 13 patients with right TLE) with fMRI and language tasks conducted prior to surgery. Our expectation was that the optimal tasks would be those that combined generation and sentence-level processing, as they are likely to engage more aspects of language function, particularly components that depend on the integrity of the anterior temporal lobe.

2. Methods

2.1. Subjects

Thirty-one patients with pharmacologically intractable unilateral TLE were recruited from the Neuropsychology and Epilepsy Surgery program at Toronto Western Hospital. Eighteen patients presented with seizures localized in the left temporal lobe (mean age = 38.94, range = 24–62), and the other 13 presented with seizures localized in the right temporal lobe (mean age = 36.30, range = 22–57). Seizure focus was determined using scalp EEG and (if necessary) intracranial EEG. Refer to Table 1 for a summary of patient demographics. Informed consent was obtained from all patients for this study, which was approved by the UHN Research Ethics Board.

Table 1
Patient demographic data.

	LTLE	RTLE
Age, y	38.9 (9.91)	33.9 (11.63)
Sex, M/F	6/12	6/7
Education, y	15.1 (3.05)	13.8 (4.15)
Age of onset, y	22.3 (13.50)	15.9 (11.95)
Duration, y	17.8 (12.29)	17.2 (13.62)
IQ	105.6 (9.82)	102.2 (14.31)
Handedness	15 R, 3 L	12 R, 1 L

LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy; M, male; F, female; y, years; R, right; L, left.

2.2. Neuropsychological assessment

All patients were administered a standard neuropsychological battery of tests in the course of investigations aimed at evaluating surgical candidacy. For the current study, we used three measures as clinical outcome variables: total number of words produced in phonemic fluency (PFLU) (60 s each for F, A, and S), total number of words produced in semantic fluency (SFLU) (60 s each for animals, fruits, and vegetables), and total number of correct words without phonemic cueing on the Boston Naming Test (BNT).

2.3. fMRI data acquisition

Data were collected on a 3-T Signa MR system (GE Medical Systems, Milwaukee, WI). A high-resolution 3D anatomic scan was collected first for visualization and normalization of fMRI data to a common anatomic template (T1-weighted sequence, FOV = 220 mm, slices = 146, flip angle = 12°, TE = 3 ms, TR = 8 ms, 256 × 256 matrix, resulting in voxel size of .85939 × .85939 × 1.0). Echo planar imaging sequences (TE = 20 ms, TR = 2000 ms, 32 5-mm oblique slices angled to be orthogonal to the long axis of the hippocampus to maximize signal and minimize partial volume effects in the MTL) were run during functional scan.

2.4. fMRI tasks

During scanning, patients were trained to perform four interleaved language tasks (2 SGTs and 2 SLTs). Each task was performed over three blocks (26 s each), and each block was preceded by a fixation period (21 s each) (see Fig. 1). The two SGTs involved broad lexical searches with multiple items being covertly generated. In the first task, patients performed a verb generation (VG) task in which they were presented with a noun (e.g., ball; 5 trials at 5 s each) and were instructed to generate verbs that would be associated with the noun (e.g., catch, throw, kick, and toss). In the second task, patients performed a category fluency task (CAT) and were given a category (e.g., flowers; 2 categories at 12.5 s each) and were asked to generate examples of that category (e.g., rose, tulip, violet, and daffodil). The two SLTs involved sentence-level comprehension with more limited time available for covert generation. The first was a sentence completion task (SENT) where patients were asked to complete a provided sentence (e.g., The boy wore red _____; 5 trials of 5 s each) with words that would make logical sense (e.g., shorts and socks). The second was a naming to description task (NAME) where patients were provided with a description (e.g., a piece of furniture you sleep on; 5 trials of 5 s each) and were asked to generate words that match that description (e.g., bed and cot). During fixation blocks, cued by "Relax", a string of symbols appeared (e.g.,*$#*(@&#, 5 at 4 s each), and patients were simply told to fixate on the middle of the strings. An instruction screen was provided for 1 s at the beginning of each task block to ensure that subjects understood requirements for that block of trials.

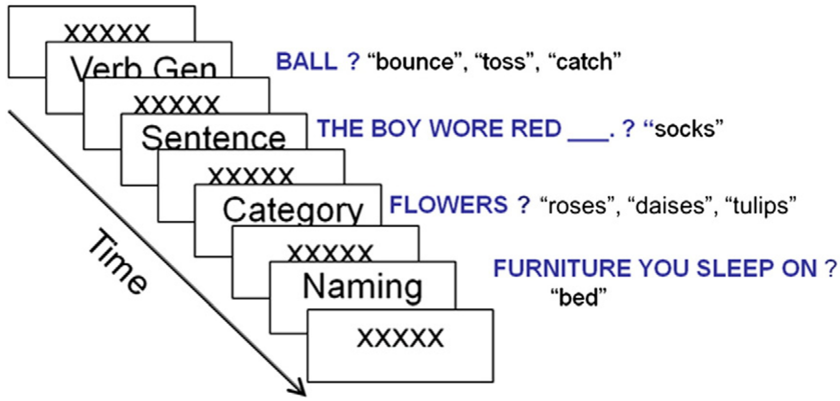

Fig. 1. Illustration of the fMRI task presentation used to elicit language activation in this study; there were three replications of this series within a single scanning sequence.

2.5. fMRI preprocessing

Preprocessing was performed using SPM8 (Statistical Parameter Mapping 8; Wellcome Department of Imaging, London) through MATLAB 7.9 (MathWorks, Inc.). Anatomical and functional scans were reoriented to the anterior commissure, following which the functional images were coregistered to the anatomical scan. Motion correction was implemented using realignment and unwarping. The anatomical scans were segmented into gray matter, white matter, and cerebral spinal fluid and then normalized to MNI space. Functional images were transformed into MNI space by using the same normalization parameters. Spatial smoothing was performed using an 8-mm FWHM smoothing function. The Artifact Detection Toolbox [20] was used to identify fluctuations in global signal greater than 3 standard deviations, translational motion greater than 1 mm, or rotational motion greater than 0.05 rad. This process produces artifact regressors that were then entered as covariates of no interest in the statistical models described below.

2.6. fMRI analyses

For each patient, we modeled fMRI data using the general linear model and computed seven one-sample t-test contrasts. Four of these contrasts were used to examine each language task against fixation. We also examined the activity of the SGTs (VG/CAT) and of the SLTs (SENT/NAME) against fixation. The final contrast looked at the SGT language activation against the SLT language activation as a means for comparing the two types of task directly. Finally, we performed a two-sample t-test to evaluate differences between the patient group with LTLE and the patient group with RTLE. Second-level analyses were corrected for using false discovery rate (FDR), $p < 0.05$.

2.7. Laterality indices

Determining laterality from fMRI data can be heavily influenced by the threshold selected to evaluate language versus control activity. Too liberal and the differences between hemispheres are likely to be obscured; too strict and most of the voxels in the brain will be excluded from the calculation potentially rendering laterality indices (LIs) meaningless. To evaluate language lateralization, we used the LI toolbox [21] implemented in SPM8 (Wellcome Department of Imaging, London). The toolbox extracts the voxel values for a set of ROIs at a range of thresholds and computes a LI for each threshold according to the formula $(\text{Left}_{\text{activation}} - \text{Right}_{\text{activation}}) / (\text{Left}_{\text{activation}} + \text{Right}_{\text{activation}})$. We implemented the bootstrapping option and calculated the weighted mean of the LIs produced over a range of 10,000 thresholds. In the weighted mean, each LI is assigned a weighting based on the threshold with which it was calculated. Those LIs which were calculated with more conservative thresholds are weighted more heavily compared with those calculated with more liberal thresholds. The LIs from every threshold are included in this weighted mean, which is expressed as a value between −1 and 1, with numbers closer to −1 reflecting greater voxel activity in the right hemisphere and numbers closer to 1 reflecting greater voxel activity in the left hemisphere. This method has been used in the past by another group [9], and the details of this analysis have been described elsewhere [21].

Laterality indices for SGTs and SLTs were computed separately for each patient. Frontal, parietal, and temporal lobe LIs were independently calculated using anatomically defined masks included in the LI toolbox which were derived from the AAL atlas [22]. We also computed LIs using a mask that included the frontal, parietal, and temporal lobes conjunctively. The occipital lobe and regions 5 mm from the midline were excluded from LI calculations as it has been previously reported that activation in these areas is a major source of discrepancy between Wada and fMRI laterality results and that such discordance could be corrected by removing the influence of these regions [23].

To examine the effects of task type (SGTs versus SLTs) on LIs, we employed a mixed model ANOVA using seizure focus as a between-subjects factor and task type as a within-subject factor. Paired t-tests were used to break down within-subject factor effects.

2.8. Correlations with behavior

Using REX [24], we extracted the percent signal change in four ROIs. We extracted from left and right BA45 and BA21 defined from Talairach Daemon Atlas [25] following registration to MNI152 space and application of a correcting affine transformation [26]. Percent signal changes from each task contrast were correlated with neuropsychological language scores (PFLU, SFLU, and BNT) using the Bonferroni correction for multiple comparisons. Neuropsychological performance on the PFLU, SFLU, and BNT was also correlated with patients' LIs using SYSTAT13 (Systat Software Inc., Chicago, IL). Because of missing neuropsychological data (2 patients with RTLE), our sample was reduced to 29 patients. To attain a larger spread of performance, we pooled patients with left and right TLEs together for the regression analyses.

2.9. fMRI connectivity

Preprocessed fMRI data were loaded into the CONN toolbox [20], the task onset times were modeled, and covariates of no interest were regressed out. White matter and CSF signal were regressed out using CompCor [27]. Time series of voxels within ROIs (left and right BA45 and BA21 described above) were averaged, and those average time series were correlated with each other within hemisphere. The resulting correlation coefficients were then Fisher z-transformed to normalize their distribution. These values represent the connectivity between the anterior and posterior language regions during each task.

Table 2
Patient neuropsychological performance.

	LTLE	RTLE
BNT	47.5 (9.97)	52.3 (4.27)
SFLU	42.8 (10.61)	42.5 (11.08)
PFLU	38.6 (10.04)	35.8 (10.13)

LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy; BNT, Boston Naming Test; SFLU, semantic fluency; PFLU, phonemic fluency.

Group-level contrasts were performed to look at group differences between patients with LTLE and RTLE. Second-level analyses were corrected for using false discovery rate (FDR), $p < 0.05$.

Finally, connectivity values between the anterior (BA45) and posterior (BA21) language areas during task performance were correlated with neuropsychological language performance. To attain a larger spread of connectivity, we pooled patients with left and right TLEs together for the analyses. We employed the Bonferroni correction to account for multiple comparisons.

3. Results

3.1. Neuropsychological assessment

No significant differences between patients with LTLE and RTLE were observed on phonemic fluency ($t = 0.57$, $p > 0.1$) or semantic fluency ($t = 0.042$, $p > .1$), but there was a trend towards decreased performance in patients with LTLE compared with those with RTLE on the Boston Naming Test ($t = 1.9$, $p = 0.07$) (see Table 2).

3.2. Task activation

Each of the four tasks elicited significant activation in the bilateral inferior frontal gyrus, left supplementary motor area, left superior frontal gyrus, left angular gyrus, and cerebellum ($p < 0.001$, FDR-corrected). These activation patterns are shown in Fig. 2. There was no significant difference between patients with LTLE and RTLE across task activation. We found significantly greater activation for SLTs over SGTs in the bilateral middle temporal gyrus, bilateral inferior frontal gyrus, medial superior frontal gyrus, and left temporal pole ($p < 0.05$, FDR-corrected). This is shown in Fig. 3 and summarized in Table 3. There were no regions which were significantly more activated by SGTs than SLTs at corrected levels.

3.3. Laterality indices

Our mixed model ANOVA analysis revealed that across all ROIs and task types, there were no differences between patients with

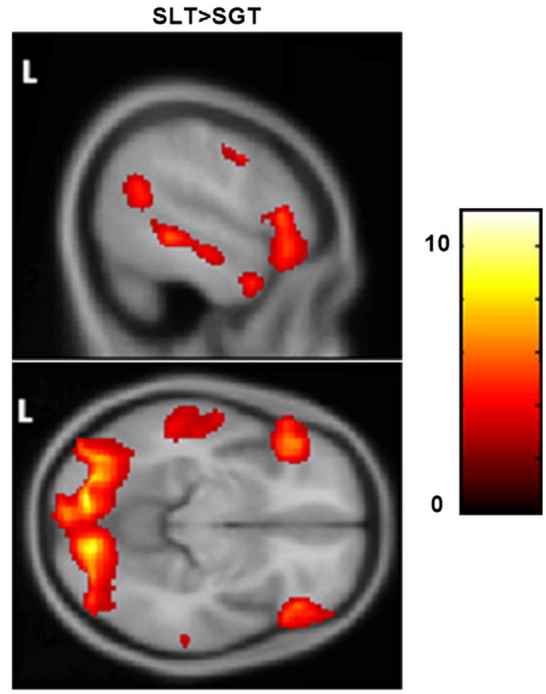

Fig. 3. Group-level activation showing contrast of SLTs > SGTs ($p < 0.05$, FDR-corrected). SLTs elicited greater activation in the bilateral middle temporal gyrus, bilateral inferior frontal gyrus, and left temporal pole.

LTLE and patients with RTLE (frontal: $F(1,29) = 0.58$, $p > 0.1$; parietal: $F(1,29) = 1.2$, $p > 0.1$; temporal: $F(1,29) = 0.78$, $p > 0.1$; conjunctive: $F(1,29) = 0.07$, $p > 0.1$). We did find a significant effect of task type, showing that SLTs provided significantly greater lateralization compared with SGTs, when considering all language regions in the conjunctive mask ($F(1,29) = 8.502$, $p < 0.01$). This effect was significant in the frontal lobe ($F(1,29) = 4.28$, $p < 0.05$), nearing significance in the temporal lobe ROI ($F(1,29) = 3.36$, $p = 0.08$), and absent in the parietal ROI ($F(1,29) = 1.3$, $p > 0.1$). There were no interaction effects of seizure focus and task type for any of the ROIs (Fig. 4).

3.4. Correlations with behavior

We found no significant correlations between task-related activations in our selected ROIs in any of our tasks with neuropsychological tests of language (all $r < 0.48$). No LIs correlated with any of the neuropsychological tests of language in patients with LTLE or RTLE (all $r < 0.21$).

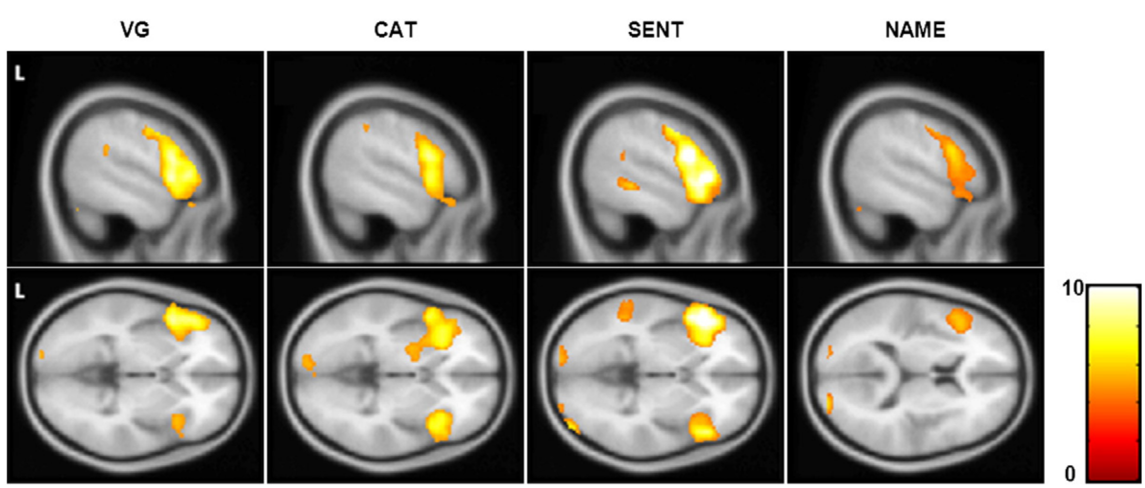

Fig. 2. Group average activation results from verb generation, category fluency, sentence completion, and naming to description for patients with TLE ($p < 0.001$, FDR-corrected).

Table 3
fMRI activation peaks for sentence-level language tasks (SLTs) greater than simple generative tasks (SGTs).

Anatomical region	Peak coordinate in MNI space	Z-score	Corrected p-value (FDR)
Right IFG	52 30 6	5.32	0.001
Left temp pole	−60 10 −30	5.20	0.001
Left IFG	−46 30 −12	5.19	0.001
Left SFG	−16 34 52	4.92	0.014
Right IFG	46 34 −12	4.81	0.002
Left IFG	−56 24 8	4.77	0.014
Left MTG	−52 −38 −6	4.63	0.047
Left MTG	−62 −6 −18	4.35	0.047

MNI, Montreal Neurological Institute; IFG, inferior frontal gyrus; temp pole, temporal pole; SFG, superior frontal gyrus; MTG, middle temporal gyrus.

3.5. Language connectivity

We found a significant positive correlation between BNT performance and left frontal–temporal connectivity during NAME ($r = 0.5$, $p = 0.04$), and approaching significance for SENT ($r = 0.49$, $p = 0.051$), but not during VG ($r = 0.096$, $p > 0.1$) or CAT ($r = 0.37$, $p > 0.1$). Semantic fluency performance and left frontal–temporal connectivity during NAME were significantly positively correlated (SFLU: $r = 0.57$, $p = 0.01$) (see Supplementary Fig. 1), but this was not true for any other task. No task connectivity was correlated with phonemic fluency. There was no significant correlation between right hemisphere connectivity and neuropsychological performance (all $r < 0.37$). These results are summarized in Table 4.

4. Discussion

This study aimed to examine the differences between fMRI language tasks that emphasize word generation with limited comprehension and language tasks that incorporate both generation and comprehension. We analyzed these differences in terms of task activation, as well as the relationship between laterality indices and neuropsychological measures. We also aimed to explore whether connectivity between the frontal and temporal language areas provides a useful measure for explaining behavioral performance.

Our analyses revealed greater activation in the temporal and frontal language areas for SLTs when compared with SGTs, indicating that SLTs indeed activated language networks more robustly. We found modest, nonsignificant correlations between current neuropsychological measures of language and either regional activation or LIs, in contrast to some previous findings [11]. However, such correlations with clinical measures were identified when we explored the connectivity between the left frontal and temporal language areas. Specifically, we found significant correlations between Boston Naming Test performance and connectivity in both of our SLTs, while category fluency was correlated with connectivity during one of the SLTs (NAME).

4.1. Greater language network activation in SLTs compared with SGTs

The results supported our hypothesis that fMRI language tasks which combine comprehension and production in a naturalistic way (i.e., SLTs) generate more robust activation compared with tasks that emphasize production and may require novel search strategies (i.e., SGTs). Specifically, we expected greater activation in the temporal language regions, as shown in some other sentence reading tasks [28]. However, we saw increased activation in both the temporal and frontal language regions for SLTs. Furthermore, this effect was strongly lateralized to the left hemisphere. These results suggest that a broader or more comprehensive engagement of aspects of language function provides a better assessment of language dominance. Importantly, we were able to observe greater anterior temporal lobe activation using SLTs, perhaps due to greater demands on semantic processing [29,30], which can be elusive in many presurgical language mapping protocols [9,11,31]. In contrast, verb generation in particular likely emphasizes other processes such as response selection [32,33]. A similar finding of increased activation in the frontal and temporal language regions for naming to description compared with verb generation has been reported [11]. Considering that we see morphological changes in the temporal lobe regions [29,30] and since surgical intervention targets the temporal lobe, it is of critical importance to evaluate language networks there. Indeed, Sabsevitz and colleagues [12] reported that temporal lobe LIs were the major predictor of presurgical to postsurgical change in naming.

4.2. Correlation between fMRI activation and laterality with behavior

In this study, we did not find a relationship between the magnitude of activity during our language tasks or LIs and performance on any of our neuropsychological measures. Magnitude of task activation has been shown in previous research to correlate with neuropsychological measures [9,34] but with much larger numbers of patients with TLE. Bonelli et al. reported positive correlations between naming and the left middle frontal gyrus ($r = 0.45$) and left inferior frontal gyrus ($r = 0.46$) in patients with RTLE during an fMRI phonemic fluency task. Our measured correlation between the left frontal regions and naming during verb generation ($r = 0.36$), though not reaching significance, was within the confidence interval of those reported by

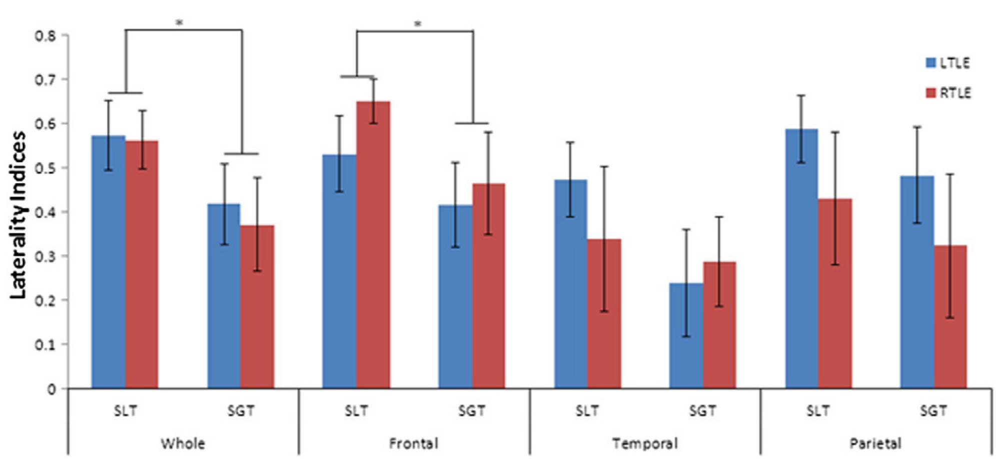

Fig. 4. Laterality indices obtained from all the language areas and from the separate frontal, temporal, and parietal lobes for SLTs and SGTs in patients with LTLE and RTLE. Error bars correspond to standard error. * indicates significant effect at $p < 0.05$.

Bonelli et al. [9]. Our method of LI calculation also differs from research showing correlations between LIs and language performance [11,35]. There is no consensus in the literature on the optimal method for determining lateralization [31,36,37], and differing methods between our study and previous ones may have contributed to our inability to detect this relationship. This is the method we employed to calculate LI samples from a large range of thresholds to counteract the influential effects of individual thresholds [21]. We opted to use this method because we believe that it provides a more stable measure of laterality and, despite failing to show a correlation with presurgical language performance in our sample, it was able to reveal discrepancies between SLT and SGT lateralization. Also, Rosazza et al. [11], who were able to demonstrate a significant relationship between laterality and preoperative language performance, employed an active baseline for a subset of their tasks which has been shown to affect activation laterality in the temporal lobes [38,39]. This, however, was specific to tasks presented aurally, whereas all of our tasks were presented visually.

4.3. Correlation between frontal–temporal connectivity and behavior

We demonstrated that connectivity between the frontal and temporal language regions was significantly correlated with naming performance and semantic fluency. The correlation with naming was seen for both of our SLTs and for semantic fluency with one of our SLTs (NAME); all correlations involving SGTs were considerably weaker. These findings suggest that tasks requiring sentence-level processing may be more sensitive to network-level differences that are related to clinical language performance.

Connectivity provides insight beyond that of magnitude of activation as natural language processes clearly involve the coordinated activity of networks of regions rather than disconnected modules [40]. In conversation, multiple aspects of language must work together seamlessly in order to produce coherent speech. Functional connectivity provides an index of this coordinated activity which, at a minimum, complements information gleaned from focal activation metrics. Indeed, even at rest, the connectivity among core language regions is reduced in patients with TLE [14]. Furthermore, it is possible that some language deficits postsurgery are not caused by damage to a specific node of the language network but rather by disruption of the connections that allow these regions to communicate fluidly. Indeed, several studies have found that damage to white matter tracts or reduced white matter volume in the temporal lobe was specifically related to naming [2,41]. Thus, functional connectivity among language regions may provide critical information regarding a patient's language network integrity. For example, a recent study found that weaker connectivity between the inferior frontal gyrus and the anterior cingulate cortex was related to poor fluency performance in patients with focal (frontal or temporal lobe) epilepsy [42]. To the best of our knowledge, we are the first to show a correlation between behavioral performance and task-related functional connectivity between the frontal–temporal language regions in a population with TLE. Further exploration of this relationship may yield useful clinical information in presurgical language mapping.

Table 4
Correlation coefficients for left frontal–temporal connectivity and neuropsychological performance for each language task.

	BNT	PFLU	SFLU
VG	0.10	0.07	0.18
CAT	0.37	0.2	0.33
SENT	0.49*	0.18	0.26
NAME	0.50*	0.43	0.57*

BNT, Boston Naming Test; SFLU, semantic fluency; PFLU, phonemic fluency; VG, verb generation; CAT, category fluency; SENT, sentence completion; NAME, naming to description.; * denotes significance at $p < 0.05$, Bonferroni corrected

4.4. Limitations

All patients were taking anticonvulsant medication during the scanning and neuropsychological testing procedures. This is a very common, and essentially unavoidable, limitation in this clinical context. While such medications may influence behavioral performance, capacity for task-related activation, or both, we note that only 2 of the 31 patients were taking topiramate, an anticonvulsant medication known to have a specific negative impact on verbal fluency [43]. Though our sample was small, the patients we included were extremely well characterized in terms of clinical and cognitive variables and representative of the type of patient considered for ATL in most epilepsy centers. Given the sample size, we were unable to examine age of onset or impact of MTS on these activation/connectivity patterns and their relation with behavioral performance, although both are known predictors of postoperative decline in visual naming [5].

Next, our task activation was contrasted against a fixation baseline. Some researchers have suggested that during fixation, it is common for mind-wandering and "inner speech" to occur [44]. These processes may draw on language comprehension and production systems which could attenuate the observed effects of the language task. This problem is compounded by the use of a single threshold for LI calculation (unlike our procedure) which makes the attenuated temporal lobe activation more likely to fall below the threshold. It has, therefore, been suggested that an active control task, which stresses a decision-making process that does not use language (e.g., tone decision and backward speech), is preferable in order to increase the robustness of temporal lobe activation [38,39]. While it has been shown that an active control task may provide a more robust depiction of language networks in the temporal lobes [39], we are confident in our findings because our method of LI calculation samples over a large range of thresholds for many iterations. This calculation method provides greater sensitivity with which to detect the signal present in the temporal lobes, thus making the influence from this region more prominent in LI calculation. Furthermore, active control tasks have mainly been explored during auditory decision tasks for language mapping, whereas our protocol presented stimuli visually.

We did not collect any patient responses during fMRI scans. Covert generation without the collection of behavioral data allows for less motor and motion artifact and is in fact the typical procedure in presurgical language mapping. One concern that may arise is that patients were not actively participating in the required tasks. We find this unlikely given the observed correlations between fMRI connectivity and clinical language performance. We also see no reason to expect differing patient participation between SLTs and SGTs that might have confounded our activation results as they were presented as interleaved blocks repeating across the duration of the scanning session. Finally, all patients were debriefed following scanning about their ability to perform the tasks, and none indicated a particular difficulty or disengagement on specific tasks.

4.5. Conclusions

Based on the evidence that sentence-level tasks produce more robust language network activation specifically within the temporal lobe regions (the site of surgical intervention), we see it as beneficial to incorporate some form of sentence-level language task into language lateralization procedures for patients with TLE. In our experience, patients also find word generation to be much easier when given sentence cues than single word cues. Finally, connectivity metrics yield important additional information about the functional viability of language regions before surgery and should be explored further as predictors of postsurgical language change.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2014.01.010.

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