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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.