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Multimodal imaging of language reorganization in patients with left temporal lobe epilepsy

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ABSTRACT

This study explored the relationships among multimodal imaging, clinical features, and language impairment in patients with left temporal lobe epilepsy (LTLE). Fourteen patients with LTLE and 26 controls underwent structural MRI, functional MRI, diffusion tensor imaging, and neuropsychological language tasks. Laterality indices were calculated for each imaging modality and a principal component (PC) was derived from language measures. Correlations were performed among imaging measures, as well as to the language PC. In controls, better language performance was associated with stronger left-lateralized temporo-parietal and temporo-occipital activations. In LTLE, better language performance was associated with stronger right-lateralized inferior frontal, temporo-parietal, and temporo-occipital activations. These right-lateralized activations in LTLE were associated with right-lateralized arcuate fasciculus fractional anisotropy. These data suggest that interhemispheric language reorganization in LTLE is associated with alterations to perisylvian white matter. These concurrent structural and functional shifts from left to right may help to mitigate language impairment in LTLE.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common localization-related epilepsy in adults and it is highly refractory to pharmacological treatment (Zimprich et al., 2004). Due to the involvement of the temporal lobes in language and semantic processing (Pujol, Deus, Losilla, & Capdevila, 1999; Springer et al., 1999), patients with chronic TLE often have language impairment, including poor auditory naming, visual naming, and verbal fluency (Bell et al., 2001; Hamberger & Tamny, 1999; N'Kaoua, Lespinet, Barsse, Rougier, & Claverie, 2001; Oyegbile et al., 2004). This is particularly characteristic of patients with left TLE (LTLE) who may have damage to the left hippocampus, lateral temporal neocortex, and perisylvian white matter (Ahmadi et al., 2009; Lin, Riley, Juranek, & Cramer, 2008; McDonald et al., 2008).

Standard of care for patients with well-localized pharmacoresistant TLE is anterior temporal lobectomy (ATL), which typically consists of the removal of anterior portion of the hippocampus, parahippocampal gyrus, and amygdala, with variable resection of the temporal lobe neocortex and underlying white matter (Jetté, Sander, & Kezzer, 2016; Wiebe, Blume, Girvin, & Eliasziw, 2001). Thus, removal of the left (i.e., typically language dominant) temporal lobe may exacerbate language deficits in patients with LTLE if language networks have not relocated in response to injury (Bonelli et al., 2012; Hermann et al., 1999). Fortunately, in many patients with LTLE, language networks may "shift" to homologous regions in the right hemisphere in an adaptive process called

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reorganization. This is most frequently observed in patients with an early age of seizure onset, left-handedness and the presence of mesial temporal sclerosis (MTS) on magnetic resonance imaging (MRI) (Pataraia et al., 2004; Springer et al., 1999). However, because the likelihood and degree of reorganization differs significantly across patients, a major goal of the presurgical evaluation is to localize language networks in TLE in efforts to quantify the risk for language decline following ATL.

In recent years, functional MRI (fMRI) has emerged as a popular method for lateralizing language networks in patients with LTLE, and there is some evidence that it can successfully predict language decline following ATL (Bonelli et al., 2012; Sabsevitz et al., 2003). Specifically, studies have shown that patients with LTLE who have a more bilateral or right-sided language activation pattern in perisylvian regions, including inferior prefrontal and posterior superior temporal lobe regions, experience less decline on neuropsychological measures of language than those with a left-lateralized pattern (Sabsevitz et al., 2003). However, only a portion of the patients with LTLE with right-sided language on fMRI have preserved language functions, suggesting that the blood-oxygen-level dependent (BOLD) response may not reflect all the factors involved in successful language reorganization (Labudda, Mertens, Janszky, Bien, & Woermann, 2012).

Recent studies have suggested that language reorganization *may* depend on the degree of structural or microstructural alterations within perisylvian networks, but the evidence in patients with TLE is mixed. In healthy controls, some studies have shown a relationship between structural asymmetry of arcuate fasciculus (ARC) and functional asymmetry (e.g., Propper et al., 2010), whereas others have not (e.g., Vernooij et al., 2007). In patients with LTLE, Powell et al. (2007) found that rightward asymmetry in fractional anisotropy (FA) of frontotemporal fiber tracts in LTLE was associated with rightward asymmetry in fMRI language activations, suggesting that language reorganization in LTLE may be explained by alterations to the left hemisphere white matter. Conversely, Rodrigo et al. (2008) found that an association between reduced asymmetry in FA of the ARC and reduced asymmetry in fMRI activations was only observed in patients with right TLE, but not in patients with LTLE, suggesting a de-coupling of white matter microstructure and the BOLD response. This inconsistency highlights the complexity of language reorganization in patients with LTLE, warranting additional research into the underlying architecture of language networks in TLE.

There is also emerging evidence that reorganization within neocortical structures may accompany and/or facilitate a shift in the BOLD response. Labudda et al. (2012) studied 20 LTLE patients with typical and 20 LTLE patients with atypical (i.e., right-sided) language dominance on fMRI. They found that LTLE patients with atypical language dominance had increased gray matter volumes within right-sided temporo-lateral and frontal regions relative to those with typical language dominance. Furthermore, the degree of atypical fronto-temporal language activation correlated with temporal and frontal lobe gray matter volumes. However, patients with typical and atypical language dominance did not differ in terms of language performance. These findings complement those from multimodal imaging studies of fMRI- diffusion tensor imaging (DTI), suggesting that functional reorganization within language networks may depend, in part, on underlying structural changes. However, these structural and functional "shifts" do not always co-occur, nor do they appear to necessarily facilitate language performance.

Although existing studies have examined associations between fMRI-DTI *or* fMRI-volumetric MRI to understand language reorganization in TLE, no studies have combined all three imaging modalities to our knowledge. Therefore, the goals of this study were (1) to characterize the relationship between fMRI language lateralization and asymmetries in both DTI and volumetric MRI measures, and (2) to determine the contribution of each brain imaging derived measure to language performance in LTLE. In addition, we examined the contribution of important clinical/demographic variables (i.e., age of seizure onset, handedness, presence of MTS) to both our imaging and neuropsychological measures. Such information could yield critical insight into the neurobiological underpinnings of language reorganization in LTLE, which may help to explain variability in pre-operative language functioning as well as post-operative language decline following left ATL.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board at the University of California, San Diego (UCSD) and all participants provided informed consent according to the Declaration of Helsinki. Fourteen patients with a diagnosis of LTLE and 26 healthy controls were included in this study. All patients were medically-refractory and under evaluation for surgical treatment at the UCSD Epilepsy Center and were diagnosed by board-certified neurologists with expertise in epileptology, according to the criteria defined by the International League Against Epilepsy (Kwan et al., 2010). Patients were classified as LTLE based on seizure onsets recorded by video-EEG telemetry, supported by seizure semiology and neuroimaging results. Clinical MRI scans were available on all patients (i.e., T1-weighted, T2-weighted, and coronal FLAIR sequences with 1 mm slices through the mesial temporal lobe). MRIs were visually inspected by a board-certified neuroradiologist for detection of MTS and the exclusion of contralateral temporal lobe structural abnormalities. MRI findings revealed that nine patients had ipsilateral MTS and five patients had normal MRIs. No patients showed evidence of contralateral MTS or extra-hippocampal pathology on clinical MRI. The clinical characteristics and medication information for all patients are presented in Table 1. Control participants were screened for neurological or psychiatric conditions.

The mean age of the LTLE group ($M = 40.1$, $SD = 12$) was not statistically different from the control group ($M = 36.3$, $SD = 14.2$), $t(38) = 0.85$, $p = 0.4$. However, the healthy controls attained more years of education ($M = 15.9$, $SD = 2.4$) than patients with LTLE ($M = 14.1$, $SD = 1.8$), $t(38) = -2.46$, $p = 0.019$. The distribution of the sex and handedness were comparable between groups (sex: $\chi^2 = 1.71$, $p = 0.191$; handedness: $\chi^2 = 3.13$, $p = 0.077$), and the distribution of the language status (i.e., English as first language versus second language) was also comparable between groups ($\chi^2 = 1.91$, $p = 0.386$). One patient and three controls' fMRI data was removed due to excessive head motion.

2.2. Materials and procedures

fMRI, volumetric MRI, DTI, and neuropsychological testing of language were performed on all participants according to the procedures described below.

2.2.1. Neuropsychological tasks

Participants were administered the Boston Naming Test, a visual confrontation naming measure (BNT; Kaplan, Goodglass, & Weintraub, 1983); Auditory Naming Test, an auditory naming test in which participants are provided with verbal cues (ANT; Hamberger & Seidel, 2003), and Category Fluency (CF) and Letter Fluency (LF) subtests from the Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001), as part of a larger neuropsychological test battery. Category fluency and letter fluency