Original Article

Language fMRI activation declines in patients with left medial temporal lobe epilepsy

Xue-Zheng Liu[1], De-Zhi Kang[2]

ABSTRACT

Objective: Patients with epilepsy commonly have language deficits. This study investigates whether language fMRI activation and language dysfunction are systematically related in patients with left medial temporal lobe epilepsy (left-mTLE).

Methodology: We studied sixteen patients with left-mTLE and 16 healthy controls. Semantic judgment task functional MRI scanning and neuropsychological tests were performed. Activation maps of language function MRI analyzed by analysis of functional neuroimages (AFNI).

Results: There was no difference in activation maps of the semantic judgment task fMRI between left-mTLE and healthy controls group. Compared with a healthy control group, in the left-mTLE group, there was significantly less activation volume in the left language regions of the inferior frontal and Superior temporal gyrus; the left-mTLE group also had significantly lower neuropsychological language scores.

Conclusion: Language dysfunction in left-mTLE patients is associated with decline of language fMRI activation.

KEY WORDS: Function MRI; Language; Epilepsy; Neuropsychology; Left Medial Temporal Lobe.

Pak J Med Sci October - December 2011 Vol. 27 No. 5 976-980

How to cite this article:

Liu XZ, Kang DZ. Language fMRI activation declines in patients with left medial temporal lobe epilepsy. Pak J Med Sci 2011;27(5):976-980

INTRODUCTION

Mesial temporal lobe epilepsy is characterized by the epileptiogenic focus and neuropathological changes in the mesial temporal regions, i.e., the usually pathologic substrate of hippocampal sclerosis (HS) or atrophy.[1] Clinically patients with epilepsy commonly have cognitive problems, ranging from language deficits to global cognitive deterioration.[2]

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* Received for Publication: July 20, 2011
* Accepted: October 17, 2011

Functional imaging has become an important tool to study plasticity and reorganization of language. Recent fMRI studies in patients with epilepsy showed activation patterns which differed from those of normal controls. The relation between fMRI and cognitive performance (i.e. language, emotion, vision, and memory) has been demonstrated previously, in pediatric, adult studies of normal subjects and patients with epilepsy. A group of left-mTLE patients showed reduced connectivity between the precuneus and hippocampus compared to controls.[3] Abnormalities of language networks were also detected in lesional and non-lesional complex partial epilepsy.[4] Language lateralization correlates with verbal memory performance in patients with left-sided epilepsy.[5] Left HS causes more reduction of functional connectivity than right HS in subjects with left hemisphere dominance for language.[6]

The relation between cognitive function and language organization in epilepsy is complex due to possible intrahemispheric and interhemispheric language reorganization in localization-related epilepsy and highly variable epilepsy characteristics.[7-9] Moreover, cognitive functions such as language result from interactions of various rather than isolated brain regions.[10,11]

However, the relationship between language dysfunction and language fMRI activation is still unclear, particularly in patients with epilepsy. In this study, we explored language fMRI activation and neuropsychological tests in patients with left-mTLE and healthy controls. We expected patients with left-TLE to show less activation and lower neuropsychological language scores when compared with healthy controls.

METHODOLOGY

Participants: Sixteen left-mTLE patients participated in this study. The patients' ages were between 14 and 52 (10 males and 6 females, mean age 26.8 years ± 9.1). All patients underwent a comprehensive clinical evaluation according to the epilepsy classifications of the International League Against Epilepsy. Selection criteria for left-mTLE patients included the following: the diagnosis of left-mTLE was based on a combined review of the clinical history, EEG findings (including video-EEG) and high-resolution MR images with the absence of MRI abnormalities other than hippocampal sclerosis and atrophy. All patients had been treated with conventional medicines for more than two years, but their seizures could not be controlled. No other neurological disorder was known to be present.

The control group consisted of 16 gender and age-matched healthy volunteers (10 men and 6 women, mean age 26.3 years ± 2.8, range 15–51 years). None of the controls had neurological or psychiatric disorders. All participants were native Mandarin Chinese speakers and were right handed. Handedness was determined using the Edinburgh Handedness Inventory, Oldfield.[12] Written informed consents were obtained from all subjects prior to participation. The research protocol was approved by the local Medical Ethics Committee in First Affiliated Hospital, Fujian Medicine University. Participants received monetary compensation for their participation.

Neuropsychological tests: Language was assessed with an aphasia test battery to all participants that includes the word generation task and text reading test.[13] For word generation, the participants were asked to name as many animals as possible in two minutes. For text reading, the participants were instructed to overtly read a meaningful text as quickly as possible. Raw scores of language tests were transformed to standard scores using age norms from the test. Differences in scores between the two groups were analyzed using the Wilcoxon/ Mann–Whitney test. In order to make results comparable, z-scores were constructed from the respective transformed test score according to the formula [$Z=X-\mu/\sigma$].

MRI technique: MR imaging was performed on a 3.0-Tesla scanner (Siemens Verio, Germany). Participants were instructed to rest with their eyes closed and keep their heads still. All data were acquired using a standard quadrature birdcage head coil for both RF transmission and reception. Anatomic images were acquired for clinical diagnosis, including axial T1-weighted images (TR/TE = 2,200 ms/24 ms, matrix = 512×512, FOV = 24×24 cm^2, slice thickness/ gap = 4.0mm/0.5mm, 23 slices covered the whole brain), coronal T1 and T2 FLAIR images (4 mm thickness without gap and 14 slices) used for measuring hippocampal volume and detecting hippocampal lesions.

For the language tasks fMRI, A gradient echo T2-weighted echo-planar MR sequence was acquired [TR 3,000ms, TE 50ms, matrix = 64 ×64 ×29, voxel size = 3.94×3.94×6, slice thickness = 5 and 1 mm gap, flip angle=15°], We acquired 36 interleaved axial slices parallel to the anterior–posterior commissure plane covering the entire brain. The first three acquisitions were discarded due to saturation effects.

Language task paradigms: All the participants performed semantic judgment task. Before entering the scanner, participants practiced both tasks overtly but were instructed to respond silently inside the scanner in order to minimize the motion artifacts associated with speech. All the stimuli were presented aurally via earphones. Exposure and timing of stimuli were controlled by DMDX software.

An adapted version of the Binder et al semantic judgment paradigm was used.[14] A total of 40 items, half dangerous and half no-dangerous objects or animals, were selected from Snodgrass and Vanderwart's 260 picture norm. All items were disyllabic, conceptually familiar to participants and had a relatively high frequency according to the CMCR corpus (Corpus for Modern Chinese Research; Beijing Language Institute, 1995). In the fMRI experiment, stimuli in the activation condition were spoken with a duration of 600ms (e.g. crocodiles, pistols, book). Each stimulus was followed by an interstimulus interval of 1800ms. Participants were asked to judge if each item (e.g. gun, crocodiles) was dangerous. Participants responded per button press 'yes' with the index finger of their right hand; otherwise they had to press 'no' with the index finger of their left hand.

fMRI analysis: fMRI data were analyzed using AFNI. Pre-processing steps included discarding first 4 volumes, slice timing correction, head motion correction, co-registration, spatial normalization, spatial smoothing (8 mm full-width half-maximum), and signal normalization.

Statistical parametric maps were generated according to general linear model. A time shifted box-car design reference function was used to determine activation related to the difference between the alternating baseline and activation blocks. A fixed effects model was calculated for every subject. Brain activation was assessed in terms of activation contrast between the task and baseline condition according to the general linear model in SPM2. SPSS13.0 software was used for the statistical analysis of the task performance. A simple standard random-effects analysis was performed to assess differences in cerebral activation between the groups thresholded at the $p<0.01$ level, corrected for multiple comparisons.[15] First, the activation maps of the two groups were compared on a pixel-by-pixel basis and clusters of significantly activated brain regions were reported. SPSS13.0 software was used for the statistical analysis, with $P < 0.01$ indicating a statistically significant difference. Second, based on the activation maps of the control group, masks were created to select the regions of interest significantly activated. The average individual BOLD response value was expressed as percentage signal change.[16]

RESULTS

Neuropsychological assessment revealed that average accuracy scores for the word generation task were 68.6%±10.3 (left-mTLE) and 94.4%±5.2 (controls), for text reading test 62.4%±18.1 (left-mTLE) and 91.3%±6.5 (controls), the left-mTLE group also had significantly lower neuropsychological language scores(77±10, median ± SD), compared to healthy controls (113±15, $p < 0.01$).

Furthermore, fMRI analysis demonstrated that the same region activated in both groups was an extensive area of the known language region, including the bilateral inferior and middle frontal cortex, posterior parietal lobule, middle temporal gyrus, superior temporal gyrus, cerebellum gyrus, the left cingulate gyrus, the left nucleus caudatus and the left thalamus. Activation maps of the semantic judgment task fMRI revealed that no significant differences were found between controls and patients with left-mTLE (Fig 1 and 2). However, quantitative analysis revealed that the left-mTLE group had significantly lower activation volume in the language regions of the left inferior frontal and Superior temporal gyrus (42 ± 3, 35 ± 4, median ± SD), compared with a healthy control group (68 ± 9, 56 ± 7, $p < 0.01$). It isn't significant differences between controls and patients with left-mTLE in the right inferior frontal and Superior temporal gyrus (Fig.3).

DISCUSSION

The study described here was performed to expand our understanding of left-mTLE language impairment through fMRI investigation of the underlying cortical activation pattern changes. It was demonstrated that patients with left-mTLE display difficulties in language functions, which relate to decrease of language fMRI activation. The present study revealed no significant difference between activation maps of the semantic judgment task fMRI in patients with left-mTLE compared to healthy

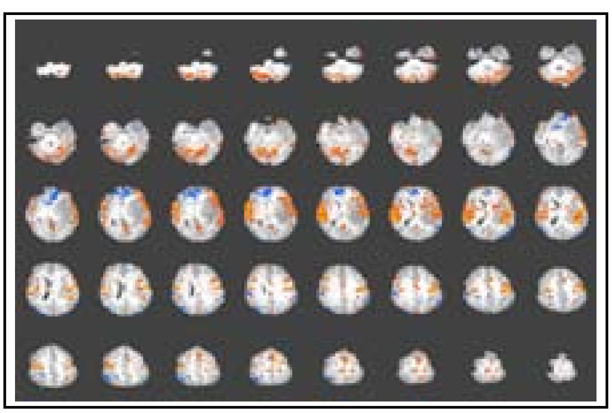

Fig-1: Activation maps of the semantic judgment task paradigm in the healthy controls group (red representative activate area).

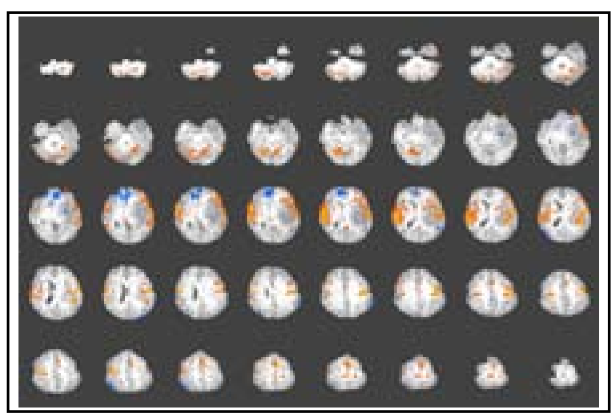

Fig-2: Activation maps of the semantic judgment task paradigm in the left-mTLE group (red representative activate area).

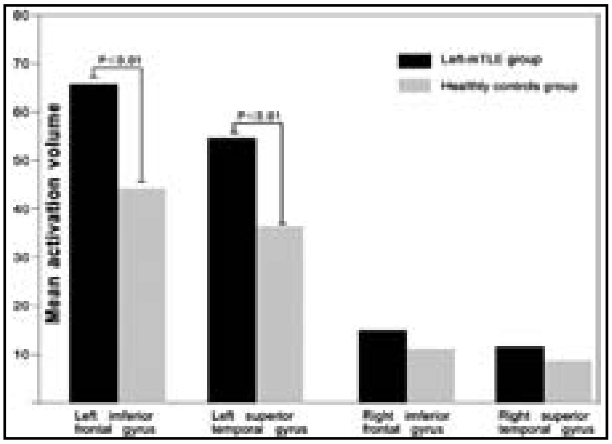

Fig-3: Mean activation volume comparison between left-mTLE and healthy controls group.

control group. This finding is surprising. Our sample is selected sample of epilepsy patients, including left-mTLE people with the absence of MRI abnormalities other than hippocampal sclerosis and atrophy. Secondly, patients with left-mTLE can perform fMRI language task and have certain language cognitive function. However, quantitative analysis revealed that the left-mTLE group had significantly lower activation volume in the left language regions of the inferior frontal and Superior temporal gyrus compared with a healthy control group. The results showed there must be neural connections between language areas and hippocampus. Meanwhile, hippocampal sclerosis and atrophy may impaired the neural connections.

The recent research investigated the plasticity and reorganisation of language in patients with epilepsy. Mbwana J et al provides evidence for intra and inter-hemispheric language reorganization in epilepsy patients using a novel quantitative data driven method for comparing individual patient fMRI data to controls. Patients clustered into several groups based on difference activation patterns.[9] Electro-cortical stimulation studies show widespread disruption, including anterior temporal lobe and middle frontal gyrus, of object naming and auditory response naming in patients with epilepsy and gliomas.[17] An fMRI study showed that language is reorganized in children who have early onset lesions of the left hemisphere.[18] These findings may indicate that seizures originating from the sclerotic hippocampus and amygdala often spread to the contralateral non-sclerotic hippocampus and amygdala though the hippocampal commissure or the anterior commissure so that mirror lesions and typical epileptic damage to the contralateral hippocampus and amygdala might occur after prolonged insults. Next, we describe how the cerebral plasticity and reorganisation could occur in each of the "plastic" regions.

Several factors can influence the language plasticity and reorganisation pattern. Younger age, shorter epilepsy duration and female gender were associated with the group showing temporal lobe intra-hemispheric reorganization. The age of seizures influences cerebral plasticity. Although it is difficult to distinguish between neuropathological changes and normal language development, it is largely accepted that the age is the primary factor for predicting recovery with prognosis so far better in children under age of six.[19] Brain injury or epilepsy onset before the age of six is associated with the inter-hemispheric transfer of language capacity identified by IAT or fMRI.[4] Thus, under the age of six, the language plasticity is reflected by supplementary involvement of the homologue hemisphere and decrease of the degree of specialization, and age of seizures onset was significantly correlated with the activity of each ROI taken into account.[20] In our study, the language plasticity and re-organization in patients with left-mTLE is not significant, possible causes is patients with epilepsy are older than 10 years of age.

Language is an important cognitive function of the human brain, and the language damage mechanism is quite complex, limitations exist in our study. Different language tasks and different imaging analysis techniques may show different activation results, so optimizing the design of the language tasks and improving the imaging analysis techniques are important future considerations.[21] Therefore, including two or more language tasks in the language evaluation has the advantage of avoiding these problems and will save the need for test repetition.

CONCLUSION

Language dysfunction in left-mTLE patients is associated with decline of language fMRI activation.

ACKNOWLEDGMENT

We thank Yuan-Xiang Lin and Liang-Hong Yu for assistance with clinical data, Ying Liu for fMRI data acquisition, and Fu-Yong Chen for contribution to the statistical analysis. We also acknowledge the support of Neurosurgery Research Institute Fujian Medical University for financing that made this study possible.

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