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Statistical parametric mapping for analyzing interictal magnetoencephalography in patients with left frontal lobe epilepsy

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ABSTRACT

Purpose: Frontal lobe epilepsy is a common epileptic disorder and is characterized by recurring seizures that arise in the frontal lobes. The purpose of this study is to identify the epileptogenic regions and other abnormal regions in patients with left frontal lobe epilepsy (LFLE) based on the magnetoencephalogram (MEG), and to understand the effects of clinical variables on brain activities in patients with LFLE.
Method: Fifteen patients with LFLE (23.20 ± 8.68 years, 6 female and 9 male) and 16 healthy controls (23.13 ± 7.66 years, 6 female and 10 male) were included in resting-stage MEG examinations. Epileptogenic regions of LFLE patients were confirmed by surgery. Regional brain activations were quantified using statistical parametric mapping (SPM). The correlation between the activations of the abnormal brain regions and the clinical seizure parameters were computed for LFLE patients.
Results: Brain activations of LFLE patients were significantly elevated in left superior/middle/inferior frontal gyri, postcentral gyrus, inferior temporal gyrus, insula, parahippocampal gyrus and amygdala, including the epileptogenic regions. Remarkable decreased activations were found mainly in the left parietal gyrus and precuneus. There is a positive correlation between the duration of the epilepsy (in month) and activations of the abnormal regions, while no relation was found between age of seizure onset (year), seizure frequency and the regions of the abnormal activity of the epileptic patients.
Conclusion: Our findings suggest that the aberrant brain activities of LFLE patients were not restricted to the epileptogenic zones. Long duration of epilepsy might induce further functional damage in patients with LFLE.

1. Introduction

Epilepsy is a common neurological disorder. The essential feature of epilepsy is the intermittent occurrence of epileptic seizures, which are caused by abnormal synchronous discharges of large numbers of neurons (including neocortex, paleocortex and archicortex). The frontal lobes cover a large portion of cerebral cortex—40% of the mass of the hemisphere, which contain multiple brain functions, such as motor function, working and behavioral memory, action integration, speech articulation, impulse control, ideation, and creativity. The frontal lobe seizures affect functional heterogeneity of the frontal lobes at large, as well as the direct intra-hemispheric connections to temporal and parietal cortices [1,2]. The seizure onset zone (SOZ) is defined as a region of the

Abbreviations: LFLE, left frontal lobe epilepsy; MEG, magnetoencephalogram; SOZ, seizure onset zone; EEG, electroencephalogram; iEEG, intracranial EEG; IED, interictal epileptiform discharge; MST, multiple subpial transection; DMN, default mode network.

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cortex that can generate epileptic seizures. For intractable epilepsies, complete removal of epileptogenic zone is necessary and sufficient to be seizure-free and is the primary goal in epilepsy surgery. However, the relationship between the epileptogenic zone and other altered brain regions in front lobe epilepsy (FLE) network is still unclear.

Epilepsy is being seen not as a disorder affecting one discrete brain region but as a disorder of widespread brain networks. Traditionally, SOZ was thought be a sole one. However, this traditional point of view had been challenged by epilepsy network models. There are growing evidences from neuroimaging that focal epilepsies involve an abnormal functional network rather than a single epileptogenic region [3–7]. Propagation of seizure activity from onset zones to remote brain sites may give rise to a seizure pattern implicating the brain region to which activity has propagated, leading to incorrect localization of seizure onset [8]. Especially for FLE, the frontal lobe cortex takes up around 40% of the total cortex and rapid propagation of epileptic activity occurs over large networks, causing difficulties in localizing epileptic clusters [9].

With the development of medical imaging technology, there are many advanced image techniques used to study the epileptogenic zone and other brain activity. During the past decade, there have been an increasing number of studies using structural or functional connectivity methods to research the clinical impact of epilepsy on neural networks [10–12]. Of the various preoperative diagnostic modalities to approximate the epileptogenic zone, the ictal onset zone on the intracranial EEG (iEEG) following subdural electrode placement has been considered as a gold-standard in determining the resection area [13–15]. A limitation of the iEEG method is that investigating long distance propagation may require widespread employment of larger intracranial electrode grids, which may increase the risk of complication.

MEG is a noninvasive technique most commonly used to record epileptic spikes and to determine their locations from magnetic fields picked up extracranially [16]. It can also aid in determining locations for iEEG electrode placement [17,18]. Previous studies have shown that MEG is a clinically valuable diagnostic tool in presurgical evaluation for both the localization of the epileptogenic zone and prognosis of surgical outcome [19–21].

In this study, our hypotheses were as follows: (1) the resting-state brain activity may be different across numerous brain regions, rather than limited in SOZs, in left frontal lobe epilepsy (LFLE) patients and healthy controls; (2) these differences could be related to the clinical variables of LFLE; (3) the brain abnormalitiesof LFLE patients could be relieved from surgery of the epileptogenic zone. To confirm SOZs, LFLE patients who planned to undergo surgical treatments were included in our study. Risk factors, such as the age of initial oneset, seizure frequency, and duration of seizures, were recorded and followed up after surgery. The goal of this study was to find the relationships between abnormal brain activations measured by MEG and SOZs and clinical risk factors of LFLE.

2. Materials and methods

2.1. Subjects

This study was approved by the Medical Ethics Committee of Nanjing Brain Hospital. Informed consent for the study was obtained from all participants. From the period of January 2010to August 2013, 141 patients with refractory epilepsy were admitted to the epilepsy center of the Brain Hospital of Nanjing Medical University (Nanjing, China) and underwent presurgical evaluation. One hundred and eleven patients (78.7%) ultimately had cortical resection to treat their epilepsy. Fifteen LFLE patients (all right-handed, 6 female and 9 male, mean age 23.20 ± 8.68 yr) were recruited from the patients who underwent surgical resection for medically intractable epilepsy. Inclusion criteria included (1) seizures with typical frontal lobe semiology that were not controlled with antiepileptic drugs; (2) an epileptogenic zone was located in the left frontal lobe; (3) left hemispheric dominance for language determined by neuropsychological evaluations (etomidate speech and memory test); (4) patients who underwent surgery for resection of epileptogenic zone; and (5) follow-up time >12 months. In our study, there were 3 lesional and 12 nonlesional patients. General information of the patients is summarized in Table 1.

Sixteen healthy volunteers (all right-handed, 6 female and 10 male, mean age 23.13 ± 7.66 years) were recruited as controls, from local community by advertising in the Brain Hospital of Nanjing Medical University. Healthy controls were interviewed and confirmed to have no history of neurological disorders or psychiatric illnesses and no gross abnormalities in brain MRI images. In this study, none of the patients and controls took antidepressants.

2.2. MEG data acquisition

Resting state MEG data were acquired by a 275-channel CTF whole-head system (CTF VSM MedTech Systems Inc., Coquitlam, BC, Canada) in a magnetically shielded room (Vacuumschmelze, Hanau, Germany). Before MEG examinations, no reduction in the antiepileptic medication was performed considering the potential risks of epilepsy. The head position associated with the sensor arrays of each subject was localized by three coils affixed to the nasion, left and right ears. A 3D T1 MRI was acquired to record the locations of these three coils for later spatial registration. To increase the likelihood of capturing interictal epileptiform discharges (IEDs), we recorded 15 epochs (120 s/epoch) of spontaneous brain activities using MEG to localize the epileptic focus in clinical. At sampling rate 400 Hz, 120 s MEG data was recorded for each subject as an epoch, which contained IEDs and 36,000 time points. During MEG recording, all subjects were asked to close their eyes and keep their heads still. If head motion was greater than 5 mm, the epoch was resampled.

2.3. Data processing

MEG data was band filtered (range from 20 Hz to 70 Hz) by CTF software (VSM MedTech Systems Inc. Canada, Version CTF-5.2.1) in our MEG clinical center. After filtering, MEG data was loaded into SPM8 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). MEG source localization was based on an empirical Bayesian formalism [22]. To yield significant differences at the between-subject level, group inversion of SPM8 was used for 3D source reconstruction. For each subject, the T1 MRI was used for registration. Three markers on T1 MRI, i.e., nasion, left and right ears, were clicked to co-register the MEG of each subject to MNI space. The single sphere model was used as the forward model and then the MEG data was inversed by the Bayesian framework. The MEG activation maps were smoothed by FWHM of 8 mm before group-level statistical analysis.

2.4. Statistical analysis

One-way analysis of covariance (ANCOVA) with age and gender as covariates was applied to compare SPM activation maps of LFLE patients and those of healthy controls. Voxel-based P values less than 0.05 were considered statistically significant. Based on the voxel-wise significant differences, brain regions with suprathreshold clusters were defined as regions of interests (ROIs). Mean activation value was computed using Automated Anatomical Labeling atlas. Group-level analysis was performed between the LFLE and control groups. Regional differences were detected by