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Patient-specific connectivity pattern of epileptic network in frontal lobe epilepsy

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ABSTRACT

There is evidence that focal epilepsy may involve the dysfunction of a brain network in addition to the focal region. To delineate the characteristics of this epileptic network, we collected EEG/fMRI data from 23 patients with frontal lobe epilepsy. For each patient, EEG/fMRI analysis was first performed to determine the BOLD response to epileptic spikes. The maximum activation cluster in the frontal lobe was then chosen as the seed to identify the epileptic network in fMRI data. Functional connectivity analysis seeded at the same region was also performed in 63 healthy control subjects. Nine features were used to evaluate the differences of epileptic network patterns in three connection levels between patients and controls. Compared with control subjects, patients showed overall more functional connections between the epileptogenic region and the rest of the brain and higher laterality. However, the significantly increased connections were located in the neighborhood of the seed, but the connections between the seed and remote regions actually decreased. Comparing fMRI runs with interictal epileptic discharges (IEDs) and without IEDs, the patient-specific connectivity pattern was not changed significantly. These findings regarding patient-specific connectivity patterns of epileptic networks in FLE reflect local high connectivity and connections with distant regions differing from those of healthy controls. Moreover, the difference between the two groups in most features was observed in the strictest of the three connection levels. The abnormally high connectivity might reflect a predominant attribute of the epileptic network, which may facilitate propagation of epileptic activity among regions in the network.

1. Introduction

Epilepsy is characterized by abnormal neuro-electrical activity in the brain. In focal seizures and focal epilepsy the epileptic activity arises primarily within networks limited to one hemisphere. The origin of focal seizures may be associated with the localization of radiologically visible brain lesions or electrophysiological abnormalities. However, there is growing evidence from neuroimaging that focal epilepsies involve an abnormal functional network rather than a single epileptogenic region (Kramer and Cash, 2012; Constable et al., 2013; Laufs, 2012). Using combined EEG and fMRI recordings (EEG/fMRI), our group showed that focal interictal epileptic discharges (IEDs) are associated with specific networks of widespread metabolic changes in different focal epilepsies (Fahoum et al., 2012). The abnormal neuronal activity in epileptic networks may lead to interictal and ictal epileptic activity. Therefore, the characteristic of the epileptic network may be important to assess seizure initiation or propagation.

Recently, functional connectivity (FC) analysis based on resting state fMRI has revealed more than ten reproducible brain networks in healthy controls. Disturbed FC maps are observed in different types of epilepsy and are associated with cognitive impairment and propagation of epileptic activity (Bettus et al., 2009; Vaessen et al., 2013; Liao et al., 2011; Luo et al., 2012; Zhang et al., 2011). Seed-based FC analysis can identify the remote regions connected with the seed. For example, the motor network can be defined when the seed is placed at the primary motor cortex (Biswal et al., 1995). Using this approach, we demonstrated abnormal FC in some resting state functional networks in generalized epilepsy (Luo et al., 2011; Maneshi et al., 2012). The FC map seeded at the epileptogenic focus might provide a window to investigate seizure initiation and propagation. For example, FC seeded at the hippocampus was used to identify the lateralization of temporal lobe epilepsy (TLE) (Morgan et al., 2012), and to identify abnormal connectivity in this condition (Pittau et al., 2012). EEG/fMRI may provide a priori information useful to define part of the epileptic network, because it can help delineate epileptogenic regions

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non-invasively, by pointing to regions where there are hemodynamic changes correlated with the epileptic activity as detected on EEG. FC analysis based on EEG/fMRI findings has been performed in previous studies.

Most of these FC analysis studies investigate the differences between two groups in the strength of voxel-based FC with the potential epileptogenic region, such as FC with the hippocampus in patients with TLE and in controls (Pittau et al., 2012). However, it is difficult to perform FC strength analysis in a group of epileptic patients with epileptic foci in different regions, because the seeds of FC are different for each patient. The pattern of FC, i.e. the distribution of FC regions rather than the strength of FC would be another attribute to delineate interaction between the seed and other regions in the brain. For example, the symmetry of FC map is often evaluated as a spatial feature. The lateralized index of FC maps may predict surgical outcome for candidates of epileptic surgery (Negishi et al., 2011). Specific brain regions in epileptic network are associated with seizure initiation or propagation, with their activity modulating or modulated by the occurrence of epileptic activity. Therefore, the patterns of FC seeded at a given brain structure could be different between patients and controls. Evaluating the characteristics of FC patterns would help uncover the difference between patient-specific pathways and normal pathway in control subjects, and provide detailed information to understand the connectivity of a particular epileptogenic region.

In the current study, we investigate the patterns of epileptic networks in a group of patients with frontal lobe epilepsy (FLE), using the FC map seeded at the epileptogenic regions defined by EEG/fMRI. We hypothesize that epileptic networks are reflected in patient-specific pathways different from the FC maps seeded at the same region in healthy controls.

2. Materials and methods

2.1. Participants

Between April 2006 and September 2012, 41 patients with frontal lobe epilepsy were evaluated with 3 T EEG–fMRI scans at the Montreal Neurological Institute and Hospital (MNI/MNH). The diagnosis was established according to the diagnostic criteria published by the International League Against Epilepsy (Engel, 2001). Only patients without distinct structural brain abnormality, such as atrophy caused by surgery or injury, tumor, or significant malformation of cortical development leading to distortion of brain anatomy, were included in the functional connectivity analysis. Therefore, patients with minor structural abnormalities such as focal cortical dysplasia consisting of a trans-mantle sign or a localized cortical thickening were included. Sixty-three age- and gender- matched healthy controls were also included in the current study, and they underwent a resting state fMRI scan. The study was approved by the Research Ethics Board of MNI/MNH. Written informed consent as approved by the MNI/MNH Research Ethics Committee was obtained from all subjects.

2.2. Data acquisition

EEG was recorded inside a 3 Tesla MRI scanner (Trio; Siemens, Germany) with 25 MR compatible scalp electrodes placed according to 10–20 (reference FCz) and 10–10 (F9, T9, P9, F10, T10, P10) systems, using a BrainAmp system (Brain Products, Munich, Germany, 5 kHz sampling). A T1-weighted anatomic image was acquired first using the following sequences: until July 2008: 1-mm slice thickness; 256 × 256 matrix; echo time (TE) 7.4 ms; repetition time (TR) 23 ms; flip angle 30°; from July 2008: 1-mm slice thickness; 256 × 256 matrix; TE 4.18 ms; TR 23 ms; flip angle 9°. T1 image was used for superimposition with functional images. Functional data were collected in 6-min runs lasting 60–90 min, with a T2*-weighted echo planar imaging (EPI) sequence: until July 2008: TR 1.75 s; TE 30 ms; 64 × 64 matrix; 25 slices; voxel 5 × 5 × 5 mm; flip angle 90° and from July 2008: TR 1.9 s; TE 25 ms; 64 × 64 matrix; 33 slices; voxel 3.7 × 3.7 × 3.7 mm; flip angle 90°. This MR protocol was used for all patients and for 25 healthy controls; the control subjects had no EEG. The remaining 38 of the 63 healthy controls were scanned in a 3 Tesla MRI scanner (GE Discovery MR750). T1-weighted image was collected using the following parameters: 1-mm slice thickness; 256 × 256 matrix; TE 1.98 ms; TR 6.008 ms; flip angle 90°. Resting state functional data with 205 volumes were acquired using gradient-echo EPI sequence (TR 2 s; TE 30 ms; 64 × 64 matrix; 33 slices; voxel 3.7 × 3.7 × 3.7 mm; flip angle 90°). The first five volumes were discarded to ensure magnetic field stabilization.

2.3. EEG and EEG/fMRI processing

The method is identical to that used in prior studies (Fahoum et al., 2012; Pittau et al., 2012). BrainVision Analyzer was used to remove MR gradient artifacts. The ballistocardiographic artifact was removed with independent component analysis (Benar et al., 2003). IEDs similar to those obtained outside the scanner were marked. IEDs were separated according to different spatial distributions, and events with different distributions were analyzed independently. Then, fMRI images were motion corrected and smoothed (6-mm full width at half maximum). Temporal autocorrelations were accounted for by fitting an autoregressive model of order 1, and low frequency drifts were modeled with a third-order polynomial fitting to each run. Timing and duration of each IED were built as a regressor and convolved with four hemodynamic response functions (HRFs) peaking at 3, 5, 7, and 9 s (Bagshaw et al., 2004). Six motion parameters were modeled as confounds. A statistic t map was created for each regressor of interest (IED or event type) using the other regressors as confounds for each event type. A combined t map was created by taking, at each voxel, the maximum t value from the four t maps based on the four HRFs. The single combined t map was used for determination of the seed. To be significant, activation required five contiguous voxels having a t value >3.1 corresponding to $p < 0.001$, corrected for multiple comparisons. Responses outside the cerebral cortex were excluded.

In addition, based on simultaneous EEG recordings, patients were divided into those in whom all runs had IEDs and those in whom at least one run had no IED. In the patients having at least one run without IEDs, we compared runs with and without IEDs, as described below.

2.4. Functional connectivity analysis

Patients who had IEDs inside the scanner and showed activation to IEDs resulting from the EEG/fMRI analysis were included in the following analysis. The activation was identified and selected as the seed according to the following criteria: (i) the seed was centered at the local maximum activation located in frontal regions or anterior cingulate cortex and ipsilateral to the maximum spike amplitude in the EEG; and (ii) the seed was shaped by the cluster of significant voxels found with EEG/fMRI. The number of voxels in the seed was limited to less than 200, because a seed larger than 200 voxels might increase the variability of time signals within the seed. This threshold is of course somewhat arbitrary. If the size of the cluster around the local maximum defined in (i) was larger than 200, the threshold was gradually increased until the size of the seed became smaller than 200; (ii) if more than one type of IEDs are present in a patient, one seed is selected for each spike type. If two such seeds overlap in a patient, they are merged.

For FC analysis, two runs were analyzed for each patient: one run with IEDs and one without IED if such a run could be found. The fMRI datasets were preprocessed with the SPM8 software package [Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm]. Slice