Altered intrinsic brain activity in patients with familial cortical myoclonic tremor and epilepsy: An amplitude of low-frequency fluctuation study

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ABSTRACT

Purpose: To investigate localized cerebral function abnormalities in patients with familial cortical myoclonic tremor and epilepsy (FCMTE) using resting-state functional magnetic resonance imaging (fMRI).

Methods: Seven patients with FCMTE from a Chinese family, seven patients with essential tremor (ET), and ten healthy controls were recruited. Amplitude of low-frequency fluctuation (ALFF) analysis was utilized to reveal the potential functional changes in patients with FCMTE.

Results: Significant differences in the bilateral frontal lobe and fusiform gyrus among the three groups were revealed by one-way analysis of variance (ANOVA). The t-tests between groups were performed to compare ALFF in these ROIs. The FCMTE subjects exhibited decreased ALFF in the right fusiform gyrus and posterior cingulate cortex (PCC) with increased ALFF in the frontal lobe, compared with the ET and healthy control groups. Furthermore, the ALFF in the frontal lobe was positively correlated with the duration of tremor in patients with FCMTE and ET.

Conclusion: These findings suggest that frontal cortex and PCC impairment might be related to the epileptic activity and that the abnormality of the fusiform gyrus may be associated with impairment of visuospatial in FCMTE. Due to the positive correlation between the duration of tremor and ALFF in the frontal lobe, changes in the frontal lobe could be a potential indicator of a candidate causative gene for FCMTE.

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1. Introduction

Familial cortical myoclonic tremor and epilepsy (FCMTE) is a rare autosomal inheritance syndrome, characterized by an adolescent or adult onset of myoclonus of the extremities, tremor, infrequent epileptic seizures and non-progressive diseases [1,2]. Four autosomal dominant inherited loci have been reported, including 8q23.3–q24.13 (OMIM: 601068), 2p11.1–p12.2 (OMIM: 607876), 5p15.31–p15.1 (OMIM: 613608) and 3q26.32–3q28 [3–6]. In parallel, one autosomal recessive inherited locus was linked to 1q31.3–22.2 [2]. However, only one candidate causative gene, CNTN2, has been identified in autosomal recessive FCMTE [2]. No causative gene has been identified in autosomal dominant FCMTE [3–7]. Thus far, the pathophysiology of this condition remains speculative. FCMTE patients demonstrated abnormalities in the cortical and subcortical areas, such as the frontoparietal lobe, and the cortical deficits may lead to complex partial seizures, intractable seizures, and mental retardation [4,5,7]. In addition, routine electroencephalography (EEG) and 24 h-video EEG show irregular bursts, slow waves and spikes predominantly in the centrotemporal regions [4,8].

The clinical characteristics of essential tremor (ET), including postural and kinetic tremors that generally affect the hands and head [9,10], are similar to those of FCMTE. To date, studies examining systematic clinical analysis, neuropathology, and genetics in both FCMTE and...
ET indicate changes in the cortex and subcortical regions [11–15]. However, epileptic seizures were experienced in FCMTE patients. Therefore, an investigation combining FCMTE and ET may help to determine the cause of the epileptic activity in FCMTE and the difference between two types of tremor.

Blood oxygen level-dependent (BOLD) signals of resting-state functional magnetic resonance imaging (fMRI) are thought to reflect oxygen metabolism in response to synaptic activity [16], and spontaneous low-frequency fluctuations (~0.08 Hz) of BOLD signals reflect intrinsic neuronal activity [17,18]. Zang et al. proposed a measure, called the amplitude of low-frequency fluctuation (ALFF), which is obtained by calculating the square root of the power spectrum in a frequency range (usually, 0.01–0.08 Hz) to assess the spontaneous brain activity [19]. ALFF has been widely applied to several neuropsychiatric disorders, such as schizophrenia [20,21], attention deficit hyperactivity disorder in children [22], Alzheimer’s disease [23] and epilepsy [24]. However, there are still few investigations regarding the spontaneous brain activity of patients with FCMTE in resting-state fMRI.

In this study, we first hypothesized that the FCMTE patients may have potential changes of ALFF in the resting-state, which may reflect the abnormality of brain function. Then, the ALFF maps of FCMTE patients, ET patients, and healthy controls were analyzed. In addition, the correlation between the duration of tremor and ALFF was further investigated.

2. Materials and methods

2.1. Subjects

Seven FCMTE patients (7 male; mean age: 57 years; range: 46–69 years) from a Chinese FCMTE genealogy showing autosomal dominant inheritance were investigated in this study. The diagnosis of FCMTE was established according to the diagnostic review by Sharifi and colleagues [8]. All of the FCMTE patients who underwent a 24 h-video EEG had a history of cortical myoclonic tremor in the upper limbs and experienced rare generalized tonic–clonic seizures (GTCS). The detailed demographic information and clinical characteristics of FCMTE. The EEG showed a burst of sharp waves in 3 patients, frequent runs of sharp slow waves were observed in 3 patients, and the EEG of the remaining 1 patient was irregular. Seven patients (five from two familial and two sporadic cases) with ET, who were diagnosed according to the diagnostic criteria of the Tremor Investigation Group [25], were recruited as a control group. Only two patients received medication (one ET patient was treated with atenolol, and the other was treated with propranolol), and the remaining patients with ET did not receive any treatment. Ten age matched healthy controls (10 male; mean age: 62.8 years, range: 45–69 years) participated in our study. They had no history of neurological or psychiatric conditions. All subjects were right-handed with normal hearing and showed normal levels on routine laboratory tests. Written informed consent according to the Declaration of Helsinki was obtained from all 24 participants, and the study protocol was approved by the ethics committee of Sichuan Provincial People’s Hospital.

2.2. Image acquisition

MRI scanning was performed on a 3.0 T scanner (Discovery MR750, GE, USA). T1-weighted anatomical images were acquired using a 3-dimensional fast spoiled gradient echo (3D FSPGR) sequence to generate 152 slices, and the scan parameters were as follows: TR/TE = 6.008 ms/1.984 ms; flip angle = 90°; matrix size = 256 × 256; FOV = 25.6 × 25.6 cm²; and slice thickness (no gap) = 1 mm. The subjects are summarized in Table 1. The mean age at onset of tremor was 30 years (range: 20–40 years). Visuospatial processing was evaluated using the Copy of Rey’s Complex Figure (the subject is instructed to copy the figure, a complex design containing 18 scorable elements). The scores were illustrated in Table 1. Two FCMTE patients were treated with valproic acid (VPA) only, and one FCMTE patient received VPA and carbamazepine (CBZ). Three patients on drug treatments showed improved tremulous movements and a diminished number of seizures. However, the remaining two patients with FCMTE did not receive any treatment due to financial constraints. In general, sharp or slow waves were observed in the frontocentral region. Fig. 1 demonstrates typical epileptic activity in the bilateral frontocentral region in a patient with FCMTE. The EEG showed a burst of sharp waves in 3 patients, frequent runs of sharp slow waves were observed in 3 patients, and the EEG of the remaining 1 patient was irregular. Seven patients (five from two familial and two sporadic cases) with ET, who were diagnosed according to the diagnostic criteria of the Tremor Investigation Group [25], were recruited as a control group. Only two patients received medication (one ET patient was treated with atenolol, and the other was treated with propranolol), and the remaining patients with ET did not receive any treatment. Ten age matched healthy controls (10 male; mean age: 62.8 years, range: 45–69 years) participated in our study. They had no history of neurological or psychiatric conditions. All subjects were right-handed with normal hearing and showed normal levels on routine laboratory tests. Written informed consent according to the Declaration of Helsinki was obtained from all 24 participants, and the study protocol was approved by the ethics committee of Sichuan Provincial People’s Hospital.

Table 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sex/age (years)</th>
<th>Age at onset of tremor</th>
<th>Seizure type/onset (years)</th>
<th>Medication</th>
<th>Other</th>
<th>Interictal EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 FCMTE</td>
<td>M/63</td>
<td>31</td>
<td>GTCS/38</td>
<td>VSP (22)</td>
<td>–</td>
<td>Burst of diffuse slow waves and intermixed spikes</td>
</tr>
<tr>
<td>2 FCMTE</td>
<td>M/46</td>
<td>22</td>
<td>GTCS/45</td>
<td>VSP (30)</td>
<td>–</td>
<td>Bilateral bursts of spikes and slow waves, single and 2–3 short clusters</td>
</tr>
<tr>
<td>3 FCMTE</td>
<td>M/66</td>
<td>35</td>
<td>GTCS/39</td>
<td>VSP (28)</td>
<td>–</td>
<td>Bilateral bursts of sharp–slow waves</td>
</tr>
<tr>
<td>4 FCMTE</td>
<td>M/69</td>
<td>33</td>
<td>GTCS/36</td>
<td>VSP CBZ</td>
<td>–</td>
<td>Bilateral bursts of spikes and slow waves, single and 2–3 short clusters</td>
</tr>
<tr>
<td>5 FCMTE</td>
<td>M/63</td>
<td>40</td>
<td>GTCS/48</td>
<td>VSP (32)</td>
<td>–</td>
<td>Bilateral bursts of sharp–slow waves</td>
</tr>
<tr>
<td>6 FCMTE</td>
<td>M/46</td>
<td>32</td>
<td>GTCS/38</td>
<td>VSP (34)</td>
<td>–</td>
<td>Bilateral burst of theta sharp waves</td>
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<tr>
<td>7 FCMTE</td>
<td>M/48</td>
<td>20</td>
<td>GTCS/28</td>
<td>VSP (36)</td>
<td>–</td>
<td>Irregular EEG</td>
</tr>
<tr>
<td>1 ET</td>
<td>M/68</td>
<td>60</td>
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<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>3 ET</td>
<td>M/25</td>
<td>18</td>
<td>–</td>
<td>Propranolol</td>
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<tr>
<td>4 ET</td>
<td>M/21</td>
<td>16</td>
<td>–</td>
<td>Atenolol</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5 ET</td>
<td>F/74</td>
<td>56</td>
<td>–</td>
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<td>–</td>
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<tr>
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<td>–</td>
<td>–</td>
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<td>–</td>
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<tr>
<td>10 HC</td>
<td>M/62</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>


* The low value of VSP (≤26) means the disturbed visuospatial performance.
resting-state functional images were acquired using a gradient-echo planar imaging (EPI) sequence, and the scan parameters were as follows: TR/TE = 2000 ms/30 ms; flip angle = 9°; matrix size = 64 × 64; field view = 24 × 24 cm²; and thickness = 4 mm. A total number of 255 volumes (35 slices per volumes) were obtained over a 510 s period. Participants were explicitly instructed to close their eyes and relax without falling asleep during scanning.

2.3. Data preprocessing

Preprocessing of fMRI data, which was conducted using the SPM8 toolbox (statistical parametric mapping, http://www.fil.ion.ucl.ac.uk/spm), included slice time correction, motion correction, and spatial normalization (3 × 3 × 3 mm³) to the MNI template. Data were excluded if head motion exceeded 1 mm (translation) and 1° (rotation) during fMRI acquisition. Finally, these functional images were smoothed with a 6-mm full-width at half maximum (FWHM) of an isotropic Gaussian filter.

2.4. ALFF analysis

The amplitude of low-frequency fluctuation maps were calculated using the REST toolbox (http://www.restfmri.net/forum/REST). First, using fast Fourier transform, the time series of each voxel was transformed to a frequency domain, and the square root of the power spectrum was calculated. Then, the averaged square root of the power across 0.01–0.08 Hz was determined as the ALFF. In addition, the ALFF of each voxel was divided by the global mean ALFF for each subject. Voxel-based comparison of ALFF maps among the three groups (FCMTE, ET, and healthy controls) was performed using a designed model of one-way analysis of variance (ANOVA). To illustrate clearly the difference between groups, we furthermore performed the comparison on the regions of interest (ROI) with significant difference in ANOVA analysis.

2.5. Correlation analyses between ALFF and clinical characteristics

To investigate the underlying linear association of different ALFF values across the FCMTE and ET groups, a linear correlation between the altered ALFF and the clinical characteristics (duration of tremor and age of onset of tremor) was calculated, controlling for the effects of age and gender. Although the number of patients with FCMTE was only seven, we calculated the correlation between the altered ALFF and the duration of seizures to perform a preliminary investigation of the effect of seizures on ALFF.

3. Results

3.1. Alterations of ALFF

To obtain the difference in ALFF among the three groups, one-way ANOVA was performed (p < 0.001, uncorrected). Table 2 illustrated the cerebral regions with significant differences among groups, which included the left inferior frontal gyrus (Brodmann area, BA10), left superior frontal gyrus (BA10), right fusiform gyrus (BA23), right middle frontal gyrus (BA11), right superior frontal gyrus (BA10), right inferior frontal gyrus (BA10) and posterior cingulate cortex (PCC, BA31/7). Seven cubic ROIs (27 voxels) were extracted with peak at these regions. The ALFF value was averaged in each ROI for each subject.

The t-tests between groups were performed to compare ALFF in these ROIs. Histograms of the ALFF in the seven regions in the three groups were shown in Figs. 2 and 3 (p < 0.001, uncorrected). Compared with ET group and healthy controls, increased ALFF in the FCMTE group was observed in the left superior frontal gyrus (BA10), left inferior frontal gyrus (BA10), right middle frontal gyrus (BA11), right superior frontal gyrus (BA10) and posterior cingulate cortex (PCC, BA31/7). Seven cubic ROIs (27 voxels) were extracted with peak at these regions. The ALFF value was averaged in each ROI for each subject.

The ALFF values in the left inferior frontal gyrus, left superior frontal gyrus, right middle frontal gyrus and right inferior frontal gyrus were significantly positively correlated with the duration of tremor in the FCMTE and ET groups (Fig. 4a–d), after controlling for the effects of age and gender. Additionally, a marginally significant correlation was found in the right superior frontal gyrus (Fig. 4e). Fig. 4f demonstrates that a significant negative correlation existed between the duration of tremor and ALFF in the right posterior cingulate cortex. No significant correlations were observed between ALFF and duration of seizures in the FCMTE group.

4. Discussion

To date, ALFF has been extensively used to uncover the features of resting state fMRI in different types of neuropsychiatric disorders, such as schizophrenia [20,21], attention deficit hyperactivity disorder in children [22], Alzheimer’s disease [23] and epilepsy [24]. However, there are few studies investigating ALFF abnormalities in patients with FCMTE during resting-state fMRI. Compared with ET patients and healthy controls, the patients with FCMTE showed increased ALFF in the bilateral frontal cortex, and they showed decreased ALFF in the...
PCC and fusiform gyrus. In addition, aberrant ALFF of several brain regions was associated with clinical variables. The abnormality of intrinsic activity in the frontal lobe could be a potential indicator of a candidate causative gene for FCMTE.

4.1. Increased ALFF in the frontal lobe

Whole-brain voxel-based analysis of ALFF indicated that patients with FCMTE showed increased ALFF mainly in the bilateral superior frontal gyrus and inferior frontal gyrus (Table 2 and Fig. 2a, b, and d–f). FCMTE studies including several genealogies have presented evidence of a sensorimotor origin for tremulous movements [1,3–7]. Meanwhile, electromyography (EMG)-fMRI and neurophysiological studies have demonstrated that the tremulous movements in FCMTE patients may be correlated with the activity in the sensorimotor cortex [14,26]. Our findings indicated that the impairment in motor-related regions might be associated with tremulous movements. Impairments in motor-related areas are caused by a γ-aminobutyric acid (GABA) synaptic impairment [4,27]. Furthermore, the duration of tremor significantly influenced the ALFF in the frontal lobe (Fig. 4), even though no difference of ALFF in the frontal lobe was observed between ET and healthy controls.

Additionally, the increased ALFF in the bilateral frontal lobe found in patients with FCMTE might also be related to the epileptic activity. The EEG predominance of the frontocentral region in epileptic activity was also observed in patients with FCMTE in this study, which supports the notion that frontal lobe impairment might be related to epileptic activity (Fig. 1). Taken together, our findings might imply that dysfunction of the frontal lobe may play a crucial role in cortical myoclonic tremor and seizures in patients with FCMTE. In addition, it is worth noting

<table>
<thead>
<tr>
<th>Cerebral region</th>
<th>Brodmann</th>
<th>MNI coordinate</th>
<th>F value</th>
<th>Cluster volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior frontal gyrus—L</td>
<td>BA10</td>
<td>−48 48 3</td>
<td>17.25</td>
<td>8775</td>
</tr>
<tr>
<td>Superior frontal gyrus—L</td>
<td>BA10</td>
<td>−18 57 0</td>
<td>19.36</td>
<td>1485</td>
</tr>
<tr>
<td>Fusiform gyrus—R</td>
<td>BA23</td>
<td>42 −93 −6</td>
<td>20.47</td>
<td>918</td>
</tr>
<tr>
<td>Middle frontal gyrus—R</td>
<td>BA11</td>
<td>33 42 −12</td>
<td>19.11</td>
<td>8208</td>
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<tr>
<td>Superior frontal gyrus—R</td>
<td>BA10</td>
<td>25 57 6</td>
<td>18.16</td>
<td></td>
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<tr>
<td>Inferior frontal gyrus—R</td>
<td>BA10</td>
<td>15 48 3</td>
<td>15.89</td>
<td></td>
</tr>
<tr>
<td>Posterior cingulate cortex—R</td>
<td>BA23/7</td>
<td>9 −63 24</td>
<td>11.39</td>
<td>270</td>
</tr>
</tbody>
</table>

L: left and R: right.

Fig. 2. ALFF analysis results in the cortex. Results of one-way ANOVA (p < 0.001, uncorrected) are shown in the middle column, and the results of t-tests (*: p < 0.001, uncorrected) are shown in boxes that represent the peak significant effects that existed in the various lobes (a–f). ET: essential tremor; HC: healthy control; FCMTE: familial cortical myoclonic tremor and epilepsy; F: F-value; L: left and R: right.
that a lessening of tremulous movements and a decrease in the number of seizures were found in three FCMTE patients after treatment with VPA and CBZ. These anti-epileptic drugs (AEDs) could raise the inhibitory neurotransmitter (e.g., GABA) concentrations by increasing GABA synthesis and decreasing GABA degradation, thus reducing the excitability of neurons and inhibiting seizures [28]. Here, this result is in line with the view that some AEDs (especially VPA and clonazepam) could improve the tremulous movements and lessen the number of seizures [4,7,8].

The causative genes of this syndrome have not yet been identified, and its pathogenesis remains speculative. Here, the results of EEG and ALFF (bilateral frontal lobe impairment in patients with FCMTE) might provide a possibility that the gene associated with frontal lobe epilepsy might be a candidate causative gene for FCMTE. It is suggested that FCMTE, similar to autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), is a channelopathy [29]. In the past few years, several causative genes of ADNFLE have been identified, such as CHRNA4 [29], CHRNA2 [29], CHRNQ2 [29], KCNT1 [30], CHD2 [31] and SYNGAP1 [31]. Therefore, this information may be helpful for the investigation of a candidate causative gene for FCMTE in the future. Additionally, the causative gene of this disorder could be determined by whole exome and genome sequencing [32,33] in future studies.

4.2. Functional impairment in the PCC

In this study, apart from the commonly affected bilateral frontal lobe, the group of patients with FCMTE showed reduced ALFF in the PCC, compared with patients with ET and healthy controls (Fig. 3). The PCC is a major node of the default mode network (DMN) [34], which is characterized by decreased activity during attention-demanding tasks and increased brain activity during the resting-state. Decreased ALFF in the DMN was reported in temporal lobe epilepsy (TLE) patients by a previous fMRI study [24], and diminished functional connectivity in the DMN was also observed in patients with epilepsy [35,36]. The current result that the ALFF in BOLD signals was decreased in the PCC supports the idea that altered low frequency fluctuation might be related to the epileptic seizures in patients with FCMTE.

4.3. Decreased ALFF in the visuospatial regions

Decreased ALFF was found in the fusiform gyrus in FCMTE patients, compared with ET patients and healthy controls (Table 2, Fig. 2c). The fusiform gyrus plays major roles in the visual system; altered connection might indicate a reorganization of the visual system. A visuospatial impairment has been reported in a single FCMTE family [7]. In addition, visual impairment was also observed in two of the seven subjects in this study. Therefore, in this study, these decreased ALFF values in the fusiform gyrus might be associated with visuospatial impairment in patients with FCMTE.

4.4. Limitations of this study

Several limitations were involved in the present study. Firstly, the main limitation of the present study was the small number of patients in each group. Only one genealogy with FCMTE was recruited. This study is a preliminary work and it would be useful to increase the patients with FCMTE and siblings from more than one genealogy for further analyses. Second, the age of the ET group was not matched with the other groups, which might affect the results, although the effects of age and gender were controlled in our study. Third, the AEDs taken by some patients might confound the results; in future studies, homogeneous patients should be grouped more appropriately and the medication dose should be detailed. Finally, CNTN2 is a candidate causative gene for autosomal recessive inheritance FCMTE; however, it remains unclear whether there are functional changes (e.g., ALFF measures) between FCMTE patients with and without CNTN2 mutations during the resting-state. Further research investigating FCMTE patients with CNTN2 mutations using fMRI is needed in the future.

5. Conclusions

Results from the present resting-state fMRI study provide evidence for ALFF abnormalities in patients with FCMTE. These findings suggest that bilateral frontal cortex and PCC impairment might be related to the epileptic activity, and abnormality of the fusiform gyrus was
associated with visuospatial impairment in FCMTE. In addition, the duration of tremor significantly influences the ALFF in the frontal lobe. The current results might also reflect chronic, abnormal alterations and anatomo-functional integration in the brain of FCMTE patients. Moreover, the abnormality of intrinsic activity in the frontal lobe could be a potential indicator of a candidate causative gene for FCMTE.

Conflict of interest

There is no conflict of interest.

Acknowledgments

The authors thank the FCMTE patients, ET patients and healthy controls for participating in this study. This study was funded by grants from the 973 Project 2011CB707803, the National Natural Science Foundation of China (81170883 and 81430008 (Z.Y.)), and the Department of Science and Technology of Sichuan Province, China (2014SZ0169 and 2015SZ0052 (Z.Y.)).

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