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Microstructural alterations of white matter in juvenile myoclonic epilepsy

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ABSTRACT

Juvenile myoclonic epilepsy (JME) is a common type of idiopathic generalized epilepsy that is characterized by myoclonic jerks of the upper limbs and generalized tonic-clonic seizures. Frontal cognitive dysfunctions and abnormal coupling of the thalamocortical system have been found in neuropsychological and neuroimaging studies. This study intended to explore white matter (WM) measurement changes in JME using MRI. Twenty-six patients with JME and 25 healthy controls (HC) were recruited for the acquisition of diffusion MRI and structural MRI data. Then, a tract-based spatial statistics approach was used to investigate the disease effects on WM microstructural diffusion characteristics. Subsequently, the associations between clinical features and characteristics of the tracts that connect the impacted regions were also evaluated. Compared with HC, JME showed an increased mean diffusivity in the anterior corpus callosum connected to the bilateral frontal lobe. Decreased axial diffusivity was observed in the body of the corpus callosum connected to the bilateral supplementary motor area as well as, in the region connecting the left thalamic radiation, the superior longitudinal fasciculus and corticospinal tract. Furthermore, the microstructural metrics of the tracts connecting these regions, especially the projection fibres that connect the cerebral cortex, subcortical regions and cerebellum, were correlated with disease duration. These findings likely reflect the alterations in WM microstructural connectivity, which may be associated with frontal cognitive and motor dysfunction in JME. In addition, the projection fibres connecting these impacted regions are progressively affected by the disease duration. Based on our findings, we propose that the cerebellum may play a potential role in the pathomechanism of JME.

1. Introduction

Juvenile myoclonic epilepsy (JME) is a common idiopathic generalized form of epilepsy, accounting for 5–10% of all epilepsy cases (Janz and Christian, 1957; Panayiotopoulos et al., 1994). Myoclonic jerks and generalized tonic-clonic seizures are the principal characteristics of JME and initially manifest during the mid-teens and mainly occur early in the morning. JME patients reportedly suffer from behavioural disturbances in self-regulation and personality traits, such as impressionability, unreliability, and emotional instability, similar to those of patients with frontal lobe lesions. The pathogenesis of JME has not yet been fully clarified (Hommet et al., 2006). Typical characteristics of electroencephalography (EEG) in JME are 3–4 Hz polyspikes with slow wave discharges and a fronto-central predominance, which are important for clinical diagnosis. Unfortunately, conventional neuroimaging still fails to detect structural abnormalities in JME patients even now.

Nevertheless, increasing neuroimaging evidence supports the theory that JME is involved in abnormalities of the frontal cognitive system, frontal-thalamic network and motor system. A hypothesis that characterized JME by impaired thalamofrontal networks was proposed (Deppe et al., 2008; O'Muircheartaigh et al., 2012) and later reinforced by a MRI spectroscopy study that found decreased thalamic NAA/Cr ratios in patients with JME (Mory et al., 2003). Animal and human studies have suggested that thalamic interactions with the cerebral cortex are involved in the generation of the generalized spike-wave discharges (GSWDs) (Blumenfeld, 2003; Danober et al., 1998; Dong et al., 2016; Li et al., 2016). Moreover, recent studies have demonstrated cognitive dysfunction and abnormal motor function in JME, which could also be induced by an abnormal thalamofrontal network (Bernhardt et al., 2009; Deppe et al., 2008; Jiang et al., 2016).

White matter (WM) alterations in epilepsy patients have been

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revealed using diffusion magnetic resonance imaging (dMRI) (Luo et al., 2011; Xue et al., 2014; Yang et al., 2012). In patients with JME, Deppe and co-workers studied the fractional anisotropy (FA) of the anterior limb of the bilateral internal capsule, providing structural evidence to support the hypothesis that the thalamocortical network of JME is abnormal (Deppe et al., 2008). Studies merging functional MRI and dMRI found that both functional and structural connections in the prefrontal cortex and motor regions were altered in JME (O'Muircheartaigh et al., 2012; Vollmar et al., 2012). One study revealed that abnormal thalamic connections with the superior frontal and supplementary motor area (SMA) regions may underlie the functional abnormalities in JME. In particular, using the tract-based spatial statistics (TBSS) method, three recent articles that focused on local WM changes in JME have been published. O'Muircheartaigh and colleagues' results revealed decreased FA in two regions of the corpus callosum that connect to the bilateral supplementary motor area and bilateral posterior cingulate cortex, respectively (O'Muircheartaigh et al., 2011). In the findings of Kim and colleagues, differences in WM microstructural metrics were found in the superior corona radiate and forceps minor. These findings likely reflect the structural basis of the frontal lobe dysfunction in patients with JME (Kim et al., 2012). Most recently, a TBSS study demonstrated abnormal WM diffusivity in widespread extra-frontal areas Kim et al., 2015). All of these studies suggest that the WM pathway is affected in JME patients.

Abnormal motor behaviour during seizures is a significant clinical feature of JME patients. Accumulating evidence suggests that altered WM might contribute to this abnormality. However, more evidence is needed to reveal whether the alteration in a key region in the WM affects information transmission between the thalamus and cortex in JME patients. We would like to hypothesize that JME patients may demonstrate significant differences in the motor-related WM pathways and frontal WM, specifically the fronto-thalamic loops, compared with healthy controls (HC). In this study, we acquired high resolution dMRI data and explored WM alterations in patients with JME using TBSS. Subsequently, we investigated the correlations between microstructural measurements and clinical features.

2. Methods

2.1. Participant characteristics

Twenty-six patients with JME (12 males, mean age: 23.5 ± 8.1 years) and twenty-five age-matched healthy controls (12 males, 23.8 ± 5.6 years) were recruited in this study. They were all confirmed as right-handed after performing the Edinburgh Handedness Inventory assessment. JME was diagnosed based on clinical and seizure semiology information consistent with the International League Against Epilepsy (ILAE) guidelines. None of the participants exhibited structural abnormalities detectable by routine MRI, any other seizure types except JME, or any other neurologic or psychiatric disorders. This study was permitted by the ethics committee of the University of Electronic Science and Technology of China (UESTC). After completing a structural clinical evaluation and an assessment of general neuropsychological functions, all subjects were confirmed to exhibit normal cognitive functions. We also assessed the clinical information corresponding to the onset of epilepsy and epilepsy duration (Table 1). MRI data were acquired after the subjects provided their informed consent.

Table 1
Demographic information of subjects.

Label	JME	Healthy controls
General characteristics.		
No.	26	25
Age (years)	23.5 (8.1)	23.8(5.6)
Sex (F:M)	14:12	13:12
Clinical assessment		
Symptom onset (years)	12.8 (6.1)	n/a
Symptom duration (years)	10.7 (7.5)	n/a

2.2. MRI acquisition

MRI data, including diffusion tensor image (DTI) and T1 images, were acquired using a 3.0-T GE Discovery 750 system (GE Medical Systems, Milwaukee, WI) in the Center for Information in Medicine of UESTC. Whole-brain dMRI data were acquired using a single-shot, spin-echo, echo-planar sequence (TR = 8500 ms; TE = 70 ms; voxel size is isotropic 2 mm; FOV = 256 × 256 mm^2; 76 axial slices; 64 diffusion directions; b factor = 1000 s/mm^2). Three sequences without diffusion weighting were also acquired (b = 0 s/mm^2).

Isotropic T1-weighted anatomical images were acquired using a fast-spoiled gradient-recalled echo (FSPGR) sequence (TR = 6000 ms; TE = 2 ms; flip angle = 9°; voxel size 1 × 1 × 1 mm^3).

2.3. MRI preprocessing

Individual T1-weighted anatomical images were nonlinearly registered to a standard T1 image in the Montreal Neurological Institute (MNI) space using the FLIRT tool in FSL (Jenkinson et al., 2012) while preserving the warp image.

Diffusion-weighted images were affine registered to the average of the non-diffusion-weighted volumes to correct for eddy currents and head motion. Non-brain tissues were deleted from the dMRI data using the brain extraction tool (BET) of FSL.

A diffusion-tensor model was applied to the corrected diffusion data at each voxel to acquire the FA and mean diffusivity (MD) map, which was derived from the tensor eigenvalues, including L1, L2 and L3. The L1 is also called the longitudinal diffusivity or the axial diffusivity (AD). The radial diffusivity (RD), which reflects the averaged diffusivities in the two minor axes (L2, L3), was also acquired.

Lastly, all the individual diffusion measurement images were transformed to standard MNI templates by applying the warp image mentioned above after registering individual non-diffusion-weighted images (b0 images) to their own T1 image.

2.4. Statistical analyses

A voxel-wise statistical analysis of the FA map across subjects was performed using tract-based spatial statistics pipelines (Smith et al., 2006). MNI-space FA maps of all subjects were used to generate a mean FA map. Then, the FA maps of all subjects were projected onto a skeletonized FA map derived from the mean FA image, which was thresholded by 0.2. Similar to the FA maps, MNI-space MD, AD, and RD maps were also projected onto the skeleton for further statistical analysis.

Intergroup differences in DTI measurements were analysed using permutation-based non-parametric testing (permuted 2000 times) within the general linear model framework, with age and gender as control variables (Winkler et al., 2014). Finally, threshold-free cluster enhancement (TFCE) was employed (Smith and Nichols, 2009).

2.5. Correlation between WM and clinical indicators

In addition to identifying epilepsy-related WM changes, Pearson's correlation coefficients were calculated between DTI measurements on the skeleton tracts connected to intergroup difference regions that were found in the TBSS analysis and disease duration. False discovery rate (FDR) correction ($P_{FDR} < 0.05$) was performed to adjust for multiple comparisons.