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Altered structural and functional thalamocortical networks in secondarily generalized extratemporal lobe seizures

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ABSTRACT

Structural and functional abnormalities in the thalamocortical network in primary generalized epilepsies or mesial temporal lobe epilepsy have recently been identified by voxel-wise analyses of neuroimaging. However, evidence is needed regarding the profiles of the thalamocortical network in patients with secondarily generalized seizures from focal neocortical sources. We used high-resolution T1-weighted, diffusion-tensor and resting-state functional MR imaging (rs-fMRI) to examine 16 patients with secondarily generalized extratemporal lobe seizures and 16 healthy controls. All the patients were medically effective and MRI-negative. Using whole brain voxel-based morphometry (VBM) to compare the patients with the normal controls, we observed significantly decreased gray matter (GM) density in the thalamus and 3 frontal gyri and significantly reduced white matter (WM) fractional anisotropy (FA) in the bilateral anterior corona radiata of the patients. Alterations in the thalamocortical functional connectivity with different cortices were identified by the rs-fMRI analysis seeding of the whole thalamus. The prefrontal gyri with the greatest functional connectivity were also traced by seeding a sub-thalamic region that is demarcated in an atlas, in which the thalamic parcellation is based on the WM connectivity to the cortices. This sub-thalamic region anatomically contains the mediodorsal thalamic nucleus where, concordantly, there was a significant decrease in thalamic GM density in the VBM study. In contrast to the negative correlation between the disease duration and reduced thalamic densities and subcortical FA values, the strength of the functional thalamocortical connectivity had a paradoxical correlation. Our results conclusively indicate that generalized seizures with a focal cortical source are associated with structural and functional alterations in the thalamocortical network.

1. Introduction

In both primary and secondarily generalized seizures, the electroclinical features, such as bilateral stiffening, jerking of limbs, or bilateral synchronous EEG discharge, suggest that there is a system responsible for the dynamic connection between the bilateral hemispheres during the phase.

The thalamus, one of the deep brain structures, is reciprocally linked with the cerebral cortex. Widespread cortical connections are assumed to be involved in the bilateral synchronization or propagation of epileptic electricity. In addition to previous electrophysiological studies implicating the thalamus in epileptogenesis, emerging technologies used in the acquisition and processing of neuroimaging have allowed the further characterization of the structural and functional connections between the cerebral cortex and the thalamus.

With respect to the structures of the thalamocortical network, volume changes in the thalami and alterations of nerve tract imaged parameters have been found in patients with idiopathic generalized epilepsies (IGEs) and mesial temporal lobe epilepsy (mTLE) through group comparisons using voxel-wise statistics (Keller and Roberts, 2008; Focke et al., 2014; Ciumas and Savic, 2006). Extending the voxel-wise comparison to address the functions of the thalamocortical network, functional alterations in the thalamocortical network were found in patients with IGEs and mTLE (Kim et al., 2014; Keller et al., 2014; Chen et al., 2015).

However, the methods used to investigate the structural and functional connectivity of the thalamocortical network have rarely been employed in patients with secondarily generalized seizures from focal cortical sources. In this study, we investigated the structural and functional connectivity of the thalamocortical network in a medically effective patient group identified as having a history of generalized convulsions, a localizable seizure source beyond the medial temporal region and no visible lesions on magnetic resonance imaging (MRI). We studied the structural difference by measuring the gray matter (GM) density via T1-weighted MRI, the white matter (WM) integrity

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via diffusion tensor imaging (DTI), and the functional connectivity via resting-state functional MRI (rs-fMRI). Our aim was to identify changes in the structures of the thalamus and thalamus associated fiber bundles and the functional connection between the thalamus and cortex. In the event of any change in the thalamocortical network, we further examined the possible progression of that change.

2. Methods and materials

2.1. Subjects

We retrospectively reviewed the clinical database of Hualien Tzu Chi General Hospital to collect MR data of patients with secondarily generalized seizures. We excluded patients as "lesional" when the radiologists identified any questionable lesions on the MRIs (such as possible sclerotic or atrophic changes in the mesial temporal lobe or possible blurred gray-white matter junction). Patients who possibly had mTLE with maximal interictal or ictal epileptiform discharges localized to the temporal lobe and with classic semiological features of mTLE were excluded. Patients who probably had conventionally termed primarily generalized epilepsies with symmetric interictal or ictal epileptiform discharges and non-lateralized presentations of clinical seizures were also excluded. Recruited patients were categorized as having pharmacoresponsive epilepsy, with a rare seizure recurrence (less than once every 6 months) under mono antiepileptic therapy. We further collected MRI data from age-matched healthy subjects as a control group. The study protocol, which consisted of retrospectively analyzing the patients' images and collecting images from the control subjects, was approved by the ethics committee of Buddhist Tzu Chi General Hospital in Hualien, Taiwan, and written informed consent was obtained from each control participant.

2.2. Image acquisition

At the Tzu Chi Hospital, most patients with epilepsy are studied with an epilepsy-specific protocol that includes an acquisition session for rs-fMRI and standard structure imaging sessions. In this study, the control subjects were imaged with the same imaging sequences. MRI was performed on a SIGNA HDX 1.5T (GE, Milwaukee, WI, USA) with an eight-channel phased-array head coil. A high-resolution axial 3D T1-weighted structure image was acquired using a fast-spoiled gradient-recalled echo (SPGR) sequence with the following parameters: repetition time (TR) = 14.024 ms; echo time (TE) = 14.024 ms; flip angle = 15°; field of view (FOV) = 220 × 220 mm^2; matrix = 256 × 256; and slice thickness = 1 mm. The DTIs were acquired axially using a single-shot spin-echo echo-planar sequence with the following parameters: TR = 8000 ms; TE = 82.4 ms; flip angle = 15°; FOV = 250 × 250 mm^2; matrix = 256 × 256; slice thickness = 3 mm; number of excitations, 2; 25 gradient directions with a b value of 1000 s/mm^2; and 1 null tensor image with a b value of 0 s/mm^2. The rs-fMRI data were obtained using an echo-planar imaging sequence with the following parameters: TR = 2.223 ms; TE = 35 ms; flip angle = 90°; field of view = 240 × 240 mm^2; matrix = 64 × 64; and slice thickness = 4 mm. During the functional scans, the subjects were instructed to keep their eyes closed, not to think about anything and stay awake during the entire session. After the scanning, the subjects were asked whether they remained awake during the entire procedure.

2.3. Statistical analyses of the structural MRIs

Voxel-based morphometry (VBM) analyses were performed using VBM8 (http://dbm.neuro.uni-jena.de/vbm/) a toolbox of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2014a (The MathWorks, Natick, MA, USA) to compare the density of the GM and the integrity of the WM between the patients and controls. Each individual SPGR image was registered into the null tensor image space and then reoriented with the original set close to the anterior commissure. The registered SPGR images were then segmented into GM, WM, and cerebrospinal fluid probability maps using a segment procedure of the SPM8 module (Ashburner and Friston, 2005). We computed the fractional anisotropy (FA) map using the FMRIB Software Library 4.0 package (http://www.fmrib.ox.ac.uk/fsl) (Koay et al., 2006) after the diffusion-weighted data were preprocessed by head motion, eddy current correction and diffusion tensor fitting. Referring to a standard Montreal Neurological Institute (MNI) template, GM probability and FA maps were transformed non-linearly and readjusted to the voxel size of 3 × 3 × 3 mm^3 using the high-dimensional DARTEL algorithm (Ashburner, 2007). To account for local compression and expansion caused by linear and non-linear transformations, we modulated the images using Jacobian determinants of the deformations (Good et al., 2001). Finally, the modulated GM probability and FA maps were smoothed using a 4 mm FWHM isotropic Gaussian kernel. To identify the differences in the GM density and the WM isotropy between patients and controls, we performed a *t*-test comparison between the two groups, and a double statistical threshold was used (combined height threshold $p < 0.05$ and a minimum cluster size = 16 voxels, as determined by the AlphaSim correction by REST software from http://www.restfmri.net/forum/REST V1.7) (Song et al., 2011). The regions with significantly different GM densities and FA values were further correlated with disease duration by a linear regression analysis. Differences with a p value <0.05 were considered significant.

In addition to VBM, Tract-Based Spatial Statistics (TBSS) functionality of FSL was also used to perform voxel-wise statistical analysis of the FA data. First, the mean diffusion metrics (FA) in the WM skeleton were extracted for each subject. Then, TBSS of the FA images was carried out using TBSS in the FMRIB software library (FSL 4.1.9; www.fmrib.ox.ac.uk/fsl) (Smith et al., 2006).

2.4. Statistical analyses of the functional MRIs

The first 10 scans of rs-fMRI data were removed to allow for magnetization equilibrium. The slice-timing correction was based on the middle slice. The functional data were realigned to the first dynamic scan by rigid body correction, and six parameters of the head movements were then generated. Participants who exhibited head motion >1 mm of translation or 1° of rotation were excluded. The data were then normalized to the MNI space with voxel size resampling of 3 × 3 × 3 using the DARTEL toolbox. Subsequently, a 4-mm FWHM Gaussian kernel was applied for smoothing. The images were then band-pass filtered within 0.01 to 0.08 Hz following a linear detrend to reduce the effects of high-frequency noise and low-frequency drift. To remove spurious signals that were unlikely to reflect neural activity, several nuisance covariates were eliminated by the linear regression. These covariates included the six head motion parameters, the global mean signal, the WM signal, and the cerebrospinal fluid signal.

One entire thalamic seed and seven thalamic subregion seeds were generated in the MNI template utilizing the AAL map (http://www.mccauslandcenter.sc.edu/mricro/) and Oxford thalamic connectivity atlas (Tzourio-Mazoyer et al., 2002; Behrens et al., 2003), respectively. The mean time series for the entire thalamus and each of the seven thalamic subregions was calculated by averaging the time series of all voxels within each seed. The correlation maps were obtained by conducting Pearson's correlation analyses on the time series of each seed and voxel across the whole brain. The resulting correlation coefficients for each voxel (r values) were converted to z scores using Fisher's r-to-z transformation to improve the normality of their distribution. The statistical analyses of the z-scaled functional connectivity data were conducted using REST software. Two-tailed two-sample *t*-tests ($p < 0.05$) were performed for the second-level analysis to determine the significance of the differences in the z-scaled functional connectivity values for the entire thalamus and each of the seven thalamic subregions. An AlphaSim correction was applied after each *t*-test to correct