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Opinion paper

Juvenile myoclonic epilepsy may be a disorder of cortex rather than thalamus: An effective connectivity analysis

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ABSTRACT

Although juvenile myoclonic epilepsy has been considered as a disorder of thalamo-cortical circuit, it is not determined the causality relationship between thalamus and cortex. The aim of this study was to evaluate whether juvenile myoclonic epilepsy is a disorder of thalamus or cortex. Twenty-nine patients with juvenile myoclonic epilepsy and 20 normal controls were enrolled in this study. In addition, we included 10 patients with childhood absence epilepsy as a disease control group. Using whole-brain T1-weighted MRIs, we analyzed the volumes of the structures, including hippocampus, thalamus, and total cortex, with FreeSurfer 5.1. We also investigated the effective connectivity among these structures using SPSS Amos 21 based on these volumetric measures. The structural volumes in juvenile myoclonic epilepsy were not different from those in normal controls. There was a statistically significant effective connectivity from the total cortex to the thalamus in the patients with juvenile myoclonic epilepsy. In addition, a significant effective connectivity from the hippocampus to the ipsilateral thalamus was revealed. Unlike the patients with juvenile myoclonic epilepsy, neither the patients with childhood absence epilepsy nor normal controls had a significant effective connectivity from the total cortex to the thalamus or from the thalamus to the cortex. The connectivity of brain in patients with juvenile myoclonic epilepsy could be different from that in patients with childhood absence epilepsy, and the cortex rather than the thalamus might play a critical role in the pathogenesis of juvenile myoclonic epilepsy.

1. Introduction

Juvenile myoclonic epilepsy (JME) is a well-defined clinical syndrome that usually manifests around puberty [1]. The main symptoms are bilateral, arrhythmic, irregular myoclonic jerks predominantly in the arms, which usually occur after awakening [1]. The seizures are often precipitated by sleep deprivation, fatigue, and alcohol intake. Approximately 90% of patients with JME have generalized tonic–clonic seizures, and one-third of patients have absence seizures, which are brief with subtle impairment of consciousness [1]. Although the fundamental pathogenesis of JME is not fully elucidated, many evidences using highly sensitive neuroimaging techniques have suggested a critical role of abnormal thalamo-cortical circuit. A study using voxel-based morphometry (VBM) has demonstrated that there are significant volume alterations in the frontal cortex and thalamus in patients with JME [2]. In addition, recent studies have shown an alteration of structural and functional thalamo-cortical circuit using diffusion tensor imaging (DTI) and resting state functional MRI (rs-fMRI) [3,4]. They detected changes in a thalamo-cortical bundle in patients with JME compared with normal controls by DTI and demonstrated an alteration in task-modulated connectivity in a region of frontal cortex directly connected to the thalamus by rs-fMRI [4]. It has been also reported that generalized spike and wave discharges (GSWDs), usually seen on electroencephalography (EEG) in idiopathic generalized epilepsy (IGE) including JME, are related with thalamo-cortical circuit [5]. All of these findings suggest that JME is a disorder of thalamo-cortical circuit. However, it is not yet determined the causal relationship between thalamus and cortex in JME.

Unlike functional connectivity measures, which explore non-directional statistical dependencies between brain regions, effective connectivity refers to patterns of directed causal influences

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and information flows that manifest as synchronized coherent neural activity between brain regions [6]. Effective connectivity analyzes the direction, interaction, and effect of neuronal-unit activity on other units, and it can be used to understand causal relationships between entities in the brain network [7]. Causal modeling has further enhanced our understanding of neuroanatomy by modeling dynamical interactions within a network of region of interest (ROI) instead of activity in individual brain regions [8]. The most prevalent approaches to effective connectivity analysis are dynamic causal modeling, Granger causality, and structural equation modeling (SEM) [8,9]. SEM is a statistical method that analyzes the effective connectivity between observed and latent variables to test hypotheses and confirm relationships. It has the advantage of allowing fast and robust computations and can be used for rather complicated models. SEM analysis are popular in the social sciences as well as medicine, because of its long history and accessibility; packaged computer programs allow researchers to obtain results without the inconvenience of understanding experimental design and control, effect and sample sizes, and numerous other factors that are part of good research design [8,9]. SEM can utilize knowledge gained from imaging modalities, and it provides a model of the effective connectivity in a given neural system [10]. SEM has been widely used to investigate effective connectivity in brain disorders [8]. However, few studies have used SEM to investigate effective connectivity in patients with JME.

In this study, we evaluated the effective connectivity between thalamus and cortex in patients with JME, which may give some clues whether JME is a disorder of thalamus or cortex. In addition, we investigated whether the brain connectivity in patients with JME is different from normal controls and the patients with childhood absence epilepsy (CAE).

2. Methods

2.1. Patients and Controls

This study was conducted with the approval of our institution's institutional review board. This study was consecutively performed in a single tertiary hospital. We enrolled 29 patients with a clinical diagnosis of JME according to the current International League Against Epilepsy (ILAE) classification [11]. All of the patients had 1) age of seizure onset between five and 25 years, 2) normal neurologic state and development, 3) the typical seizure history compatible with JME, including morning myoclonic jerks and 4) ictal or interictal GSWDs with a normal background activity on EEG. In addition, we included 10 patients with CAE as a disease control group. The inclusion criteria for these patients were as follows: patients with 1) age of seizure onset between four and 15 years, 2) normal neurologic state and development, 3) typical seizure history with CAE, including brief and frequent absence seizures with abrupt and severe impairment of consciousness, and 4) ictal or interictal 3 Hz GSWDs with a normal background activity on EEG. All of the patients had a normal MRI on visual inspection. We collected demographic and clinical characteristics including age, sex, age of seizure onset, duration of epilepsy, and seizure types from these patients at the time of the MRI.

In addition, we enrolled the control groups (healthy subjects), who were age- and sex-matched with the patients with JME. All of the subjects had a normal neurological examination and no history of cardiovascular, neurological or psychiatric disease, diabetes, hypertension, or dyslipidemia. All of them had a normal MRI on visual inspection.

2.2. MRI data acquisition, processing and analysis using FreeSurfer

All of the scans were performed using a 3.0T MRI scanner (AchievaTx, Phillips Healthcare, Best, The Netherlands) equipped with an 8-channel head coil. All of the subjects (patients and controls) underwent conventional brain MRI protocols, including axial and coronal 2D T2-weighted images, which were obtained using a turbo-spin echo sequence (repetition time (TR)/echo time (TE) = 3000/80 ms, slice thickness = 5 mm, echo train length = 14, field of view = 210 mm, matrix size = 512 × 512, number of slices = 24), and axial and coronal 2D T1-weighted images, which were obtained using an inversion recovery sequence (inversion time (TI) = 800 ms, TR/TE = 2000/10 ms, slice thickness = 5 mm, echo train length = 7, FOV = 210 × 210 mm^2, matrix size = 512 × 512, number of slices = 24). In addition, axial and coronal 2D FLAIR images were obtained to evaluate the lesions on those images (TI = 2800 ms, TR/TE = 10,000/120 ms, slice thickness = 5 mm, echo train length = 26, FOV = 210 × 210 mm^2, matrix size = 512 × 512, number of slices = 24). Moreover, all of the patients and controls underwent sagittal-oriented high-resolution contiguous 3D volumetric T1-weighted imaging that was suitable for structural volume analysis. The 3D T1-weighted images were obtained using a turbo-field echo sequence with the following parameters: TI = 1300 ms, TR/TE = 8.6/3.96 ms, flip angle = 8°, a 1 mm^3 isotropic voxel size, FOV = 210 × 210 mm^2, number of slices = 120. To accelerate the data acquisition, SENSE (SENSitivity Encoding) parallel imaging with an acceleration factor of 2 was applied. Volumetric analysis was performed using the FreeSurfer image analysis suite (version 5.1; http://surfer.nmr.mgh.harvard.edu/) on a 64-bit Linux CentOS 5. The automated procedures for volumetric measures of the various brain structures have been described by Fischl et al. [12]. Briefly, the volumetric measurement was carried out as follows. First, image preprocessing was performed, including linear registration, B1 field correction, and non-linear registration. For linear registration, each volume was rigidly registered with a specific atlas, such as the Talairach space, that was specifically designed to be insensitive to pathology and to maximize the accuracy of the final segmentation. Next, any non-homogenous signal intensity caused by the B1 bias field was corrected. High-dimensional non-linear morphing to the atlas was then conducted. Especially, in the step of acquiring the structural volumes, this was processed through the standard manner with the following step: motion correction, intensity correction, skull stripping, normalization to the Talairach space and automatic segmentation. After image preprocessing, the volume was labeled. To label structural volume, segmentation was used for three pieces of information to disambiguate the labels: 1) the prior probability of a given tissue class occurring at a specific atlas location, 2) the likelihood of the image intensity given the tissue class, and 3) the probability of the local spatial configuration of labels given the tissue class. After the process, we checked any outliers reflected misclassification for segmentation accuracy of the label volume. We obtained the absolute structural volumes (including the hippocampus, thalamus, and total cortex) from these automated methods. Next, the volumetric measures were calculated using the following equation: the structural volumes (%) = (absolute structural volumes/total intracranial volumes) × 100.

2.3. Effective connectivity analysis using IBM Amos 21

We evaluated the effective connectivity using the automated volumetric measures. We chose five ROIs, including right and left hippocampus and thalamus, along with total cortex. The effective connectivity of ROI was assessed using path analysis within an SEM framework (AMOS version 21.0, SPSS IBM;