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Functional substrate for memory function differences between patients with left and right mesial temporal lobe epilepsy associated with hippocampal sclerosis

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ABSTRACT

Objective: Little is known about the functional substrate for memory function differences in patients with left or right mesial temporal lobe epilepsy (mTLE) associated with hippocampal sclerosis (HS) from an electrophysiological perspective. To characterize these differences, we hypothesized that hippocampal theta connectivity in the resting-state might be different between patients with left and right mTLE with HS and be correlated with memory performance.
Methods: Resting-state hippocampal theta connectivity, identified via whole-brain magnetoencephalography, was evaluated. Connectivity and memory function in 41 patients with mTLE with HS (left mTLE = 22; right mTLE = 19) were compared with those in 46 age-matched healthy controls and 28 patients with focal cortical dysplasia (FCD) but without HS.
Results: Connectivity between the right hippocampus and the left middle frontal gyrus was significantly stronger in patients with right mTLE than in patients with left mTLE. Moreover, this connectivity was positively correlated with delayed verbal recall and recognition scores in patients with mTLE. Patients with left mTLE had greater delayed recall impairment than patients with right mTLE and FCD. Similarly, delayed recognition performance was worse in patients with left mTLE than in patients with right mTLE and FCD. No significant differences in memory function between patients with right mTLE and FCD were detected. Patients with right mTLE showed significantly stronger hippocampal theta connectivity between the right hippocampus and left middle frontal gyrus than patients with FCD and left mTLE.
Conclusion: Our results suggest that right hippocampal–left middle frontal theta connectivity could be a functional substrate that can account for differences in memory function between patients with left and right mTLE. This functional substrate might be related to different compensatory mechanisms against the structural hippocampal lesions in left and right mTLE groups. Given the positive correlation between connectivity and delayed verbal memory function, hemispheric-specific hippocampal–frontal theta connectivity assessment could be useful as an electrophysiological indicator of delayed verbal memory function in patients with mTLE with HS.

1. Introduction

Episodic memory impairment is a signature cognitive deficit in temporal lobe epilepsy (TLE), and much has been learned about the relationship between memory dysfunction and hippocampal abnormalities in TLE [1]. Neuropsychological (NP) testing of patients with TLE with proven structural hippocampal abnormalities has provided evidence that memory dysfunction is related to these structural changes [2,3]. Interestingly, patients with left mesial temporal lobe epilepsy (mTLE) generally show greater memory impairment than patients with right mTLE, both before and after surgery [4–7].

Compared with healthy controls (HC), abnormal hemispheric symmetries have been detected in left mTLE, but not in right mTLE [8]. Moreover, left mTLE exhibits a wider area of atrophy related to hippocampal gray matter loss compared with right mTLE, which has been interpreted as an explanation for the more significant cognitive impairment usually observed in left mTLE [9]. Structural MRI has shown more widespread abnormalities in left mTLE relative to right mTLE, suggesting that left mTLE is different from right mTLE, possibly due to greater vulnerability of the left hemisphere to the progressive effects of seizures [10]. Patients with left mTLE exhibit more marked functional connectivity changes than patients with right mTLE [11]. In a fMRI-based study, reduced regional homogeneity in the DMN, including PCIN, was reported in adult

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patients with unilateral mTLE [12]. In a combined fMRI and DTI study, functional and structural connectivities were significantly decreased between the PCIN and the bilateral mesial temporal lobes in patients with mTLE [13]. Based on previous studies, the asymmetry of hippocampal abnormalities and brain network differences between patients with left and right mTLE could be regarded as a structural substrate for the greater memory impairment in patients with left mTLE than in patients with right mTLE [5,8–14]. However, little is known about the functional substrate for memory function differences between patients with left and right mTLE from an electrophysiological perspective.

A complex brain network, centered on the hippocampus, supports episodic memories [15], and hippocampal activity is dominated by theta oscillations [15,16]. Moreover, functional magnetic resonance imaging studies have reported a correlation between resting-state functional connectivity and memory function in patients with mTLE [7,17,18]. Thus, we hypothesized that hippocampal theta connectivity in the resting-state might be different between patients with left and right mTLE and might be correlated with memory performance. In this study, to ensure homogeneity in terms of pathology and surgical outcome following resection of the epileptogenic zone (hippocampus), we recruited patients with mTLE with histologically proven hippocampal sclerosis (HS) and postoperative seizure freedom.

2. Methods

2.1. Subjects

Forty-one patients with mTLE with histologically proven HS (hereafter, left or right mTLE indicates left or right mTLE with HS, respectively; left mTLE = 22; right mTLE = 19) included in this retrospective study were selected from 74 right-handed patients who underwent magnetoencephalography (MEG) before surgery between 2005 and 2011 at Seoul National University Hospital (SNUH) and had been followed up for more than 2 years. We presume that language dominance of our patients would be the left side, because we only included right-handed patients in the present study, even though a Wada test was not performed on all the patients. Patients younger than 18 years of age at surgery (n = 2), with electrocorticography before surgery (n = 12), or with no seizure-free period or no spike-free period in resting-state recording (n = 19) were excluded. Applied surgical techniques were either anterior temporal lobectomy with amygdalohippocampectomy (left mTLE = 10; right mTLE = 12) or selective amygdalohippocampectomy (left mTLE = 12; right mTLE = 7). Each patient underwent NP testing as a presurgical evaluation. There were no significant differences in age at surgery, age at seizure onset, duration of epilepsy, and seizure frequency between patients with left and right mTLE.

Forty-six right-handed healthy controls (HC) voluntarily participated in resting-state MEG. None of the participants had neurological abnormalities or magnetic resonance imaging (MRI)-detected lesions. No NP testing was performed for the HC. The hippocampal theta functional connectivity in HC was compared with that in patients with mTLE.

Twenty-eight patients with intractable epilepsy with focal cortical dysplasia (FCD) and with NP testing, but without HS, were also included in a control group for memory performance because there is no clear evidence of impaired memory function in patients with FCD without HS. Patients with FCD were selected from among 60 right-handed patients with epilepsy with histologically proven FCD who underwent MEG before surgery between 2005 and 2011 at SNUH and had undergone follow-up for more than 2 years. Patients younger than 18 years of age at surgery (n = 9), with FCD type III associated with other pathologies or hippocampal atrophy (n = 20), with no NP testing (n = 2), and who underwent MEG postoperatively (n = 1) were excluded. Surgical outcomes, based on the International League Against Epilepsy (ILAE) classification system [19], ranged from favorable (ILAE 1 to 3; n = 13) to unfavorable (ILAE 4 to 6; n = 15). Resection areas and surgical outcomes, based on the ILAE classification system, are summarized in Table S1. There were no significant differences in age at surgery, age at seizure onset, duration of epilepsy, and seizure frequency between the patients with mTLE and FCD. The MEG data for all 46 control subjects [20] and for some of the patients with mTLE and patients with FCD were used in our previous studies [21,22]. Demographic data for enrolled patients are summarized in Table 1.

The NP tests included the Korean version of the Rey Auditory Verbal Learning Test (K-AVLT) for verbal memory, and the Korean version of the Rey Complex Figure Test (K-CFT) for visual memory [6]. Since this study focused on memory function, we used memory performance scores. In particular, based on a previous study showing a lateralized difference in delayed verbal memory among patients with mTLE [23], the delayed recall and delayed recognition scores were analyzed.

The study protocol was approved by the local Institutional Review Board at Seoul National University Hospital (IRB H-0607-029-178). Written informed consent was submitted by all subjects.

2.2. MRI evaluation

Preoperative MRI was performed on either a GE 1.5 T or 3 T MRI scanner (GE Horizon Echospeed; GE Healthcare, Pollards Wood, United Kingdom) or on a Siemens 1.5 T scanner (MAGNETOM Avanto; Siemens, Berlin, Germany). The standard MRI protocol included T1-weighted, T2, fluid attenuated inversion recovery (FLAIR) axial, T2 and FLAIR oblique coronal, fast inversion recovery with myelin suppression, and three dimensional (3D) gradient echo coronal T1 images with whole-brain coverage. The 3D gradient echo T1 images were reconstructed to a 1 mm slice thickness, while the T2 images were acquired by using a 3 mm thickness with a 1 mm interslice gap. Preoperative MRI scans were reviewed separately and results confirmed by two neuroradiologists specializing in epilepsy and blinded to seizure focus.

2.3. MEG study

A 306-channel, whole-head system (VectorView, Elekta Neuromag Oy, Finland) was used for MEG. Recordings were done inside a magnetically shielded room at a sampling frequency of 600.615 Hz. Electrooculogram and electrocardiogram data were simultaneously recorded. For patients with mTLE or FCD, data were collected during four 15-minute epochs while patients were supine with eyes-closed, according to our MEG patient protocol. For HC, data were recorded in eyes-closed and eyes-open resting-states for 2 min each while they were sitting or supine. The eyes-closed resting-state signals were used for the analyses in this study. During MEG, each subject was instructed to remain relaxed and asked to avoid thinking about anything. A temporal-signal space-separation method [24] was applied to reduce environmental and biological noise. To minimize eye and cardiac artifacts, independent component analysis was performed by using Fieldtrip software [25]. Based on results obtained in our previous studies [20–22,26,27], for further analysis, we selected five 10-second epochs from the continuous signals. For patients, epoching was carefully done by visual inspection to avoid inclusion of epileptic spikes.

2.4. Connectivity analysis

Seventy-two predefined nodes that were selected from the automated anatomical labeling (AAL) atlas [28] were used as network nodes [20–22,27]. We attempted to include many of the nodes covered by the MEG recording, and we selected a center location inside each AAL region of interest as a node. Node abbreviations are listed in Table S2. Reconstruction of source waveforms at the 72 nodes were performed in combination with the Brain Voyager software (ver. 1.10; Brain Innovation, Maastricht, Netherlands) and BESA®2000 software (MEGIS Software, Gräfelfing, Germany). The individual MRI scans of each subject