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Altered neural synchronization to pure tone stimulation in patients with mesial temporal lobe epilepsy: An MEG study

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Objective: Our previous study of monaural auditory evoked magnetic fields (AEFs) demonstrated that hippocampal sclerosis significantly modulated auditory processing in patients with mesial temporal lobe epilepsy (mTLE). However, the small sample size (n = 17) and focus on the M100 response were insufficient to elucidate the lateralization of the epileptic focus. Therefore, we increased the number of patients with mTLE (n = 39) to examine whether neural synchronization induced by monaural pure tone stimulation provides useful diagnostic information about epileptic foci in patients with unilateral mTLE.
Methods: Twenty-five patients with left mTLE, 14 patients with right mTLE, and 32 healthy controls (HCs) were recruited. Auditory stimuli of 500-Hz tone burst were monaurally presented to subjects. The AEF data were analyzed with source estimation of M100 responses in bilateral auditory cortices (ACs). Neural synchronization within ACs and between ACs was evaluated with phase-locking factor (PLF) and phase-locking value (PLV), respectively. Linear discriminant analysis was performed for diagnosis and lateralization of epileptic focus.
Results: The M100 amplitude revealed that patients with right mTLE exhibited smaller M100 amplitude than patients with left mTLE and HCs. Interestingly, PLF was able to differentiate the groups with mTLE, with decreased PLFs in the alpha band observed in patients with right mTLE compared with those (PLFs) in patients with left mTLE. Right hemispheric predominance was confirmed in both HCs and patients with left mTLE while patients with right mTLE showed a lack of right hemispheric predominance. Functional connectivity between bilateral ACs (PLV) was reduced in both patients with right and left mTLE compared with that of HCs. The accuracy of diagnosis and lateralization was 80%–90%.
Conclusion: Auditory cortex subnormal function was more pronounced in patients with right mTLE compared with that in patients with left mTLE as well as HCs. Monaural AEFs can be used to reveal the pathophysiology of mTLE. Overall, our results indicate that altered neural synchronization may provide useful information about possible functional deterioration in patients with unilateral mTLE.

1. Introduction

The hippocampus is an integral structure of the mesial component of temporal lobe, and is involved in auditory perception as well as the memory system [1]. There is substantial evidence that hippocampal sclerosis (HS) modulates central auditory processing (CAP) in patients with mesial temporal lobe epilepsy (mTLE) [2]. In this context, altered CAP refers to changes in the perceptual processing of auditory information in the central nervous system despite normal hearing sensitivity, exhibited as poor auditory discrimination performance, auditory pattern recognition and temporal differentiation [2–4]. For example, patients with mTLE show decreased performance in dichotic listening [5–7] to both verbal and nonverbal sounds [8], poor performance in anisochrony or irregularity discrimination of rapid auditory sequences [9], and decreased temporal processing in the Gaps-In-Noise test [10] and the duration pattern sequence test [11]. Intractable patients with right mTLE are at risk of speech recognition impairment in real-world listening environments compared with extratemporal lobe epilepsy [12]. Based on these behavioral observations, functional deficits in the mesial temporal lobe may cause auditory cognitive dysfunction. Importantly, CAP refers to the efficiency and effectiveness by which the central nervous system utilizes auditory information. Thus, decreased electromagnetic responses could be attributed to CAP dysfunction [3].

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In accord with this concept, we previously reported a significant effect of unilateral HS on auditory evoked magnetic fields (AEFs) using magnetoencephalography (MEG) [13], with three main findings: 1) the amplitude of the M100 response, the magnetic counterpart of the auditory evoked N100 potential, tended to be attenuated in patients with mTLE compared with that in healthy controls (HCs); 2) the frequency of acceptable M100 dipoles was significantly decreased on the HS side; 3) a significant positive correlation between the volume of auditory cortex (AC) and M100 amplitude observed in HCs was reversed in patients with mTLE. These findings suggest that HS significantly influenced AEFs, together with disruption of the structural–functional correlation in patients with mTLE. We assumed that altered AC function is related to the pathophysiology of mTLE.

However, several issues with our previous study remain to be addressed. First, the patient groups with right and left mTLE in our previous study were combined into a group with unilateral mTLE because of the small sample size. Quantifying the functional impact of left and right HS on AC function is important because the functional roles of left and right hemispheres are differentiated for speech and music perception. We assumed that the lateralization of the epileptic focus could be revealed using AEFs if the sample size was sufficient. Second, we were previously unable to detect alterations in the M100 amplitude to differentiate the groups (HCs vs. patients with unilateral mTLE) because we mainly focused on the M100 response in the affected AC contralateral to the auditory stimulation. Because the detailed characteristics of functional differences of each AC in response to monaural pure tone stimulation remains unclear, the M100 response should be assessed in each AC of patients with mTLE. Third, altered auditory responses should be examined using other indices, such as phase synchrony. Recently, neural synchronization or rhythmic fluctuations in neuronal populations were reported to function as a fundamental mechanism enabling coordinated activity during cognitive task performance [14,15]. Neural synchronization is also sensitive to cortical dysfunction, even in normal aging [16]. Thus, altered neural synchronization has been reported in various types of neurological diseases [16–19]. In the current study, we focused on neural synchronization using two indices: phase-locking factors (PLFs) and phase-locking values (PLVs). We adopted these two measures to assess phase synchrony using MEG source waveforms targeting bilateral Heschl's gyri.

Therefore, we investigated the following two hypotheses to extend our previous findings [13]: 1) Neural synchronization indexed by PLFs and PLVs would provide more diagnostic information about the lateralization of epileptic focus in patients with mTLE compared with evoked responses (M100), and 2) monaural pure tone auditory stimulation could reveal functional differences of each AC. The rationale of the current study was that neural synchronization within ACs and between ACs was expected to deteriorate in patients with unilateral mTLE compared with that in HCs. Furthermore, if monaural auditory stimulation significantly enhances the functioning of contralateral AC, patients with unilateral mTLE would be expected to exhibit abnormal asymmetry with respect to the pure-tone-dominant hemisphere compared with HCs. Specifically, monaural auditory stimulation would be expected to evoke more neural synchronization in the contralateral AC compared with that in the ipsilateral AC, and, in turn, patients with ipsilateral mTLE might exhibit altered contralateral synchronization in relation to the affected AC. Taken together, we expected that left ear stimulation would differentiate patients with right mTLE, and vice versa, with a stronger bias to the pure-tone-dominant hemisphere.

2. Materials and methods

2.1. Subjects

We analyzed the data from our previous study [13] and data from an additional sample. Twenty-five patients with left mTLE (age range; 25–66 years, 20 females), 14 patients with right mTLE (age range; 20–51 years, eight females), and 32 HCs (age range; 21–68 years, 15 females) were recruited. All patients fulfilled the criteria of the International League Against Epilepsy (1989), and were treated with standard antiepileptic drugs. We used the same inclusion criteria for the patient group with unilateral mTLE described in a previous study [13]: (1) magnetic resonance imaging (MRI) findings showed unilateral HS or normal hippocampus; (2) long-term monitoring of video-electroencephalography (EEG) confirmed semiology and ictal-onset localization; (3) none of the patients had extratemporal lesions, prior head injuries, or any other relevant histories, such as encephalitis. All subjects were right-handed. Twenty-three patients with mTLE were treated with standard anterior temporal lobectomy after recording, and HS was later histologically proven. Although the remaining patients with mTLE did not undergo surgical treatment, their clinical, neuroimaging, and electrophysiological characteristics were consistent with unilateral mTLE (Table 1). All subjects gave written informed consent for participation, and the study was approved by the Ethics Committee of Kyushu University. This study was carried out in accordance with the latest version of the Declaration of Helsinki.

2.2. Recordings

Auditory stimulation was performed with the same protocols as those used in our previous study [13]. Briefly, tone burst stimuli with a 500-Hz frequency and 100-ms duration (10-ms rise and 20-ms fall) were monaurally presented with a 1000-ms interstimulus interval. Before each MEG recording, hearing thresholds were determined for each ear for each subject. The stimuli were delivered at intensities of 50 dB above threshold. Masking noise was delivered to the contralateral ear. Auditory evoked magnetic fields were recorded using a 306-channel whole-head system (consisting of 204 planar-type gradiometers and 102 magnetometers) (Elekta-Neuromag, Helsinki, Finland). Before MEG recording, four head-position indicator (HPI) coils were attached, and a three-dimensional (3D) digitizer (FastTrack, Polhemus, VT, USA) was used to measure anatomical landmarks (bilateral preauricular points and nasion) of the head and approximately 200 head-surface points attached to stable positions on the forehead and nose [20]. Subjects lay in a supine position in a quiet magnetically shielded room. Magnetic responses were digitally sampled at a rate of 1000 Hz with an online band-pass filter of 0.1–330 Hz. Recording was continued until at least 120 evoked responses were counted. High-resolution 3D MRI images were also acquired using a 3-T clinical scanner (Philips Healthcare, Best, the Netherlands). The whole brain was scanned using a T1-weighted fast-field echo sequence (voxel size, $1.0 \times 1.0 \times 1.0\ mm^3$).

2.3. Analysis

2.3.1. Preliminary step

All data sets were cleaned up using Maxfilter by eliminating noise outside of the brain [21]. The data were refiltered from noise-free data with a band-pass filter of 0.3–30 Hz. The anatomical information was provided from 3-T MRI images using FreeSurfer software (FreeSurfer v4.5, aparc.a2009s/Destrieux.simple.2009-07-29.gcs atlas). Trials exceeding 4000 fT/cm at gradiometers and 4000 fT at magnetometers were excluded to eliminate outliers caused by artifacts. Artifacts such as eye blinks and other eye movements were carefully excluded by visual inspection. We measured the M100 component as the evoked response to the stimuli. The M100 was defined as having a peak within 80–130 ms [13]. We obtained the M100 amplitude as an averaged amplitude within this time window.

2.3.2. Source localization

We employed minimum norm estimate (MNE) software for source localization, executed with noise-normalized dynamic statistical parametric mapping (dSPM). Here, we briefly address some implementation