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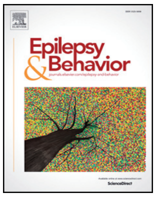

Altered neural synchronization to pure tone stimulation in patients with mesial temporal lobe epilepsy: An MEG study

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ABSTRACT

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

Table 1
Demographic characteristics of patients.

	HCs (n = 32)	Patients with left mTLE (n = 25)	Patients with right mTLE (n = 14)
Gender	17 M/15 F	5 M/20 F	6 M/8 F
Age (mean, range)	32.2 (21–68)	40.9 (25–66)	31.0 (20–51)
Seizure duration (years)		26.2 (2–49)	18.1 (7–37)
MRI (HS/normal/other structural abnormalities)		18/5/cerebral cavernous malformation 1, hippocampal malrotation 1	13/0/hemispheric atrophy 1
Operation		13	11
Histologically identified HS		13	11

HC: healthy control, mTLE: mesial temporal lobe epilepsy, HS: hippocampal sclerosis.

parameters. Specific details of the MNE and dSPM methods are described elsewhere [22,23]. After the preliminary process, the digitized anatomical head landmarks and scalp surface points were coregistered onto the scalp MRI contour. To perform forward solution, we used Boundary Element Method mesh by tessellating the inner skull surface. For dSPM noise normalization, we used the entire raw data set of each run. In our previous study [13], the volume of Heschl's gyrus in patients with mTLE was not significantly decreased compared with HCs. Thus, we selected Heschl's gyrus as a region of interest (ROI) in this study to represent AC, to avoid the effects of structural abnormalities.

2.3.3. Neural synchronization of induced responses

We performed continuous wavelet transformation for the source waveforms using the complex Morlet wavelet as a mother function. The window size was 1/4 cycle of a given frequency. Thus, the frequency resolution was 4 Hz, and the time resolution was 32.5 ms. The data were obtained every 1 Hz and also every 1 ms. Following our previous study [16,19,24,25], we evaluated two indices of phase synchrony: the PLFs and PLVs [26–28]. We applied these measures to the source waveforms extracted from the selected ROIs. Thus, PLFs indicate an index of intertrial phase synchrony changes from a local brain area, whereas PLVs represent an index of differences in phase synchrony changes between two source activities from two different brain areas. The detailed computation of PLVs for MEG source waveform analysis was described by the research group that developed MNE-suite software [29]; PLV is a type of application of PLF (or vice versa), such that all computations are performed using the tools implemented in MNE-Python [30]. The PLFs and PLVs were applied to left and right ear stimulation, respectively. We calculated PLFs from a specified ROI using cleaned raw MEG signals, so that obtained results included the angular symmetry of the distribution from both evoked and induced responses. We also calculated the synchronization index of the PLVs between the two specific ROIs, which were left and right Heschl's gyri in this study. The time windows of interest for PLFs and PLVs were set at between 80 and 130 ms along to the selection of M100 latencies. We finalized each index by averaging within this time window. We also averaged various frequency bands of interest, including the theta (4–7 Hz), alpha (8–13 Hz), and beta (14–30 Hz) bands separately.

2.4. Contralaterality index

It has been well-established that the contralateral pathway is predominant in the auditory pathway [31]. Here, to estimate the contralateral predominance after the monaural stimulation in this study, we set the contralaterality index (cLI) against the monaural stimulation:

$$cLI = \frac{V_{contra} - V_{ipsi}}{V_{contra} + V_{ipsi}} \tag{1}$$

where V represents the value of the M100 amplitude, PLF. Subscript *contra* denotes contralateral Heschl's gyrus while *ipsi* denotes ipsilateral Heschl's gyrus. The cLI indicates contralateral hemispheric predominance with positive values (0-+1) while ipsilateral predominance is indicated by negative values (0-−1). Thus, cLI itself indicates contralaterality against monaural stimulation. In contrast, symmetry or asymmetry of left/right hemispheric function can be assessed by comparing cLI scores in response to left ear stimulation with those of right ear stimulation. For example, cLI scores that are equal between left and right ear stimulation would reflect "symmetry" in terms of left/right hemispheric function. Alternatively, larger cLI scores in response to left ear stimulation compared with right ear stimulation would reflect "asymmetry", indicating right hemispheric predominance. In this case, the subtraction of left hemispheric responses from right hemisphere (by left ear stimulation) responses is greater than that of right hemispheric responses subtracted from left hemisphere (by right ear stimulation) responses. Consequently, lower cLI scores in response to right ear stimulation suggest that the degree of lateralization is toward the right hemisphere. Here, we define such relationships as "AC asymmetry" (e.g., right hemispheric predominance regarding contralaterality). Our major concern was whether the contralaterality was reduced in patients with mTLE in relation to the lesion side. Specifically, we expected that cLI scores of patients with left mTLE would be lower than those of HCs in response to right ear stimulation, but not in response to left ear stimulation, and vice versa for patients with right mTLE.

2.5. Linear discriminant analysis

To determine the clinical utility of our data as a presurgical evaluation, linear discriminant analysis (LDA) was performed. We constructed two separate classifiers, one for diagnosis (HCs vs. patients with mTLE) and the other for lateralization (patients with left vs. right mTLE) [32]. For the diagnosis classifier, sensitivity indicates the proportion of actual positives of patients with mTLE, while specificity indicates that of HCs. For the lateralization classifier, sensitivity indicates the proportion of actual positives of patients with left mTLE, while specificity indicates that of patients with right mTLE. Accuracy indicates the fraction of correctly classified subjects. We used all of the neural synchronization data obtained, including all frequency bands (theta, alpha, beta) of PLFs in response to auditory stimuli within each AC, and frequency bands of PLVs in response to auditory stimuli.

2.6. Statistical analysis

To further analyze M100 amplitude, and PLFs, we performed a three-way repeated-measures analysis of variance (ANOVA) with GROUP (HCs vs. patients with left vs. right mTLE) as a between-subject factor and HEMISPHERE (HEMI) (contralateral vs. ipsilateral Heschl's gyrus) and STIMULATION (STIM) (left ear vs. right ear) as within-subject factors. To analyze PLVs, we performed a two-way repeated-measures ANOVA with GROUP (HCs vs. patients with left vs. right mTLE) as a between-subject factor and STIM (left ear vs. right ear) as a within-subject factor. Posthoc analyses were conducted using contrast analysis. The cLI (Eq. (1)) was analyzed for each of the indices (M100 amplitude, PLFs) using a two-way repeated-measures ANOVA with GROUP (HCs vs. patients with left vs. right mTLE) as a between-subject factor and STIM (left ear vs. right ear) as a within-subject factor. The volumes of the affected hippocampus and bilateral ACs were analyzed using one-way ANOVA with a main factor of GROUP. The volume of bilateral hippocampi was averaged for HCs. The LDA and ANOVA were performed using JMP software (SAS Institute Inc., NC, USA). In all analyses, the significance level was set at 0.05.

3. Results

3.1. M100 amplitude

Fig. 1A shows the source waveforms of M100 recorded from the left and right target ROIs. Table 2 shows the ANOVA results for the M100 amplitude, and the major results are presented as bar graphs for clarity. There was a significant main effect of GROUP on M100 amplitude (Table 2). There was also a significant interaction between GROUP and STIM (Table 2). A posthoc analysis revealed that patients with right mTLE exhibited smaller M100 amplitude compared with the other two groups in response to right ear stimulation, irrespective of the hemisphere (Fig. 1B).

Table 2
ANOVA results for M100 amplitude.

M100 amplitude	df	F-value	p-Value
GROUP	2	4.99	0.0095
HEMI	1	15.6	0.0001
STIM	1	12.9	0.0004
GROUP × HEMI	2	1.63	0.20
GROUP × STIM	2	3.22	**0.042**
HEMI × STIM	1	2.91	0.090
GROUP × HEMI × STIM	2	0.164	0.85

Abbreviations: HEMI: HEMISPHERE, STIM: STIMULATION in this and subsequent Tables. Bold values indicate the main significant ($p < 0.05$) results highlighted in the text.

3.2. PLFs for theta, alpha, and beta bands

The ANOVA results for PLFs in the theta, alpha, and beta bands are shown in Table 3. Fig. 2A represents the PLF data from left and right ROIs. Monaural stimulation provided important information about hemispheric functional differences (Fig. 2A). In all frequency bands, we found a significant main effect of GROUP and a significant interaction between GROUP and STIM (Table 3). In particular, PLFs in the alpha band were the most sensitive for differentiating groups, especially patients with left and right mTLE. In the alpha band, a posthoc analysis revealed a significant difference among the three groups during right ear stimulation. Thus, PLFs in patients with right mTLE were lowest, followed by patients with left mTLE, then HCs (Fig. 2B). Compared with the alpha band, the beta and theta bands only differentiated HCs from groups with mTLE or patients with right mTLE from other groups, thus providing partial lateralizing information (Fig. 2B). In the theta band, a posthoc analysis revealed that, in response to right ear stimulation, patients with right mTLE showed decreased PLFs in the left hemisphere (i.e., the contralateral hemisphere) compared with HCs and patients with left mTLE. In the beta band, both patients with right and left mTLE exhibited decreased PLFs in response to left ear stimulation compared with HCs in the right hemisphere (i.e., the contralateral hemisphere) while patients with left mTLE exhibited more severely decreased PLFs compared with HCs in the left hemisphere (i.e., the

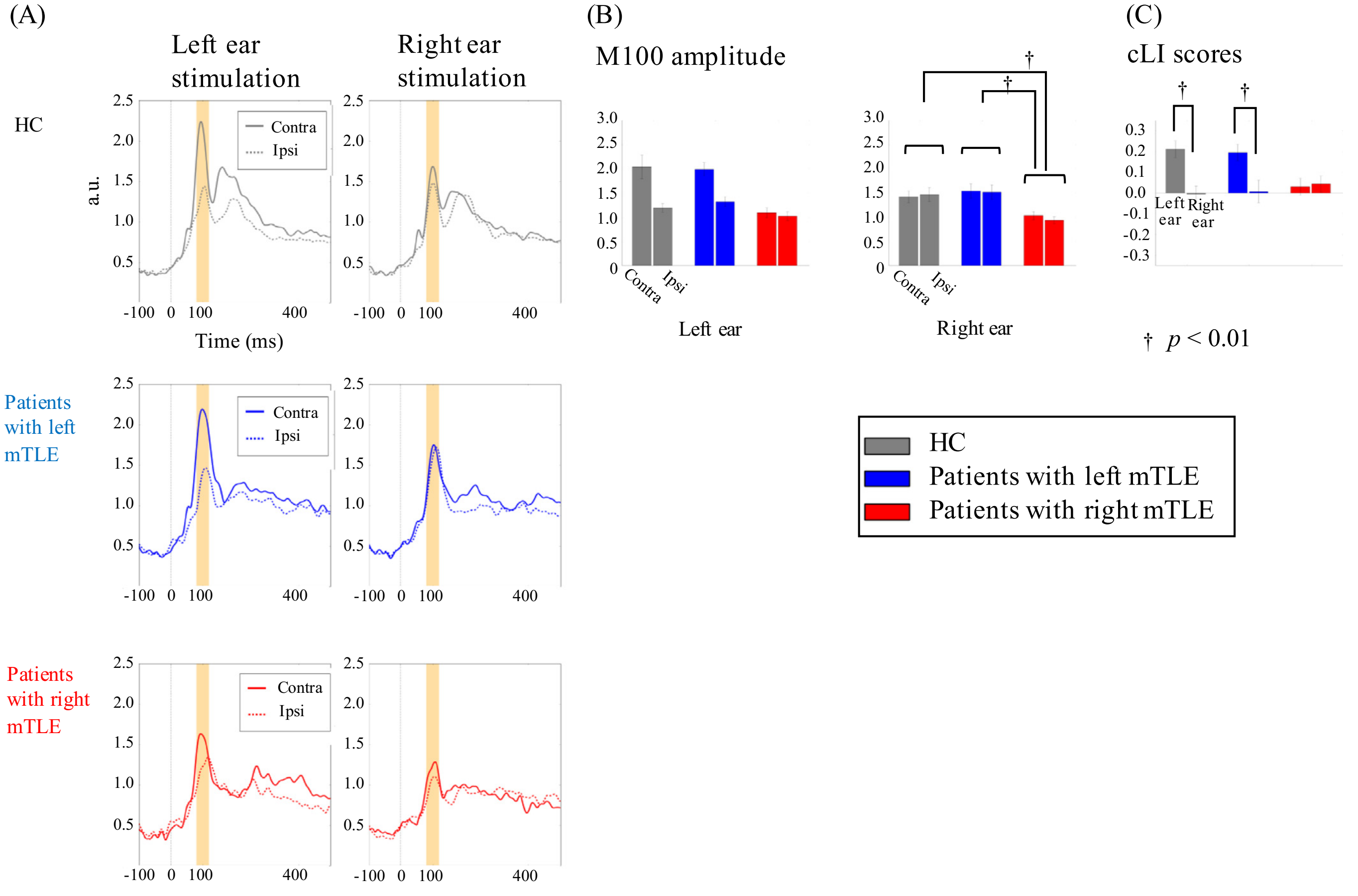

Fig. 1. Grand-averaged source waveforms of M100 recorded from contralateral and ipsilateral Heschl's gyri in healthy controls (HCs, black), patients with left mTLE (blue), and patients with right mTLE (red) (A). Right mTLE shows decreased M100 responses compared with the other two groups in response to right ear stimulation, irrespective of hemisphere (B). HCs and patients with left mTLE exhibited larger cLI scores in response to left ear stimulation compared with those (cLI scores) in right ear stimulation (C). Please note the lack of right hemispheric predominance with the lowest cLI scores in response to left ear stimulation in patients with right mTLE among the groups (C). a.u.: arbitrary unit, cLI: contralaterality index. Error bars show the standard error of the mean. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
ANOVA results for the PLFs in theta, alpha, and beta bands.

Theta band	df	F-value	p-Value
GROUP	2	3.54	0.035
HEMI	1	32.4	<0.0001
STIM	1	35.6	<0.0001
GROUP × HEMI	2	3.10	0.047
GROUP × STIM	2	3.08	**0.048**
HEMI × STIM	1	1.30	0.26
GROUP × HEMI × STIM	2	0.0649	0.94
Alpha band	**df**	**F-value**	**p-Value**
GROUP	2	11.1	<0.0001
HEMI	1	38.3	<0.0001
STIM	1	39.7	<0.0001
GROUP × HEMI	2	3.56	0.030
GROUP × STIM	2	4.11	**0.018**
HEMI × STIM	1	3.23	0.074
GROUP × HEMI × STIM	2	0.126	0.88
Beta band	**df**	**F-value**	**p-Value**
GROUP	2	10.8	<0.0001
HEMI	1	17.3	<0.0001
STIM	1	4.71	0.031
GROUP × HEMI	2	2.07	0.13
GROUP × STIM	2	3.31	**0.038**
HEMI × STIM	1	3.48	0.064
GROUP × HEMI × STIM	2	0.959	0.39

Bold values indicate the main significant ($p < 0.05$) results highlighted in the text.

ipsilateral hemisphere). In response to right ear stimulation, both patients with right and left mTLE exhibited decreased PLFs compared with HCs. Overall, monaural stimulation revealed impaired functioning of affected and nonaffected ACs in patients with mTLE.

3.3. cLI scores for M100 amplitude

The results of cLI scores of M100 amplitude are summarized in Table 4 and Fig. 1C. The right hemisphere was predominant regarding contralaterality in HCs and patients with left mTLE. There was a significant interaction between GROUP and STIM. The cLI scores for left ear stimulation in HCs and patients with left mTLE were significantly larger than those for right ear stimulation. In these groups, cLI scores associated with left ear stimulation were positive values (>0.1) while cLI scores associated with right ear stimulation were close to zero. These results suggest that the right hemisphere was predominant regarding contralaterality. In contrast, cLI scores of patients with right mTLE showed no significant main effect of STIM, along with the lowest cLI scores in response to left ear stimulation compared with those of the other two groups (Fig. 1C). Thus, the results indicate that patients with right mTLE lacked right hemispheric predominance regarding contralaterality.

3.4. cLI scores of PLFs for theta, alpha, and beta bands

The results of cLI scores of the PLFs are shown in Table 5 and Fig. 2C. Similar to the M100 amplitude results, the right hemisphere was predominant regarding contralaterality in HCs and patients with left mTLE. There was a significant interaction between GROUP and STIM in all frequency bands. The cLI scores for left ear stimulation in HCs and patients with left mTLE were significantly larger than those for right ear stimulation. In these groups, cLI scores for left ear stimulation were positive values (>0.1) while cLI scores for right ear stimulation were close to zero. In contrast, cLI scores in patients with right mTLE exhibited no significant main effect of STIM, along with the lowest cLI scores for left ear stimulation among those of the other two groups. Thus, again, patients with right mTLE appeared to lack right hemispheric predominance regarding contralaterality. In addition, in response to right ear stimulation, patients with left mTLE exhibited the lowest cLI scores in the alpha and beta bands. This finding suggests that patients with left mTLE exhibited a lack of contralaterality in response to right ear stimulation. Overall, dysfunction of AC on the affected side was more pronounced when the contralateral ear was stimulated.

3.5. PLVs for theta, alpha, and beta bands

Fig. 3A shows the PLV data between left and right ROIs. The ANOVA results of PLVs are summarized in Table 6 for theta, alpha, and beta bands. Auditory processing was predominantly performed by left ear stimulation in the alpha frequency band. There was a significant effect of GROUP in all bands except the beta band. In those frequency bands, a posthoc analysis revealed that PLVs were decreased in both patients with right and left mTLE compared with those (PLVs) in HCs (Fig. 3B), but no significant difference was found between patients with left and right mTLE. There was no significant interaction between GROUP and STIM. In addition, in the alpha band, there was a significant main effect of STIM, indicating that PLVs were larger in response to left ear stimulation compared with those in response to right ear stimulation, in all groups. Taken together, the current findings indicate that connectivity between bilateral ACs was decreased in both patients with left and right mTLE compared with that in HCs, irrespective of ear stimulation.

3.6. Accuracy of diagnosis and lateralization by LDA

The LDA results are summarized in Table 7. The diagnosis classifier achieved an accuracy of 82%, sensitivity of 82%, and specificity of 81%. For lateralization, the accuracy was 92%, sensitivity was 92%, and specificity was 93%. These results are comparable to those of a recent study [33] in which machine learning techniques were used to obtain the diagnosis (accuracy 91%), and lateralization classifier (accuracy 90%) on the basis of resting-state EEG data.

3.7. Disease duration and volumetry

There was a significant difference in the disease duration in groups with mTLE ($p = 0.04$, Mann–Whitney *U* test), suggesting that patients with right mTLE showed shorter disease duration than patients with left mTLE. There was no significant difference in the volume of ACs in all groups. A significant difference in the volume of the hippocampus was found, which indicated that HCs had greater hippocampal volume compared with the affected hippocampus in patients with mTLE. There was no significant difference in the volume of the hippocampus between groups with mTLE for the HS side.

3.8. Effects of HS on AC function

Our results could potentially be affected by the inhomogeneity of disease severity, such as HS, between the patient groups. Therefore, we only selected patients with HS (18 patients with left mTLE, 13 patients with right mTLE, and 32 HCs) after excluding patients without HS and patients with other structural abnormalities. The results were largely consistent with those of all the patients included (see Sections 3.1–3.5). The PLFs exhibited a greater decrease in patients with right mTLE than patients with left mTLE in the alpha band. The PLVs showed a significant decrement in both patients with left and right mTLE. Auditory cortex asymmetry in response to monaural stimulation was concordant with the laterality of seizure focus. Overall, our finding of altered auditory response indicated the laterality of seizure focus and pathophysiology of mTLE, rather than the severity of HS.

4. Discussion

In the present study, we analyzed previous data with additional data from patients with mTLE to investigate whether neural synchronization

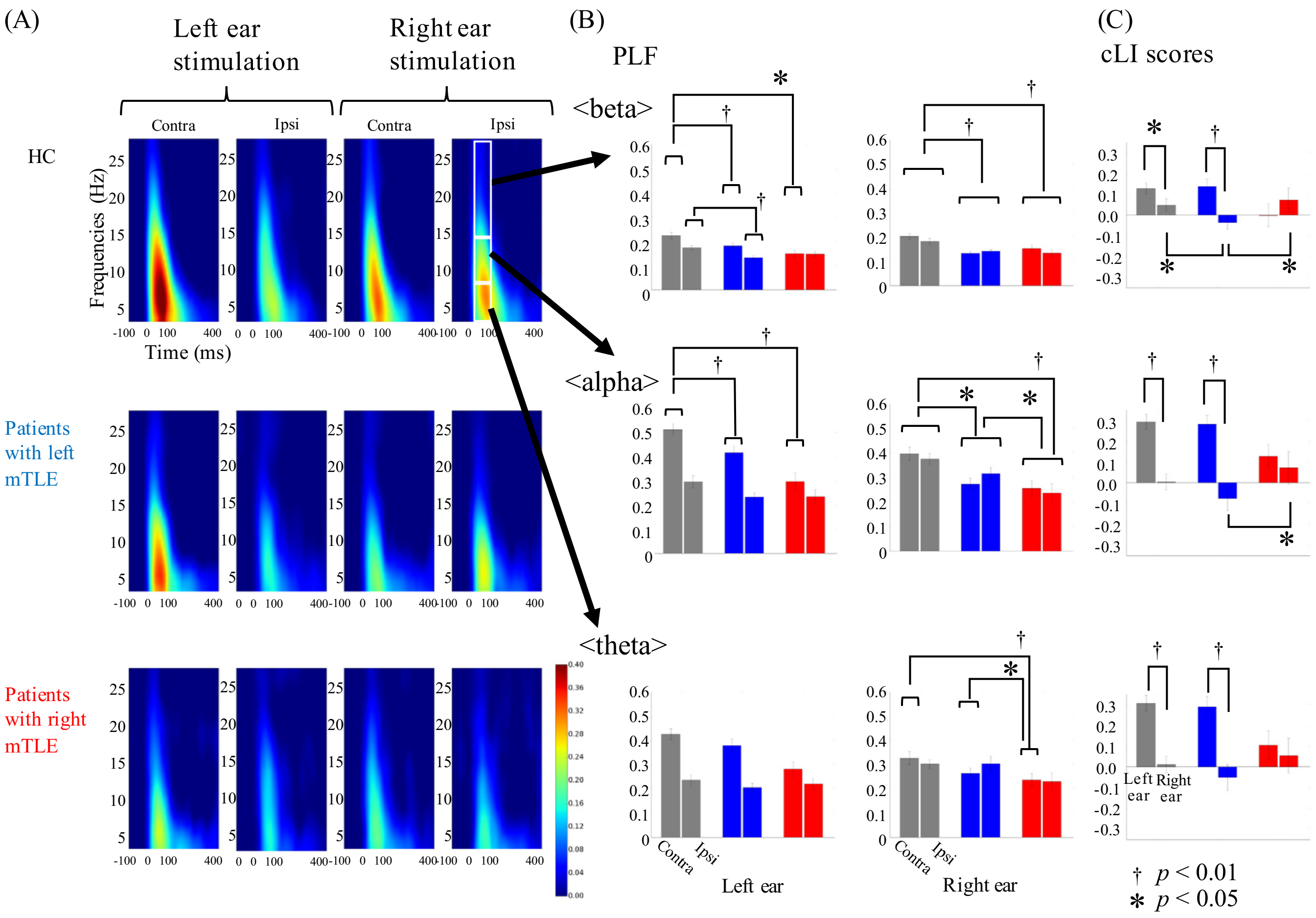

Fig. 2. Phase-locking factors (PLFs) in healthy controls (HCs), patients with left mTLE, and patients with right mTLE obtained from contralateral and ipsilateral Heschl's gyri. Time-frequency plots are shown in three groups as grand-averaged data (A). The white rectangle represents the theta, alpha, and beta bands, respectively. In the alpha band, patients with right mTLE exhibited more decreased PLFs than patients with left mTLE in response to right ear stimulation. In contrast, the theta and beta bands only differentiated HCs from groups with mTLE or patients with right mTLE from other groups (B). cLI scores indicate right hemispheric predominance in all groups except patients with right mTLE (C). In the alpha and beta bands, patients with right mTLE showed a decrement of cLI scores in response to left ear stimulation and patients with left mTLE showed a decrement of cLI scores in response to right ear stimulation.

induced by monaural pure tone stimulation provides useful diagnostic information about epileptic focus in patients with mTLE. Our major findings can be summarized as follows: 1) PLFs were sufficiently sensitive to differentiate groups with mTLE from HCs, but the M100 amplitude of each AC provided less diagnostic information; 2) PLVs suggested that both patients with left and right mTLE exhibited altered functional connectivity between bilateral ACs compared with HCs; 3) monaural stimulation was able to reveal AC asymmetry and provided significant lateralizing information about epileptic focus, particularly in patients with right mTLE; and 4) LDA revealed high accuracy of diagnosis and lateralization. Therefore, the current results indicated that monaural AEFs provide useful information for detecting mTLE pathologies [13].

4.1. Hemispheric asymmetry in monaural pure tone processing

One of the aims of the current study was to examine AC asymmetry in monaural pure tone processing in HCs. It has been previously proposed that monaural stimulation results in greater activity over the hemisphere contralateral to the side of stimulation [31,34,35], because the auditory pathway consists of a combination of large number of crossing fibers and a smaller number of noncrossing fibers. However, the current results demonstrated that the degree of lateralization was toward the right hemisphere in HCs: cLI scores of the left ear were positive (>0.1) while those of the right ear were almost zero (Figs. 1C, 2C).

Table 4
ANOVA results of cLI scores for M100 amplitude.

M100 amplitude	df	F-value	p-Value
GROUP	2	3.14	0.050
STIM	1	21.6	<0.0001
GROUP × STIM	2	5.39	**0.0052**

Table 5
ANOVA results of cLI scores for PLFs in three bands.

Theta band	df	F-value	p-Value
GROUP	2	3.48	0.036
STIM	1	44.7	<0.0001
GROUP × STIM	2	5.54	**0.0045**
Alpha band	df	F-value	p-Value
GROUP	2	2.60	0.082
STIM	1	56.0	<0.0001
GROUP × STIM	2	6.91	**0.0012**
Beta band	df	F-value	p-Value
GROUP	2	2.24	0.11
STIM	1	7.53	0.0066
GROUP × STIM	2	9.16	**0.0002**

Bold values indicate the main significant ($p < 0.05$) results highlighted in the text.

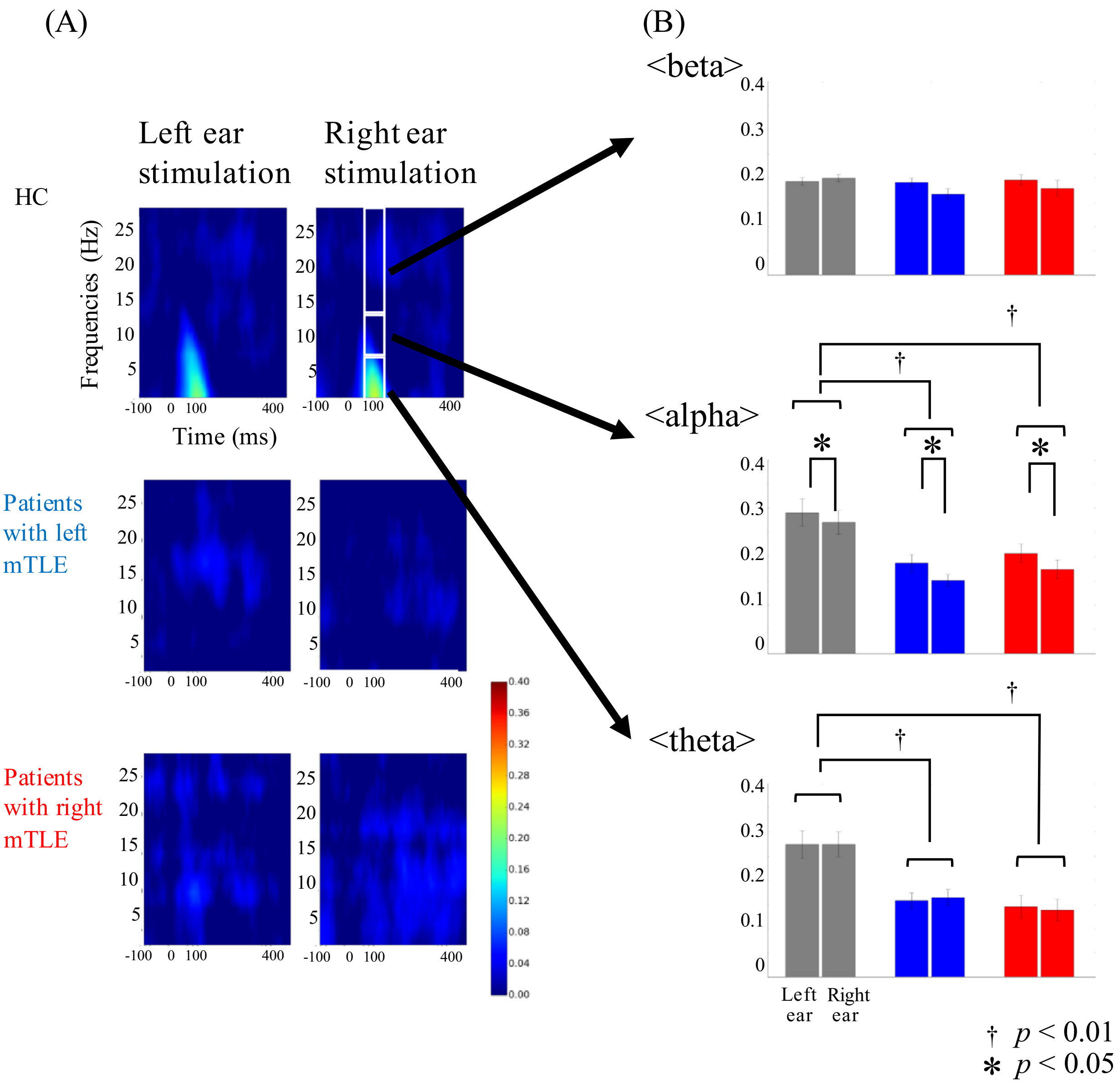

Fig. 3. Time-frequency plots of phase-locking values (PLVs) in healthy controls (HCs), patients with left mTLE, and patients with right mTLE as grand-averaged data (A). White rectangle represents neural synchronization between the right and left Heschl's gyri in the theta, alpha, and beta bands, respectively. PLVs in both patients with left and right mTLE were substantially reduced compared with those of HCs in the theta and alpha frequency bands, irrespective of the side of ear stimulation (B). In the alpha band, PLVs in response to left ear stimulation exhibited larger values compared with right ear stimulation in all groups.

Thus, the current results suggested right hemispheric predominance regarding contralaterality in pure tone processing. Our results are in accord with several MEG [32,36] and EEG studies [37–39] reporting larger responses in the right hemisphere, irrespective of the side of ear stimulation, or right hemispheric dominance for left ear stimulation but no hemispheric dominance for right ear stimulation [40]. The AC

Table 6
ANOVA results of the PLVs in three bands.

Theta band	df	F-value	p-Value
GROUP	2	10.40	**0.0001**
STIM	1	0.0022	0.96
GROUP × STIM	2	0.0833	0.92
Alpha band	df	F-value	p-Value
GROUP	2	9.01	**0.0003**
STIM	1	4.88	**0.031**
GROUP × STIM	2	0.170	0.84
Beta band	df	F-value	p-Value
GROUP	2	1.60	0.21
STIM	1	1.93	0.17
GROUP × STIM	2	1.77	0.18

Bold values indicate the main significant ($p < 0.05$) results highlighted in the text.

Table 7
Results of linear discriminant analysis.

Performance measure	Diagnosis	Lateralization
Accuracy (%)	81.7	92.3
Sensitivity (%)	82.1	92.0
Specificity (%)	81.3	92.9
Positive predictive value (%)	84.2	95.8
Negative predictive value (%)	78.8	86.7
Area under the curve	0.934	0.957

asymmetry is likely to have been caused by hemispheric activation induced by the auditory stimuli used in this study. Previous studies have reported that the right hemisphere is responsible for identification of acoustic patterns (tonal pitch or melody), while the left hemisphere is involved principally in speech, language, and temporal ordering (i.e., operating as the language dominant hemisphere) [41,42]. Pure tone, melodic, or rhythmic stimuli in this study may have activated the right hemisphere via top-down cognitive processes. Another potential explanation is related to the difference of acoustic features (pure tone, click) and the task demands used among the studies or the difference in ROIs (Heschl's gyri in this study). If AC asymmetry is present even in monaural pure tone stimulation, this may be used as a way of assessing neurological diseases (i.e., lateralization of epileptic focus).

4.2. M100 response cannot provide sufficient information about mTLE

The M100 response is a primary exogenous response originating from the AC, which is elicited without task demands, and is strongly dependent on acoustic features. However, it has been well-established that the M100 is modulated by a complex network of cortical areas such as bilateral supratemporal planes and superior temporal gyri and frontal and motor areas. Thus, the M100 is presumed to reflect higher cognitive function [43,44], and altered M100/N100 responses in patients with mTLE have been assessed [13,45,46]. However, studies of the decrement of M100/N100 amplitude in patients with mTLE in relation to the lateralization of epileptic focus have produced equivocal findings. Rosburg et al. [45] reported that N100 amplitude was not affected in patients with mTLE, but the altered N100 topography induced by affected ACs was demonstrated using binaural tone burst stimulation. In their study, patients with right HS exhibited a left-deviated N100 topography, while HCs and patients with left HS exhibited a symmetrical distribution. Our previous MEG study [13] provided the first demonstration of the tendency of M100 amplitude attenuation in patients with unilateral mTLE. In the current study, the M100 amplitude results (Fig. 1) indicated that patients with right mTLE showed decreased responses in response to right ear stimulation in both the affected and nonaffected hemispheres. Thus, focusing on the M100 response could provide partial diagnostic information for differentiating patients with right mTLE from HCs, but was not sufficient for differentiating patients with right and left mTLE.

4.3. PLFs can be useful for the diagnosis and lateralization of mTLE

In contrast to M100 amplitude, PLFs obtained from the same time window were more decreased in patients with right mTLE than in patients with left mTLE in the alpha band (Table 3, Fig. 2). Understanding why this difference may have occurred between the M100 amplitude and PLFs is an important issue, with several potential explanations. First, this finding is likely to be related to the nature of the differences between evoked responses (M100) and phase-based oscillations (i.e., PLFs). Evoked responses reflect a mixture of all components, including the amplitude, phase, and latency within each trial (jitter) [47]. In addition, evoked responses only extract phase-locked responses, but cannot reveal nonphase-locked components. In contrast, single trial analysis provides an overall evaluation of both phase- and nonphase-locked components. Second, PLFs can be evaluated in their appropriate frequency. The alpha band appears to be crucial for auditory perception [48–50]. Thus, PLFs in the alpha band may be more sensitive to the difference between patients with left and right mTLE compared with the M100 amplitude. Third, although the relationship between oscillatory activities and evoked response remains contentious, one potential explanation is phase-resetting, whereas another explanation is phase enhancing [51]. In auditory and visual evoked potential studies, the amplitude and phase were modulated concurrently, but showed different behaviors [47,49,52]. The amplitude or phase of each response to the stimuli exhibits some variability within subjects and across groups, especially in the neurological diseases. Variability in M100 amplitudes may obscure differences among groups. In contrast, phase-based oscillation is unlikely to be strongly influenced by amplitude variability. Hence, PLFs are more sensitive than evoked M100 responses even in the simple task used in the current study.

4.4. Significance of PLVs in mTLE

The PLVs showed a significant decrement in both patients with right and left mTLE, irrespective of the stimulation side (Fig. 3). A study of split-brain patients [53] reported that one hemisphere alone was not capable of processing auditory temporal patterns. In our study, PLVs reflected functional connectivity regarding auditory processing of the 500-Hz pure tone in the signals between ACs. This finding suggests that synchronous activity between bilateral ACs is necessary for auditory processing. Hippocampal sclerosis may influence organized processing of bilateral ACs, in accord with recent conceptualizations of epilepsy as a network disease [54]. To date, various cognitive and psychiatric impairments [55] and CAP impairments have been found in patients with mTLE [2,5,6,8–13]. Auditory dysfunction may be caused by impaired connectivity resulting from seizure propagation between the hemispheres. This assumption is in accord with the current finding that either the affected AC or nonaffected AC showed a decrement of PLFs in patients with mTLE (Fig. 2B).

The current PLV findings suggested that auditory processing of the 500-Hz pure tone was primarily performed in the right hemisphere. The PLVs were larger in response to left ear stimulation than right ear stimulation in all groups in the alpha frequency band (Fig. 3B). Furthermore, PLVs of patients with right mTLE were substantially more decreased than those of HCs. Previous monaural AEF studies indicated that initial contralateral processing was followed by ipsilateral processing after a delay by interhemispheric transmission, presumably via the corpus callosum [24,56]. These findings indicate that the right hemisphere is responsible for neural synchronization in response to monaural pure tone stimulation. This is particularly important when identifying the localization of epileptic focus in patients with mTLE. This issue is discussed in the next section.

4.5. Reduced neural synchronization can be useful for the lateralization of epileptic focus

The clinical impact of lateralization of epileptic focus using auditory stimulation for patients with mTLE has not yet been established. Our findings suggest that the right AC is crucial for auditory processing in HCs (see Section 4.1. and 4.3). Thus, auditory processing dysfunction may be highlighted by focal lesions in the right hemisphere. It has been reported that lesions in the right hemisphere severely impair pitch discrimination of complex sounds, indicating that impaired right AC disturbs the processing of complex sounds [57]. To the best of our knowledge, however, no previous studies have reported significant lateralization of the epileptic focus using auditory stimulation for patients with mTLE [2,8]. Rosburg et al. [45] only observed altered N100 topography in patients with right mTLE. The current study successfully demonstrated that patients with right mTLE were particularly susceptible to auditory processing dysfunction. Impaired auditory processing in right AC in patients with right mTLE could result in the lack of right hemispheric predominance regarding contralaterality (Figs. 1C and 2C), lowest PLFs (Fig. 2B), lowest cLI scores (Figs. 1C and 2C), and lower PLVs (Fig. 3B). Thus, monaural AEFs are likely to predict right hemispheric dysfunction and vulnerability in patients with right mTLE.

In addition, the use of monaural stimulation demonstrated significant lateralizing information, even for patients with left mTLE, as we initially hypothesized. Left ear stimulation was useful for examining patients with right mTLE, while right ear stimulation was useful for examining patients with left mTLE in the alpha and beta frequencies (Fig. 2C). The PLVs of patients with left mTLE were also decreased compared with HCs (Fig. 3B). Consequently, LDA accurately predicted the lateralization of epileptic focus (Table 7). Thus, the results indicated that our simple task is useful for localizing the epileptic focus in patients with unilateral mTLE.

5. Limitations

It should be noted that we only used a 500-Hz frequency pure tone in the current study, which is not the most sensitive hearing frequency for humans. Therefore, several different tones should be investigated in patients with mTLE in further studies. Unfortunately, we could not evaluate memory dysfunction in the right hippocampus in relation to auditory function because of a lack of clinically obtained memory scores (e.g., Wechsler Memory Scale-Revised (WMS-R)) in several patients. This issue should be clarified in future studies.

6. Conclusions

We confirmed that auditory processing was disrupted in patients with mTLE. In addition, we found that AC subnormal function was more pronounced in patients with right mTLE. Neural synchronization highlighted lateralization of the epileptic focus in patients with unilateral mTLE. Our noninvasive simple task was useful for localizing the epileptic focus in patients with mTLE, as well as for diagnosing patients with mTLE. Finally, our findings suggest that altered neural synchronization is exhibited by patients with mTLE, providing evidence for altered AC function in mTLE.

Conflict of interest statement

The authors have no conflict of interest relevant to this article.

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