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Monaural 40-Hz auditory steady-state magnetic responses can be useful for identifying epileptic focus in mesial temporal lobe epilepsy

Teppei Matsubara [a,*], Katsuya Ogata [a], Naruhito Hironaga [a], Taira Uehara [a], Takako Mitsudo [a], Hiroshi Shigeto [b], Toshihiko Maekawa [c], Shozo Tobimatsu [a]

[a] Department of Clinical Neurophysiology, Neurological Institute, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, Japan
[b] Epilepsy and Sleep Center, Fukuoka Sanno Hospital, Fukuoka, Japan
[c] Department of Neuropsychiatry, Amekudai Hospital, Japan

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HIGHLIGHTS

- Monaural auditory steady-state response (ASSR) was applied in mesial temporal lobe epilepsy (mTLE).
- Prominent contralateral temporal dynamics were found in controls but not mTLE.
- Left and right mTLE were accurately discriminated by monaural 40-Hz ASSR.

ABSTRACT

Objective: Patients with mesial temporal lobe epilepsy (mTLE) often exhibit central auditory processing (CAP) dysfunction. Monaural 40-Hz auditory steady-state magnetic responses (ASSRs) were recorded to explore the pathophysiology of mTLE.
Methods: Eighteen left mTLE patients, 11 right mTLE patients and 16 healthy controls (HCs) were examined. Monaural clicks were presented at a rate of 40 Hz. Phase-locking factor (PLF) and power values were analyzed within bilateral Heschl's gyri.
Results: Monaural 40-Hz ASSR demonstrated temporal frequency dynamics in both PLF and power data. Symmetrical hemispheric contralaterality was revealed in HCs. However, predominant contralaterality was absent in mTLE patients. Specifically, right mTLE patients exhibited a lack of contralaterality in response to left ear but not right ear stimulation, and vice versa in left mTLE patients.
Conclusion: This is the first study to use monaural 40-Hz ASSR with unilateral mTLE patients to clarify the relationship between CAP and epileptic focus. CAP dysfunction was characterized by a lack of contralaterality corresponding to epileptic focus.
Significance: Monaural 40-Hz ASSR can provide useful information for localizing epileptic focus in mTLE patients.

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1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most common form of surgically treated epilepsy. Magnetoencephalographic (MEG) measurements are widely used for the diagnosis and localization of epileptic focus. Precise evaluation of epileptic focus can aid treatment and lead to seizure freedom in most mTLE patients (Badier and Chauvel, 1995; Hughes, 1989). Although the main abnormalities and damage in mTLE are located in the mesiotemporal structures (e.g., hippocampal sclerosis; HS), widespread damage to connectivity is reported to involve temporal and extratemporal structures (Mueller et al., 2009; Reinsberger et al., 2010). In addition, mTLE patients have been found to exhibit dysfunctional central auditory processing (CAP) in electroencephalography (EEG) and MEG studies, as well as behavioral studies (Aravindkumar et al., 2012; Boatman et al., 2006; Chatani et al., 2016; Collard et al., 1986; Ehrle et al., 2001; Han et al., 2011; Lavasani et al., 2016; Olsen, 1983; Ortiz et al., 2002). Altered CAP refers to changes in the perceptual processing of auditory informa-

* Corresponding author at: Department of Clinical Neurophysiology, Neurological Institute, Faculty of Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan. Fax: +81 92 642 5545.
E-mail address: teppeim@med.kyushu-u.ac.jp (T. Matsubara).

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tion in the central nervous system despite normal hearing sensitivity, and is exhibited as poor auditory discrimination performance, auditory pattern recognition and temporal differentiation, or decreased electromagnetic responses (e.g., N100/M100, P300, mismatch negativity) (Han et al., 2011). Various studies have reported that some mTLE patients show decreased performance in irregularity discrimination of rapid auditory sequences (Ehrle et al., 2001), decreased temporal processing in the Gaps-In-Noise test (Aravindkumar et al., 2012) and the duration pattern sequence test (Lavasani et al., 2016). In accord with these results, a recent MEG study in our laboratory provided neuromagnetic evidence for hippocampal modulation of CAP (Chatani et al., 2016). However, the functional impact of CAP dysfunction on unilateral HS remains to be fully elucidated.

Neural activity can be noninvasively assessed using EEG and MEG, and gamma-band oscillations provide a useful marker of cortical activity during a variety of cognitive tasks, potentially reflecting a fundamental aspect of temporal coding in cortical networks (Uhlhaas and Singer, 2010). Gamma-band abnormalities are hypothesized to contribute to brain dysfunction and clinical symptoms in psychiatric disorders such as schizophrenia (Gandal et al., 2012), bipolar disorder (Oda et al., 2012), autism spectrum disorder (Rojas and Wilson, 2014), posttraumatic stress disorder (Huang et al., 2014), attention-deficit hyperactivity disorder (Wilson et al., 2012) and patients with disorders of consciousness (Binder et al., 2017). In the auditory system, assessment of gamma cortical microcircuits is commonly conducted using the 40-Hz auditory steady-state response (ASSR). The ASSR is a magneto-electrophysiological oscillation entrained to both the frequency and phase of rapid, periodic auditory stimuli delivered either in trains of clicks, or amplitude-modulated (AM) tones (Galambos et al., 1981). Several recent studies reported that the ASSR reflects both the temporal integration and temporal resolution of CAP (Lazzouni et al., 2010; Ross et al., 2002; Ross and Pantev, 2004). Primary generators of the ASSR are mainly present in the left and right primary auditory cortices (ACs) (Sohal et al., 2009). Studies of ASSR in schizophrenia have consistently reported a reduced gamma-band response (Hamm et al., 2011; Krishnan et al., 2009; Spencer et al., 2009), while patients with schizophrenia involving acute auditory hallucinations were found to exhibit a localized increase in gamma synchrony (Spencer et al., 2004; Spencer et al., 2009). In addition, a significant inverse correlation between gamma ASSR and negative symptoms has been found in schizophrenia (Griskova-Bulanova et al., 2016; Hamm et al., 2011). Overall, the ASSR is thought to reflect the efficiency of gamma-amino butyric acid (GABA) inhibitory interneuronal activity (Uhlhaas and Singer, 2010).

To date, the details of CAP asymmetry have not been investigated using monaural 40-Hz ASSR. Because most psychiatric disorders are whole-brain diseases, most previous EEG/MEG studies have examined 40-Hz ASSR using binaural presentation, and little attention has been paid to the lateralization of AC function/dysfunction. However, in focal or lesion-related diseases, binaural presentation would be expected to mask CAP dysfunction that may be affected by unilateral lesions or binaural interactions (Chaieb et al., 2015). The ascending pathway in the auditory system is predominant after intersection in the brainstem, and the contralateral auditory pathway is more efficient than the ipsilateral pathway during monaural presentation (Eggermont, 2001; Langers et al., 2005). Hence, we assumed that monaural auditory stimulation would enable the accurate evaluation of the function/dysfunction of unilateral AC in lesion-related diseases. Furthermore, in many ASSR studies carried out in patient populations, EEG has often been analyzed at the midline electrodes because of the dipole orientation situated in the supratemporal plane (Brenner et al., 2003; Galambos et al., 1981). In contrast, MEG has better spatial resolution for accurately evaluating the activity of bilateral ACs. Thus, MEG may be better suited than EEG analysis for assessing CAP asymmetry.

Applying 40-Hz ASSR for localization of epileptic focus is an intriguing possibility because epilepsy has been suggested to involve abnormal GABA interneurons (Bonansco and Fuenzalida, 2016). However, to our knowledge, no previous human studies have used the ASSR to examine lesion-related epilepsy, such as mTLE, underlying CAP dysfunction. Therefore, we hypothesized that 40-Hz monaural ASSR with MEG could reveal the epileptic focus in unilateral mTLE patients. To this end, we first examined how 40-Hz monaural ASSR was temporally modulated in each AC in terms of contralaterality in healthy controls (HCs). This examination was performed to test whether monaural ASSR exhibited temporal frequency dynamics with symmetrical contralaterality in HCs. Here, we assumed that contralaterality indicates contralateral predominance in responses to monaural stimulation. In addition, we expected that 40-Hz monaural ASSR would reveal the underlying pathophysiology of unilateral mTLE patients. Thus, we recorded 40-Hz monaural ASSR in left and right mTLE patients. We compared the ASSR results between HCs and mTLE patients to elucidate abnormal contralaterality in mTLE patients.

2. Materials and methods

2.1. Subjects

Eighteen left mTLE patients (age range; 18–66 years, 14 females), 11 right mTLE patients (age range; 18–71, six females) and 16 HCs (age range; 23–49, seven females) were recruited. All patients fulfilled the criteria of the International League Against Epilepsy (1989), and were treated with standard anti-epileptic drugs. We used the following inclusion criteria for mTLE patients: (1) magnetic resonance imaging (MRI) findings showing unilateral HS or normal hippocampus; (2) video-EEG confirmed semiology and ictal-onset localization; (3) absence of extra-temporal lesions, or prior head injuries. Table 1 shows the demographic characteristics and clinical features of the subjects. One left mTLE patient, one right mTLE patient and two HCs were left-handed (Table 1). All other participants were right-handed. Fourteen mTLE patients underwent standard anterior temporal lobectomy after MEG recording, and HS was later histologically proven in most patients. Although the remaining mTLE patients did not undergo surgical treatment, their clinical, neuroimaging and electrophysiological characteristics were consistent with unilateral mTLE. All subjects gave written informed consent for participation, and the study was approved by the Ethics Committee of Kyushu University.

2.2. Auditory stimuli

The stimuli were click sounds delivered every 25 ms (40 Hz) for a total of 500 ms. The stimuli were presented monaurally, first right then left, through earphones with plastic tubes via the transducer (Etymotic ER-2, Etymotic Research, Elk Grove Village, IL, USA). The stimuli were generated by a Tone-Burst-Generator (Kyushu-Keisokuki, Fukuoka, Japan). The intensity of the click train was equivalent to a 30 dB sensation level, measured using 500-Hz tone burst stimuli (Kikuchi et al, 2011). Masking noise (white noise) was delivered to the contralateral ear at a level of −14 dB, below the intensity of the click trains. These click trains were repeated 200 times every 1000 ms (i.e., inter-stimulus interval: 500 ms). One right mTLE patient received only right ear stimulation because of a technical error. Thus, only the right ear condition was included for further analysis in this patient.

Table 1
Demographic characteristics of patients.

Patients (No.)	Side (mTLE)	Sex	Age (years)	Handed-ness	Duration (years)	FIQ	Structural MRI	Interictal EEG findings	Ictal EEG findings	Seizure semiology	PET/SPECT hypometabolism	Surgical outcome	Pathology	AEDs
1	Lt	M	58	Rt	16	83	HS	Lt F-T	Lt F-T	FIAS, Lt arm automatism	Lt T	1a	HS type 2	LEV, ZNS, CBZ
2	Lt	F	44	Rt	4	91	Atrophy	Rt T	Lt T	FIAS	Lt T-P-O	1a	HS type 2	LEV
3	Lt	F	24	Rt	10	NA	DNT	Lt T	NA	FIAS, Rt arm clonic	Lt T	1a	DNT	CLB
4	Lt	F	52	Rt	41	NA	Atrophy	Lt T > Rt T	NA	FIAS	Lt T	NA	NA	CBZ, VPA, PB, PHT, CZP
5	Lt	F	40	Rt	30	82	HS	Lt T	Lt T	FIAS, Rt arm dystonic	Lt T	1a	HS type 1	LTG, LEV
6	Lt	F	49	Rt	37	80	HS	Lt T	Lt T, Rt T	FIAS	Lt T	1a	HS type 1	CBZ, LEV
7	Lt	M	54	Rt	35	56	HS	Lt T	Lt F-T	FIAS, Rt arm dystonic, tonic, FBTCS	Negative	1a	HS type 2	PHT, CZP, LEV, ZNS
8	Lt	M	20	Rt	3	87	Microbleeds	LtT	Lt T	FIAS, Rt arm clonic, oral automatism	Lt T	NA	NA	CBZ
9	Lt	F	52	Rt	22	82	CCM	Lt F-T	Lt F-T-P	FIAS, oral automatism, Rt arm tonic, FBTCS	Symmetry	NA	NA	CBZ, LEV, LTG
10	Lt	F	40	Rt	36	68	HS	Lt T > Rt T	Lt T	FIAS, Lt arm automatism, Rt arm tonic	Lt T	NA	NA	LTG
11	Lt	M	61	Rt	51	NA	HS	Lt T, Rt T	NA	Aura, FIAS, automatism	Lt T	NA	NA	PHT, VPA, ZNS, DZP
12	Lt	F	29	Rt	20	93	HM	Lt F-T	NA	Déjà vu, FIAS	Symmetry	NA	NA	LTG
13	Lt	F	43	Rt	32	71	Normal	Lt T	Lt T	FIAS, Lt arm automatism	Lt T broadly	NA	NA	CBZ, CLB
14	Lt	F	46	Lt.	41	77	HS	Lt T	Lt F-T	FIAS, Rt arm tonic	Lt T	NA	NA	PHT, CBZ, CLB, PHT
15	Lt	F	66	Rt	44	101	HS	Lt T	Lt T	FIAS, Rt arm automatism,	Symmetry	NA	NA	CBZ, CLB, LEV
16	Lt	F	32	Rt	26	NA	Normal	Lt T	NA	Aura, FIAS, automatism	NA	NA	NA	VPA, LEV
17	Lt	F	31	Rt	23	NA	Normal	Lt T	NA	FIAS	NA	NA	NA	LTG
18	Lt	F	18	Rt	5	68	Atrophy	None	NA	Déjà vu, FIAS, Rt arm tonic, FBTCS	Negative	NA	NA	LTG, CBZ
19	Rt	M	32	Lt	3	57	HS	Rt T > Lt T	Rt T	FIAS, oral automatism, Lt arm tonic, FBTCS	Rt T	1a	HS type 1	LEV, CBZ
20	Rt	M	71	Rt	10	125	CCM	Rt T	Rt T	Lt arm and oral automatism	Rt T	1b	CCM	CBZ
21	Rt	F	22	Rt	13	76	HS	Lt T, Rt T	Rt T	FIAS	Rt T	1d	HS type1	LTG, VPA, CLB
22	Rt	M	44	Rt	7	63	HS, AH	Rt T	Rt F-T	Aura, automatism	Rt T-P	NA	NA	LEV, PMP
23	Rt	F	20	Rt	14	71	Hemi-spheric atrophy	Rt T	Rt T-F	FIAS, oral automatism	Rt T-F	1a	HS type 1	CBZ, LCM
24	Rt	F	38	Rt	35	67	HS	Lt T > Rt T	RtT	Aura, FIAS, Rt arm and oral automatism	Rt T	1a	HS type 1	LEV, ZNS, PHT
25	Rt	F	34	Rt	15	114	HS	Rt T > Lt T	Rt T, Lt T	FIAS	Rt T	1a	HS type 2	LTG
26	Rt	M	18	Rt	3	57	Tumor	Rt T > Lt T	Rt T	FIAS, Lt arm dystonic	Rt T	1a	PLNTY	LEV
27	Rt	F	48	Rt	36	NA	Heterotopia	Rt T	NA	FIAS	Rt T, Lt T	NA	NA	CBZ, CLB
28	Rt	M	35	Rt	32	NA	Normal	Rt T > Lt T	Not localized	FIAS, Lt arm dystonic and tonic	Rt T	1a	Normal	LEV, LTG, CBZ, CLB
29	Rt	F	56	Rt	36	NA	Normal	Rt T	NA	Aura, FIAS	NA	NA	NA	LEV, VPA, LCM

Surgical outcome was classified according to Engel's classification (1993).
Abbreviations: AED, anti-epileptic drug; AH, amygdala hypertrophy; CCM, cerebral cavernous malformation; DNT, dysembryoplastic neuroepithelial tumor; F, female; FBTCS; focal to bilateral tonic clonic seizure; FIAS; focal impaired awareness seizure; FIQ, full-scale intelligence quotient; HM, hippocampal malrotation; HS, hippocampal sclerosis; M, male; MRI, magnetic resonance imaging; mTLE, mesial temporal lobe epilepsy; NA, not applicable; PLNTY, polymorphous low-grade neuroepithelial tumor of the young.

2.3. MEG recordings

ASSR was 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 3D digitizer (FastTrack, Polhemus, VT, USA) was used to measure anatomical landmarks (bilateral pre-auricular points and nasion) of the head and approximately 200 head-surface points attached to stable positions on the forehead and nose (Hironaga et al., 2014). 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. The precise location of the head with respect to the sensor array was determined using the HPI coils. In addition, high-resolution three-dimensional MRI images were 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, $1.0 \times 1.0 \times 1.0\ mm^3$). Two mTLE patients did not undergo high-resolution imaging. Thus, for later analyses we used fluid-attenuated inversion recovery images for one patient and low-resolution T1-weighted images for another patient.

2.4. Preliminary processing

A spatio-temporal signal space separation (tSSS) method was applied off-line to the recorded raw data (Taulu et al., 2005). Gradiometers were used for analysis. tSSS-reconstructed raw data with signal variation exceeding 4000 fT/cm after notch filtering (60 Hz) was applied were excluded to eliminate outliers caused by artifacts. Artifacts such as eye blinks and other eye movements and epileptic spikes were carefully excluded by visual inspection. The analyzed period included 400 ms before and 900 ms after stimulus onset.

2.5. Analysis

2.5.1. Source localization

Source localization was performed using noise-normalized minimum norm estimate (MNE), executed using dynamic statistical parametric mapping (dSPM). Specific details of the MNE and dSPM algorithms have been reported elsewhere (Hashizume and Hironaga, 2016). Digitized anatomical head landmarks and scalp surface points were co-registered onto the scalp contour extracted from the MR images. To construct a conductor model, we created a Boundary Element Method mesh by tessellating the inner skull surface. For dSPM noise normalization, we used the entire raw data set of each run. The averaged data within bilateral Heschl's gyri parcellations were analyzed. In a previous study in our laboratory (Chatani et al., 2016), we found that the volume of Heschl's gyrus was not reduced in mTLE patients compared with HCs. Thus, we selected Heschl's gyrus to represent AC in the current study to avoid the effects of structural abnormalities. The anatomical information was provided by FreeSurfer software (FreeSurfer v4.5, aparc.a2009s/Destrieux.simple. 2009-07-29.gcs atlas).

2.5.2. Time-frequency analysis

Our auditory stimuli were periodically presented, eliciting an approximately sinusoidal response at the driving stimulus frequency with precise phase-locking to the stimulus onset (Fig. 1A). In contrast to the evoked 40-Hz response, induced gamma responses appeared with a jitter in latency from one trial to another, centered around a given latency. Hence, time-varying spectral analysis of single trials is needed to detect them (Fig. 1B) (Tallon-Baudry and Bertrand, 1999). We performed continuous wavelet transformation of single-trial MEG signals using complex Morlet wavelet as a mother function. The window size was 1/2 a cycle of a given frequency. Thus, the frequency resolution was 4 Hz, and the temporal resolution was 160 ms. Data were obtained every 1 Hz (1–100 Hz) and also every 1 ms. We calculated PLF and power; PLF is a measure of the variance in phase across trials and thus reflects the temporal stability of oscillatory activity from trial to trial at specific sites (Hagiwara et al., 2010; Hagiwara et al., 2014). PLF ranges from 0 (purely non-phase-locked activity) to 1 (strictly phase-locked activity). For power, we applied baseline correction (from − 200 ms to − 100 ms), as measured by ratio. We applied PLFs and power to the source waveforms extracted from ACs and to left and right ear stimulation, respectively. The computation of PLFs and power for MEG source waveform analysis were performed using tools implemented in MNE-Python (Gramfort et al., 2014).

2.5.3. Contra-laterality index

Our main research focus was functional laterality against ear stimulation, because laterality directly indicates the predominant hemispheric function (i.e., functional laterality) and because monaural ear presentation was assumed to provide an evaluation of the contralateral hemisphere. In addition, a decrement of PLFs/power would not directly indicate a functional deficit in patients with neuropsychiatric disorders, because of the confounding effects of attention deficits leading to a low signal-to-noise ratio (SNR), or the effects of anti-psychiatric drugs (in this study, anti-epileptic drugs). Furthermore, previous studies have reported inter-subjective variability in the ASSR (Baltus and Herrmann, 2016); some subjects show a decrement of PLFs/power, irrespective of disease. Thus, to avoid those complexities, normalization is required when conducting group analysis. The commonly used laterality index (LI) (Hironaga et al., 2017) obtains the difference between left and right hemispheric responses normalized by the sum of responses. Here, we set the contra-laterality index (cLI) against the stimulation (Matsubara et al., 2018):

$$cLI = \frac{V_{contra} - V_{ipsi}}{V_{contra} + V_{ipsi}} \quad (1)$$

where V represents the value of PLF or power in a certain time-frequency window. The subscript *contra* denotes the contralateral Heschl's gyrus, while *ipsi* denotes the ipsilateral Heschl's gyrus. LI can be used as a measure of hemispheric laterality. Thus, LI indicates left hemispheric predominance with positive values (0 to +1) while right predominance is indicated by negative values (0 to −1). In contrast, the cLI represents contralateral predominance against monaural stimulation. Thus, the cLI indicates contralateral hemispheric predominance with positive values (0 to +1) while ipsilateral predominance is indicated by negative values (0 to −1).

2.5.4. Optimal time-frequency windows for cLI scores

To determine the time-frequency window of interest for contralaterality, data-driven analysis was conducted using repeated-measures analysis of variance (rmANOVA) with a non-parametric clustering method across time and frequency (Maris and Oostenveld, 2007), implemented in MNE-Python. We determined a specific time-frequency window that showed prominent contralaterality based on HC data. Thus, the same time-frequency window was applied to mTLE groups for group analysis. Using this analysis, the obtained condition effects of contralaterality (contralateral vs. ipsilateral) and ear stimulation (left ear vs. right ear) on PLF/power were free from a priori time-frequency window selection. The multiple comparisons problem was addressed with a cluster-level permutation test across time and frequency. We used 1000 permutations to test for contralaterality and ear effects. The cluster defining threshold was set at $p = 0.01$ for both PLFs and power. Selected samples were clustered on the basis of both temporal and frequency adjacency.

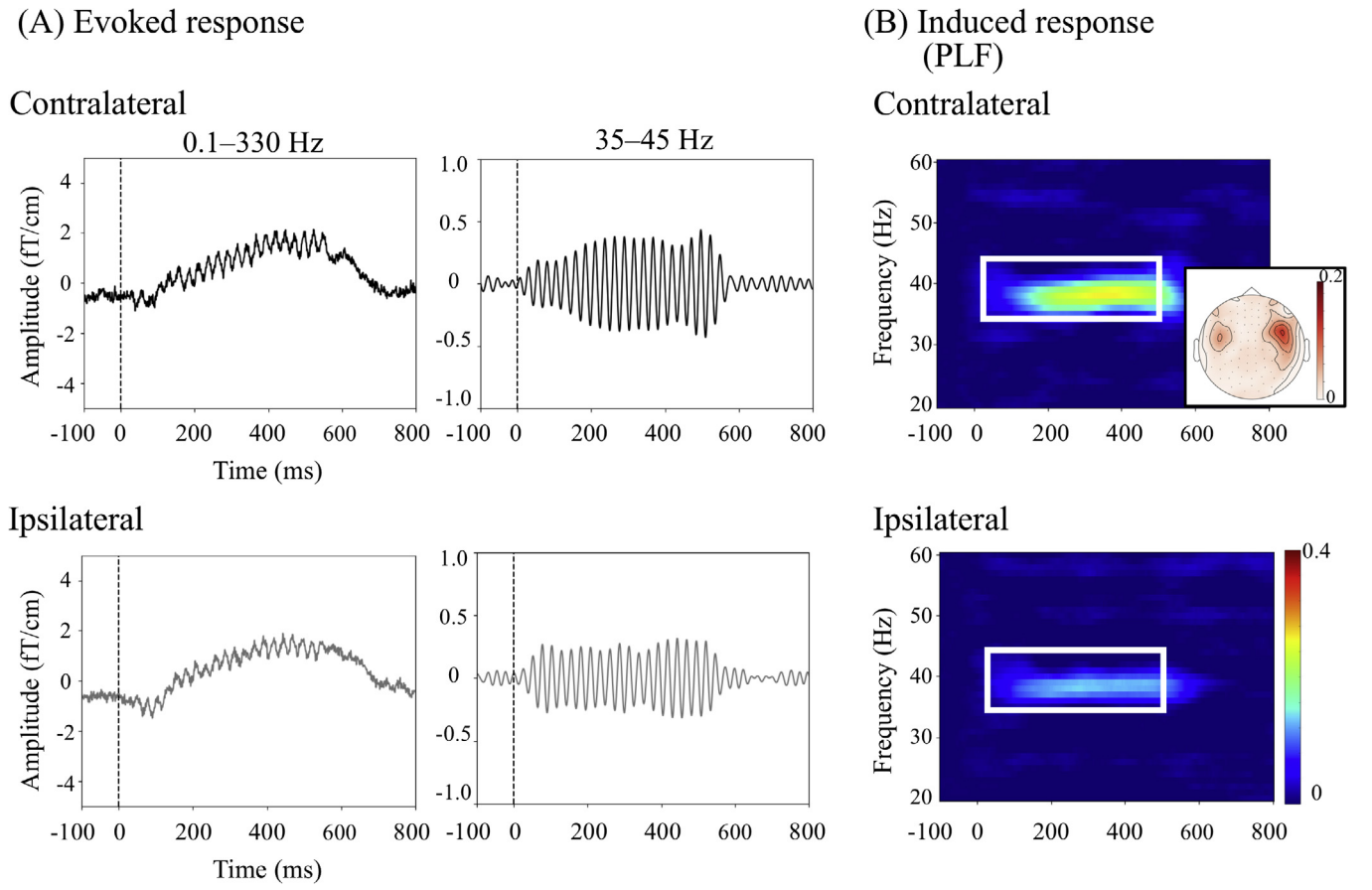

Fig. 1. The grand-averaged waveforms of the evoked responses to left ear stimulation in HCs obtained from the contralateral and ipsilateral temporal sensors (A). Evoked oscillations were evident after applying a relatively narrow bandpass filter (35–45 Hz) to the original waveform (0.1–330 Hz) during sound presentation (0–500 ms). Phase-locking factors (PLFs) were calculated after applying the time-frequency analysis of the raw data of each response (B). A clear gamma-band response was observed, approximately corresponding to a 40-Hz steady-state response. A contralateral sensor showed more prominent temporal frequency dynamics compared with those of an ipsilateral sensor. Topographical mapping as the average of 35–45 Hz oscillations during 0–500 ms (white rectangles) revealed that activity mainly occurred in the bilateral temporal regions, most likely corresponding to the bilateral auditory cortices (ACs) (inset figure).

To reduce the calculation time, data were resampled to 20 ms. The presence of the contralaterality effect was determined if there was a cluster of main effects of contralaterality (with a critical alpha-level of 0.05) that included approximately 40-Hz oscillation during the sound presentation period (0–500 ms).

2.6. Statistical analysis

One-way ANOVA was used to analyze the threshold of 500-Hz tone burst stimuli among the three groups. cLI scores (Eq. (1)) were obtained as the averages of time-frequency windows provided by the non-parametric clustering method described in the previous section (Section 2.6). cLI scores were analyzed for PLFs and power, respectively, using two-way rmANOVA with group (HCs vs. left mTLE vs. right mTLE) as a between-subjects factor and ear (left ear vs. right ear) as a within-subjects factor. Post-hoc analyses were conducted using contrast analysis. ANOVA analysis was performed using JMP software (SAS Institute Inc., Cary, NC, UCA). In all analyses, the significance level was set at 0.05.

3. Results

3.1. Auditory thresholds among the groups

One-way ANOVA revealed that the threshold of 500-Hz tone burst stimuli was not significantly different among the three groups (left ear, $p = 0.87$; right ear, $p = 0.78$).

3.2. Temporal profiles of PLFs

Fig. 1A shows the grand-averaged waveforms of evoked responses to left ear stimulation in HCs obtained from the contralateral and ipsilateral temporal sensors. Evoked responses showed the time-locked neural dynamics in response to 40-Hz sound stimulus presentation. Contralateral sensors revealed more prominent responses compared with ipsilateral sensors. Induced responses shown as PLFs revealed a clear gamma-band neural oscillation (Fig. 1B). A topographical mapping (inset figure) obtained from PLFs as the average of 35–45 Hz oscillations during the 0–500 ms period revealed that the activity was mainly generated in the bilateral temporal regions with contralateral predominance. Hereafter, the induced responses were analyzed in source space focused on Heschl's gyri (see Section 2.5.1).

Fig. 2 (upper row) shows the temporal profiles of PLF data from left and right ACs in each group. 40-Hz ASSR clearly elicited temporal frequency dynamics at approximately 40 Hz in bilateral ACs irrespective of ear stimulation in HCs (upper left). In mTLE patients, similar temporal profiles of PLFs were observed, but mTLE patients exhibited decreased responses compared with HCs bilaterally (Fig. 2, upper middle and right). More prominent responses in the contralateral AC compared with the ipsilateral AC were evident in HCs in the time courses of PLFs (35–45 Hz), whereas mTLE patients showed less marked contralaterality (Fig. 2, middle row). cLI scores also showed different response patterns among the three groups (Fig. 2, lower row). In HCs, the predominance of contralat-

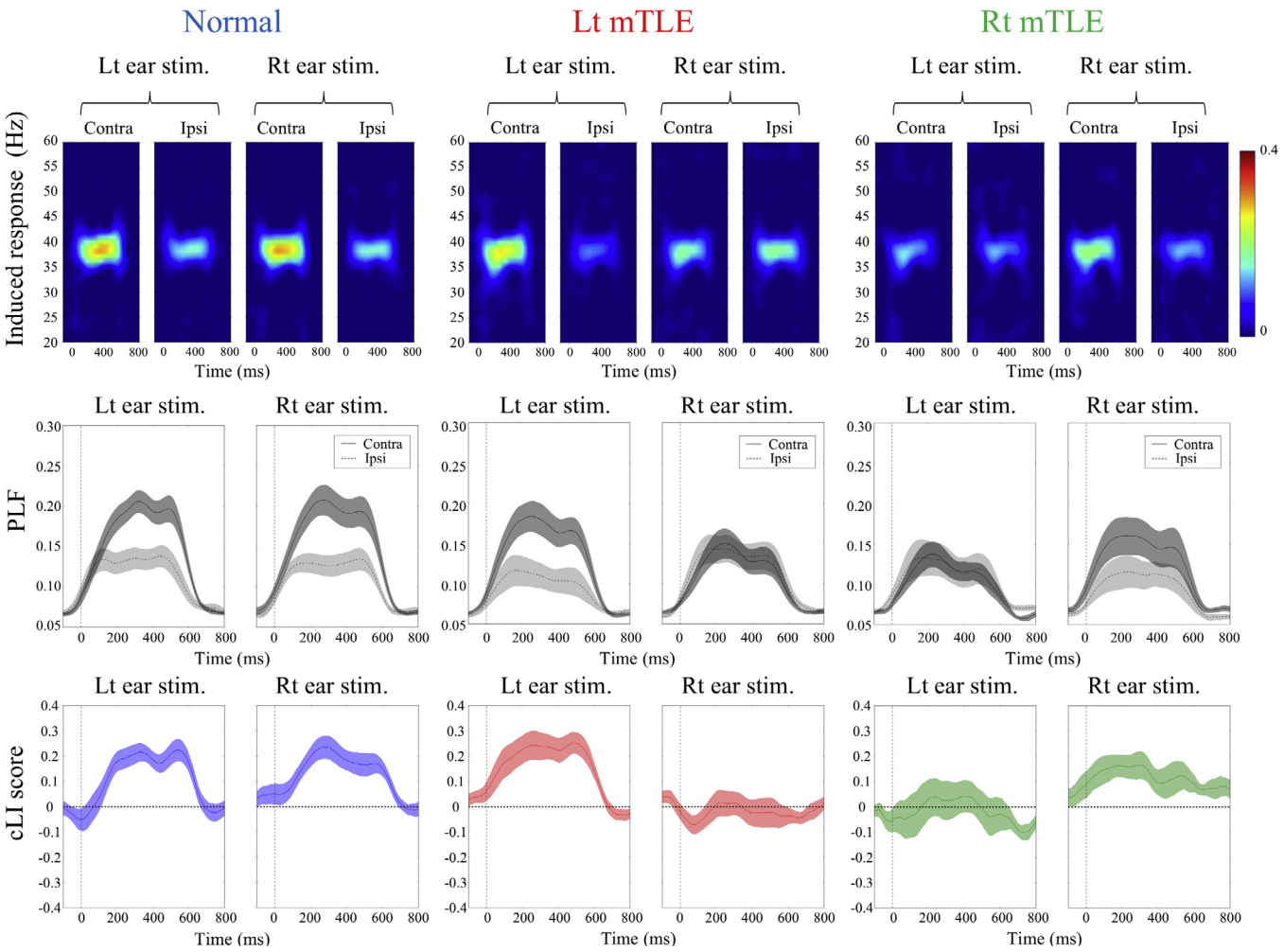

Fig. 2. Induced gamma responses of phase-locking factors (PLFs) in HCs, left mTLE and right mTLE patients obtained from contralateral and ipsilateral ACs. Time-frequency plots are shown in three groups as grand-averaged data (upper row). 40-Hz ASSR elicits temporal frequency dynamics at approximately 40 Hz in bilateral ACs irrespective of ear stimulation during sound presentation. Note that more prominent responses in the contralateral AC were evident, compared with those of ipsilateral AC. Time courses of PLFs as the average of 35–45 Hz oscillations are shown in each group by each ear stimulation (middle row). Black lines represent the mean activity of contralateral AC, while gray lines represent the mean activity of ipsilateral AC. More prominent responses were found in the contralateral AC in HCs, while mTLE patients showed less marked contralaterality. Contra-laterality index (cLI) scores are presented for each group (lower row). HCs (blue lines) exhibited symmetrical contralaterality in response to left and right ear stimulation during all time courses, while mTLE patients exhibited different response patterns. Left mTLE patients (red lines) exhibited decreased contralaterality in response to right ear stimulation, whereas right mTLE patients (green lines) exhibited reduced contralaterality in either right or left ear stimulation, with more prominent reductions in left ear stimulation. Shaded areas represent the standard error of the mean in this figure and Fig. 4. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

erality was symmetrical at around 200 to 600 ms in response to ear stimulation on both sides. In contrast, the temporal frequency dynamics of cLI scores were suppressed during right ear stimulation in left mTLE patients. In right mTLE patients, cLI scores were also suppressed during stimulation of both ears, but were predominantly inhibited during left ear stimulation.

rmANOVA was performed with a non-parametric clustering method to determine the time-frequency window that optimally represented prominent contralaterality in HCs. A main effect of contralaterality was observed, but neither a main effect of ear nor an interaction effect was found. We obtained only one cluster in which contralateral AC showed significantly higher PLFs than ipsilateral AC, at around 40 Hz (32–46 Hz) during the 120–680 ms period (Fig. 3A). Fig. 3B shows the results of an rmANOVA in cLI scores obtained from the average of the time-frequency window of interest. The results revealed a significant interaction between group and ear ($p < 0.01$) and a significant main effect of group ($p < 0.05$). A post-hoc analysis revealed no significant difference in cLI scores between left and right ear stimulation in HCs, suggesting symmetrical contralaterality. In addition, the results revealed a significant difference in right mTLE patients compared with the other groups in response to left ear stimulation (HCs $p < 0.05$, left mTLE $p < 0.01$), and in left mTLE patients compared with the other groups in response to right ear stimulation (HCs $p < 0.01$, right mTLE $p < 0.05$). These findings suggested the presence of CAP asymmetry in mTLE patients corresponding to the epileptic focus.

3.3. Temporal profiles of power data

Overall, the power data (Figs. 4 and 5) were relatively similar to the PLF results (Figs. 2 and 3). However, the power data revealed less prominent temporal frequency dynamics of contralaterality and less apparent group differences compared with the PLF data. The main effect of contralaterality was observed in rmANOVA with a non-parametric cluster permutation. Only one cluster in which

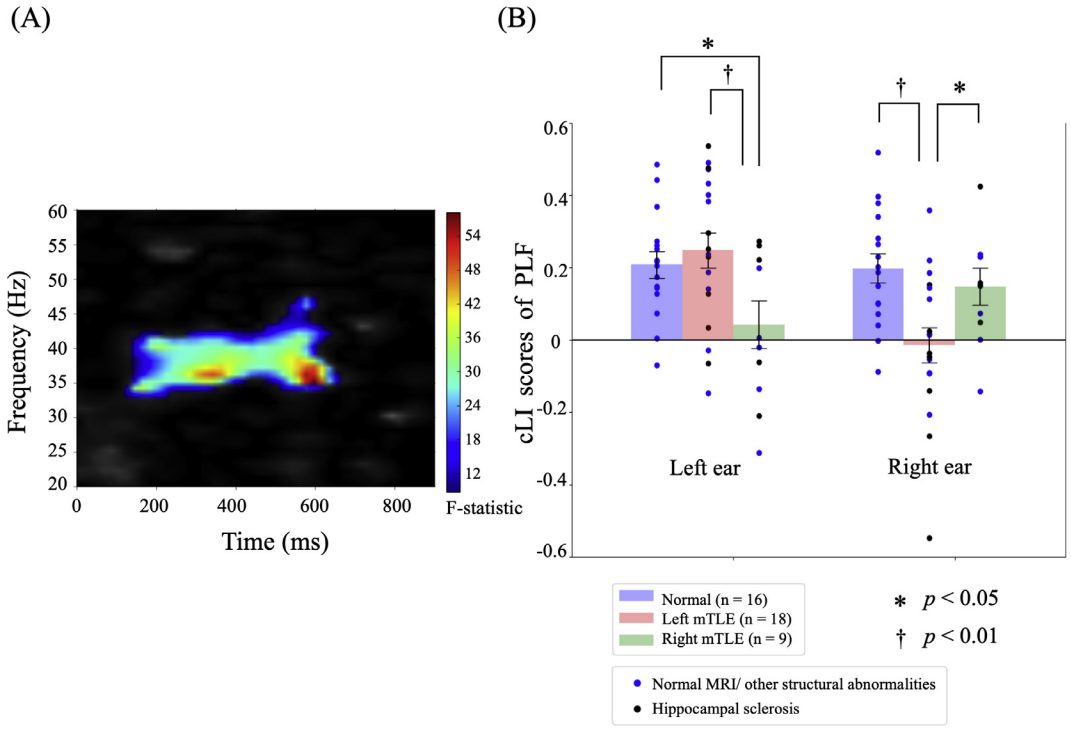

Fig. 3. (A) The results of non-parametric clustering analysis in HCs for PLF data. Regarding contralaterality, one cluster in which contralateral AC exhibited significantly higher PLFs than ipsilateral AC was found at around 40 Hz between 120–680 ms. No significant effect of ear was observed. (B) Repeated-measures ANOVA results for cLI scores of PLFs as the averages of the time-frequency window obtained from A. HCs exhibited symmetrical contralaterality, but mTLE patients exhibited a disappearance of contralaterality. Data for individual subjects are superimposed on each group. Blue circles indicate the subjects with normal MRI or with other structural abnormalities other than hippocampal sclerosis (HS), while black circles indicate the subjects with positive HS. The results revealed no major differences between them. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

contralateral AC showed significantly higher power than ipsilateral AC was obtained at around 40 Hz (31–40 Hz) in the 120–620 ms period (Fig. 5A). Fig. 5B shows rmANOVA results obtained from the average of the time-frequency window of interest. There was a significant interaction between group and ear ($p < 0.05$), and significant main effects of group ($p < 0.01$) and ear ($p < 0.05$). A post-hoc analysis revealed that HCs exhibited no differences in cLI scores between left and right ear stimulation, again suggesting symmetrical contralaterality. There was a significant difference in right mTLE patients compared with other groups in response to left ear stimulation (HCs $p < 0.01$, left mTLE $p < 0.05$), and in left mTLE patients compared with HCs ($p < 0.01$), but not compared with right mTLE patients ($p = 0.33$) in response to right ear stimulation. These findings also supported the presence of CAP asymmetry in mTLE patients, as observed in PLFs, which corresponded to the epileptic focus.

4. Discussion

To the best of our knowledge, this is the first study using 40-Hz ASSR to explore the relationship between CAP dysfunction and the epileptic focus in unilateral mTLE patients. Monaural ASSR recorded with MEG demonstrated clear temporal frequency dynamics with symmetrical cLI scores in HCs. In accord with our working hypothesis, we successfully demonstrated that monaural auditory stimulation identified the epileptic focus when the disappearance of contralaterality was used; left ear stimulation classified right mTLE patients, while right ear presentation distinguished left mTLE patients. Therefore, the current results indicated that CAP dysfunction was significantly correlated with the pathophysiology of mTLE.

4.1. Monaural ASSR for lateralization of epileptic focus

In most psychiatric diseases, binaural presentation has been adopted with 40-Hz ASSR. Thus, precise CAP asymmetry has not yet been established because binaural presentation elicits a binaural interaction in the brainstem as well as the cortex (Chaieb et al., 2015). In contrast, monaural presentation is thought to segregate the function of each hemisphere in HCs, which can be used to detect lesion-related dysfunction. In the current study, two major findings were obtained regarding CAP asymmetry: (1) monaural ASSR was processed symmetrically in a specific time-frequency window in HCs, and (2) the lack of contralaterality clearly revealed the epileptic focus in mTLE patients.

In HCs, cLI scores revealed symmetrical contralaterality (Figs. 3B and 5B) without a significant effect of ear (Figs. 3A and 5A). This finding indicates that monaural ASSR was processed symmetrically via lateralized auditory hemispheric function, largely depending on the side of ear stimulation (i.e., symmetrical CAP), in a specific time-frequency window. This finding is in accord with the general anatomical principle that the auditory pathway exhibits contralateral predominance (Eggermont, 2001; Langers et al., 2005). Thus, monaural ASSR can be used to precisely evaluate contralateral hemispheric function. In contrast, unilateral mTLE patients revealed a lack of contralaterality corresponding to disturbance of the affected side (Figs. 3B and 5B). The lack of contralaterality reflects the relative reduction of ASSR in the affected side of the AC. Reduced cLI scores of PLF/power in mTLE patients may result from greater inter-trial timing variability in the auditory response, or decreased neuronal oscillatory synchronization. The current results strongly suggest that abnormal functioning of unilateral HS influences CAP more severely in the affected side of the AC compared with the non-affected side.

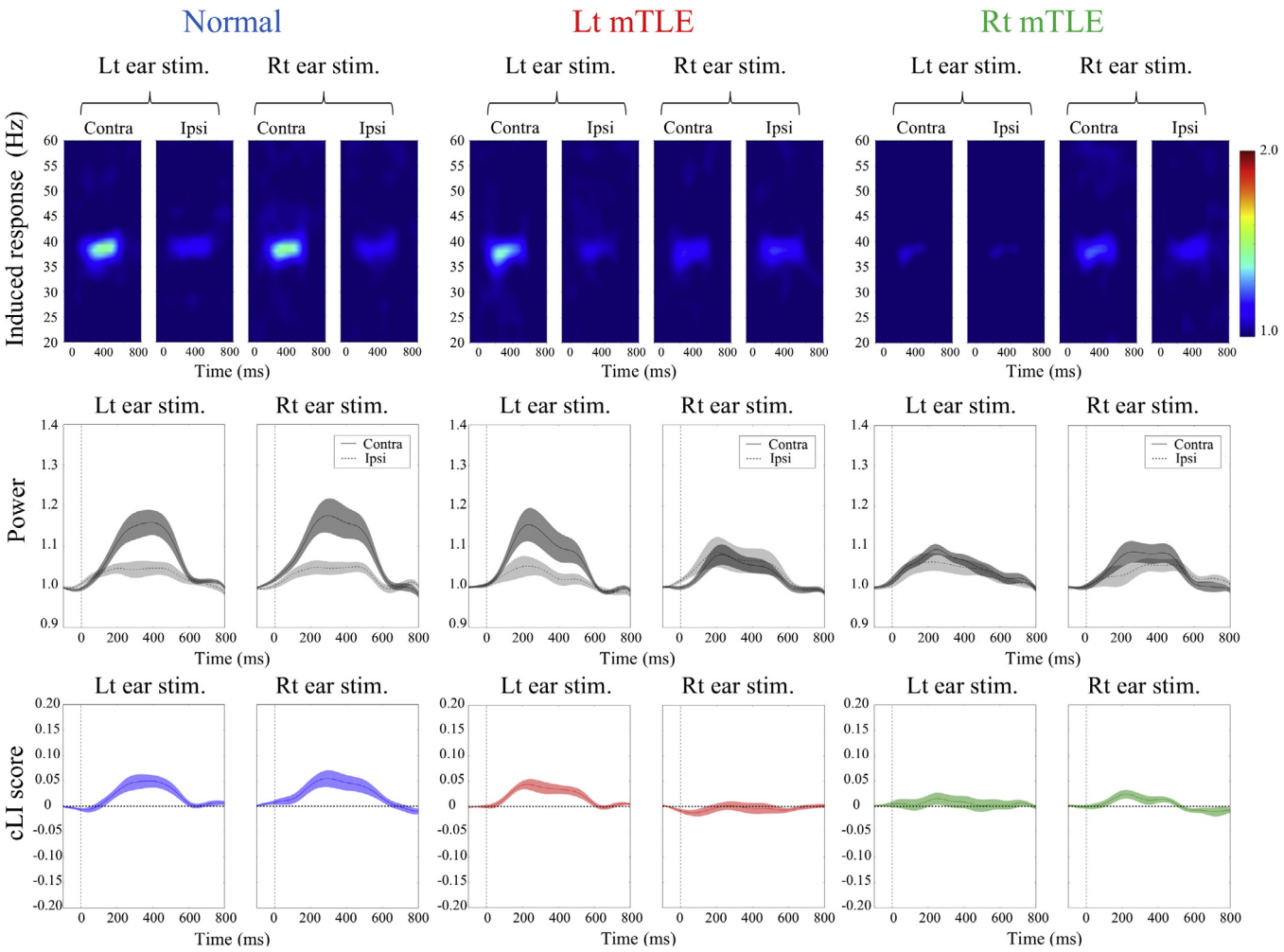

Fig. 4. Induced gamma responses of the power values in HCs, left mTLE and right mTLE patients, obtained from contralateral and ipsilateral ACs. Time-frequency plots are shown in three groups as grand-averaged data (upper row). 40-Hz ASSR elicited temporal frequency dynamics at approximately 40 Hz in bilateral ACs, irrespective of ear stimulation during sound presentation. The results revealed more prominent responses in the contralateral AC compared with the ipsilateral AC. Time courses for the average of 35–45 Hz oscillations are shown for each group by each ear stimulation condition (middle row). More prominent responses in the contralateral AC were evident in HCs, while mTLE patients exhibited less marked contralaterality. Black lines represent the activity of contralateral AC, while gray lines represent the activity of ipsilateral AC. cLI scores are shown in each group (lower row). Although HCs (blue lines) exhibited symmetrical contralaterality for all time courses, left mTLE patients (red lines) exhibited decreased contralaterality in right ear stimulation. Similarly, right mTLE patients (green lines) exhibited reduced contralaterality in response to stimulation of both ears. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the current study, we focused on contralaterality using cLI scores of PLF/power but not PLF/power in each AC because of the inter-subjective variability of ASSR (Baltus and Herrmann, 2016). In neuropsychiatric patients, several factors affect ASSR, including attentional deficits during recording, and administration of anti-epileptic drugs. These factors can result in a decrement of PLF/power in each AC (i.e., low SNR). In contrast, the cLI can be used to evaluate normalized values with the sum of bilateral ACs. Thus, the current study design avoids several complexities in the group analysis. Overall, the current results indicated that ASSR is clinically useful for evaluating the localization of epileptic focus for mTLE patients.

4.2. Gamma-band oscillations in epilepsy

In general, electrical activity in epileptic networks is associated with a disturbed balance of neural excitation and inhibition (E/I), which is mainly produced by the activity of GABA interneurons (Bonansco and Fuenzalida, 2016; Yizhar et al., 2011). GABA interneurons containing parvalbumin are thought to play an important role in the generation of synchronized excitatory pyramidal neurons at gamma frequencies. The 40-Hz ASSR protocol, therefore, is an appropriate method for gauging the functional integrity of the associated neuronal networks' ability to create and maintain gamma-band activity. Appropriate gamma oscillation is known to require precise control of the E/I balance (Sohal et al., 2009; Takei et al., 2016). Thus, disruption of the E/I balance causes a range of neuropsychiatric disease-related symptoms and various neurocognitive dysfunctions in several neuropsychiatric diseases (Gandal et al., 2012; Huang et al., 2014; Oda et al., 2012; Rojas and Wilson, 2014; Wilson et al., 2012; Yizhar et al., 2011). In these neuropsychiatric diseases, deficits in 40-Hz ASSR have been consistently reported (Hamm et al., 2011; Krishnan et al., 2009; Spencer et al., 2004). Therefore, reduced ASSR can be largely explained by structural and functional abnormalities in the GABA neurotransmitter system. Indeed, GABAergic interneurons are reported to be decreased in prefrontal, anterior cingulate, visual and motor cortices in patients with schizophrenia (Hamm et al., 2011).

To date, no human studies have investigated GABA abnormalities for epilepsy patients using 40-Hz ASSR. Although the precise mechanisms of ASSR abnormalities in epilepsy patients remain

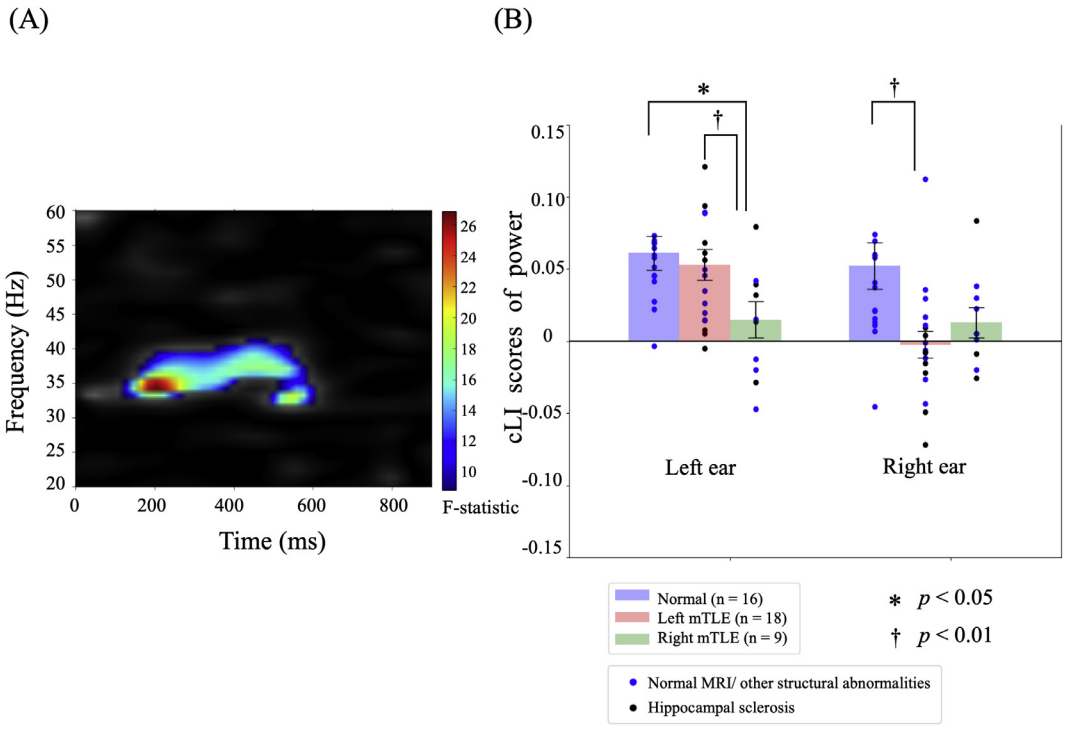

Fig. 5. (A) The results of non-parametric clustering analysis in HCs for power data. Regarding the effect of contralaterality, one cluster in which contralateral AC exhibited significantly greater power than ipsilateral AC was found at around 40 Hz during 120–620 ms. No significant effect of ear was observed. (B) Repeated-measures ANOVA results for cLI scores of power as the averages of time-frequency window obtained from A. The apparent group difference was less marked compared with PLFs (see Fig. 3B). As shown in Fig. 3B, the individual data are superimposed on each group.

unclear, there are several potential explanations that should be considered. In mTLE patients, a reduction in the number of hippocampal GABA interneurons has been reported in the dentate gyrus (Magloczky and Freund, 1993), although preservation or an increase in the number of hippocampal GABA interneurons has been observed in some mTLE patients (Tóth et al., 2010). Flumazenil-positron emission topography, a marker of GABA-benzodiazepine binding, was decreased from the ipsilateral HS to the extratemporal lobe (Hammers et al., 2001). In animal models of epilepsy, Pinto et al. (2017) applied ASSR to Wistar audiogenic seizure model rats to investigate the temporal dynamics of ASSR during the peri-ictal period, reporting decreased PLF/power in the pre-ictal state and increased synchronization during seizure progression. These findings suggested that compromised GABA inhibitory modulation in the rat model resulted in decreased neural synchronization in the pre-ictal state. Accordingly, it is plausible that ASSR could reveal state-dependent GABA abnormalities in mTLE patients. Therefore, we speculated that reduced ASSR in mTLE patients reflects alterations in GABA interneuron function, although the mechanisms of ASSR abnormalities in schizophrenia and mTLE patients may be different. In the current study, the results revealed that left and right HS have distinct neural circuits for processing monaural auditory stimulation. Taken together, these findings indicate that monaural ASSR may enable new insights into the pathophysiology underlying mTLE.

4.3. Relationship between CAP dysfunction and mTLE

We first applied monaural 40-Hz ASSR with MEG in unilateral mTLE patients to elucidate the relationship between CAP dysfunction and epileptic focus. There is substantial evidence that HS causes CAP dysfunction in mTLE patients, both from behavioral studies (Aravindkumar et al., 2012; Boatman et al., 2006; Collard et al., 1986; Ehrle et al., 2001; Han et al., 2011; Lavasani et al., 2016; Olsen, 1983; Ortiz et al., 2002) and EEG assessment using the N100 (Bougeard and Fischer, 2002; Rosburg et al., 2008), P300 (Meador et al., 1992; Trinka et al., 2001) and mismatch negativity (Hirose et al., 2014; Zhao et al., 2017). However, most previous EEG studies have failed to demonstrate the clinical significance of lateralization of epileptic focus. This finding is likely to be due to the binaural presentation of auditory stimuli in previous studies. Interestingly, a recent study in our laboratory provided neuromagnetic evidence for hippocampal modulation of the auditory cortex by recording the M100 (the magnetic counterpart of the N100) using monaural pure tone burst stimulation (Chatani et al., 2016; Matsubara et al., 2018), which successfully revealed impaired AC function on the side of the affected HS. In the present study, we adopted time-frequency analysis of induced ASSR (Fig. 1B), which allowed us to precisely evaluate the auditory integration process (Ross et al., 2002; Ross and Pantev, 2004; as discussed below). Therefore, we were able to demonstrate apparent CAP dysfunction caused by the dysfunction of medial temporal structures of the affected side in mTLE.

It is currently unclear why mTLE patients exhibit CAP dysfunction. mTLE patients do not typically exhibit auditory manifestations during seizure propagation, except when seizures originate in lateral AC (i.e., lateral TLE). However, in a study of cortico-cortical evoked responses (Enatsu et al., 2015), electrical stimulation of anterior hippocampus elicited prominent cortical evoked responses in medial and lateral temporal structures, but not contralateral responses. This finding implies that the hippocampus has a strong physiological connection with unilateral AC. The current finding of reduced ASSR may indicate disruption of the ipsilateral connection between HS and AC. Thus, monaural auditory stimuli can be used to distinctly evaluate CAP dysfunction in mTLE patients, enabling the localization of epileptic focus.

4.4. Factors that affect CAP asymmetry of monaural ASSR

The results of previous studies on hemispheric asymmetry of monaural ASSR are inconclusive (Kawase et al., 2012; Poelmans et al., 2012; Ross et al., 2005; Yamasaki et al., 2005). A series of studies by Ross and colleagues (2002, 2004 and 2005) reported right hemispheric predominance in monaural ASSR, signifying pitch processing in the right hemisphere. Several differences between our study and these previous studies should be noted. First, we analyzed the induced responses (e.g., PLF or induced power) from single trial records. In contrast, most previous reports, including those by Ross and colleagues, examined evoked responses of ASSRs for averaged waveforms. The current method extracted both phase- and nonphase-locked responses (Makeig et al., 2002). Thus, the current approach may have provided more precise evaluation of higher cognitive function. In accord with this notion, previous studies using evoked and induced responses have produced conflicting results regarding hemispheric laterality (Tang et al., 2016, Matsubara et al., 2018). Second, most previous ASSR studies used amplitude-modulated (AM) tones rather than clicks. AM tones take the form of a sine wave with less power in harmonics, whereas click stimuli have a more complex spectral response with multiple harmonics (Krishnan et al., 2009). Thus, the difference in stimulus nature may strongly affect CAP asymmetry. Third, the time-frequency window of interest affects CAP symmetry. In most previous studies of ASSR, the optimal time-frequency window was determined in a relatively subjective manner (e.g., Ross et al., 2005, 40-Hz activity between 250 ms and sound offset) focusing on strong responses in each hemisphere. However, we assumed that inter-subjective variability should be taken into account when determining the time-frequency windows in the current study. The non-parametric cluster permutation method used in the current study enabled us to assess the inter-subjective variability of ASSR perception in a data-driven manner. Specifically, a time-frequency window with relatively strong contralaterality was selected within the group in the current study, irrespective of ear stimulation (Figs. 3A and 5A), rather than selecting the strong PLF/power value itself. In any case, discrepancies between studies regarding CAP asymmetry should be further evaluated in future studies.

We observed differences between the results using PLF and power data. Although these data sources conveyed similar information regarding CAP asymmetry, PLFs were more sensitive in terms of group differences (Figs. 3B and 5B). The reason for the greater sensitivity of PLFs is currently unclear. However, many studies of patients with schizophrenia have reported discrepant results between PLFs and power (Krishnan et al., 2009; Sivarao, 2015). Thus, PLFs may provide a more accurate representation of CAP symmetry in HCs and also reflect CAP asymmetry in mTLE patients, compared with power data. This suggestion is in accord with Tan et al.'s (2015) finding that PLFs were more reliable than power with regard to test-retest reliability. Overall, PLFs and power of ASSR may partially reflect different phenomena of auditory temporal integration.

4.5. Future perspectives

In the current study, we used monaural 40-Hz ASSR to detect the lateralization of epileptic focus in mTLE patients. Our study included several patients with normal MRI findings (i.e., without HS) or equivocal findings (i.e., slight atrophy of hippocampus, hippocampal malrotation). Since MRI abnormalities have a greater impact on localization of epileptic focus, patients with no MRI abnormalities are typically challenging to diagnose, despite their potentially good prognosis in terms of post-operative seizure freedom (Muhlhofer et al., 2017). mTLE patients exhibiting only impaired awareness during seizure, with no apparent signs of lateralization, are unlikely to benefit from surgery, because of the lack of precise diagnosis regarding lateralization. Therefore, the currently proposed technique may be useful for such patients, who cannot be assessed using routine presurgical evaluation methods.

4.6. Study limitations

The current study involved several limitations that should be considered. First, the effects of anti-epileptic drugs could not be entirely excluded. Second, the sample contained patients with heterogeneous pathological backgrounds, and, because several patients received no surgical intervention, the precise pathology was not confirmed. These factors may have affected hemispheric laterality (i.e., CAP asymmetry). Third, a direct comparison between normal MRI and HS patients could not be achieved because of the small sample size. Fourth, the specificity of CAP dysfunction in mTLE patients may not be warranted. Although various studies have demonstrated CAP dysfunction in mTLE patients, most research (Aravindkumar et al., 2012; Boatman et al., 2006; Chatani et al., 2016; Collard et al., 1986; Ehrle et al., 2001; Han et al., 2011; Lavasani et al., 2016; Olsen, 1983; Ortiz et al., 2002), including the current study, did not compare mTLE groups with other epileptic syndromes (neocortical or generalized epilepsy). Thus, the clinical usefulness of monaural ASSR for the evaluation of epileptic focus may currently be limited to mTLE patients.

5. Conclusions

In the current study, monaural 40-Hz ASSR for mTLE patients exhibited abnormal contralaterality that accurately discriminated the lateralization of the epileptic focus. These results link neuromagnetic assessment and differences in clinical findings of cognitive processing (i.e., CAP) between HCs and mTLE patients, and also between left mTLE patients and right mTLE patients. Overall, our results indicate that CAP dysfunction can be used to reveal the pathophysiology of mTLE.

Conflict of interest statement

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

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