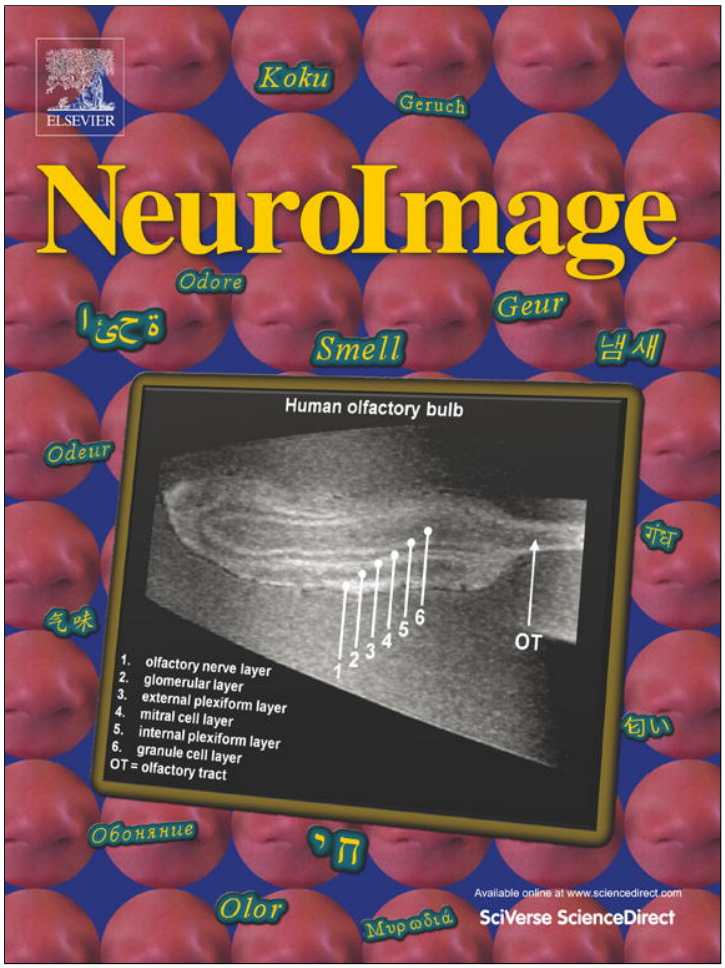

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NeuroImage 64 (2013) 356–364

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Neuromagnetic index of hemispheric asymmetry predicting long-term outcome in sudden hearing loss

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ARTICLE INFO

Article history:
Accepted 1 September 2012
Available online 8 September 2012

Keywords:
Hearing
Magnetoencephalography (MEG)
Neuroplasticity
Reorganization
Hemispheric asymmetry
Prognosis

ABSTRACT

The neuromagnetic index of hemispheric asymmetry in terms of ipsilateral/contralateral ratio at acute stage was previously revealed to prognosticate the 1-month hearing outcome of acute unilateral idiopathic sudden sensorineural hearing loss (ISSNHL), showing a dynamic relationship between top- and down-levels of auditory pathway. However, the prognostic effect of reorganization pattern for the long-term results remained elusive. This study aimed to probe the prognosticating relevance of hemispheric asymmetry to the hearing at chronic stage of ISSNHL. Using magnetoencephalography (MEG), inter-hemispheric differences in peak dipole of N100m responses to monaural tones were evaluated in 21 controls and 21 ISSNHL patients at initial and final (12 months later) stages. Predictive value of hemispheric asymmetry was assessed by correlating hearing level and ipsilateral/contralateral ratio (I/C) of N100m latency and amplitude. Healthy-side dominance of N100m was observed in ISSNHL initially, and remained in three final prognostic subgroups (complete, partial, and no recovery) of ISSNHL. The initial $I/C_{amplitude}$ on affected-ear stimulation strongly correlated with the hearing level of final stage in ISSNHL. However, there was no prognostic effect of hemispheric asymmetry pattern for the 12-month hearing improvement. The heterogeneity between neuromagnetic index and hearing levels possibly echoed different pathogeneses of ISSNHL. Since a restored hearing status did not necessarily lead toward a normal functional organization, the dynamics of hemispheric asymmetry could actually index a central resilient reorganization in the brain for sound processing in ISSNHL. Our finding showed not only a clinically relevant measure to predict final hearing of ISSNHL, but also a linkage between central plasticity and cochlear lesion. This finding suggests a new perspective, and perhaps new interventions, to diagnose and treat unilateral ISSNHL.

Introduction

Peripheral lesions such as wounds caused by amputation could initiate plastic changes in somatosensory cortices of human beings (Birbaumer et al., 1997). The scale of phantom limb pain positively correlated with the degree of cortical reorganization (Flor et al., 1995). The pattern of cortical reorganization was furthermore found to be alternating with elimination/re-emergence of pain sensation subsequent to treatment, e.g. peripheral anesthesia by brachial plexus blockade, as detected by functional brain imaging techniques (Birbaumer et al., 1997). Since deprivations of auditory input as a result of cochlear lesions could also lead to remodeling of structures and/or functions in auditory cortices of animals (Illing and Reisch, 2006), it is reasonable to infer that the remodeling pattern would be dynamic with fluctuation of hearing after treatment. The auditory evoked response pattern of hemispheric asymmetry in the acute stage of hearing loss has been shown, e.g., to be evolving in the later course of disease in previous functional magnetic resonance imaging (fMRI) and magnetoencephalographic (MEG) studies (Morita et al., 2007; Suzuki et al., 2002). One previous electroencephalographic (EEG) study also revealed that the hemispheric asymmetry of auditory evoked potentials (AEPs) in profound hearing loss of various etiologies was significantly different from that of normal-hearing subjects

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http://dx.doi.org/10.1016/j.neuroimage.2012.09.002

(Ponton et al., 2001). However, the interplay between central plastic changes and hearing status along the disease course of a peripheral hearing impairment in human beings remains unexplored. The reason might be due to the lack of a proper disease model, because most types of hearing impairment are irreversible.

Idiopathic sudden sensorineural hearing loss (ISSNHL), one of the few inner ear hearing disorders for which recovery can be observed, is supposed to be a disease model suitable for the research of the contingency between hearing and auditory neuroplasticity in the brain. ISSNHL, a disease of unknown pathogenesis, is widely varied in the presenting signs and prognosis. Incidence increases from 4.6/100,000 per year in the 2nd decade to 47.2/100,000 in the 7th decade (Byl, 1984). Though it is possible that the neural deficit(s) lie at a higher level of the auditory pathway, the cochlea has generally been considered the most probable lesion site of ISSNHL. Either spontaneously or after appropriate interventions, about half of affected persons achieve partial or complete recovery of hearing (Byl, 1984).

We have previously verified by means of MEG that unilateral ISSNHL in the acute stage can induce functional reorganization in the context of altered hemispheric asymmetry for sound presentations in the central auditory pathway on either affected- or healthy-ear stimulation (Li et al., 2006; Po-Hung Li et al., 2003). Contrary to the pattern of "contralateral dominance" in normal-hearing subjects, a pattern of "healthy-side dominance" of N100m to tone burst stimulation was observed in patients. This asymmetry was evidenced by bigger dipole moments to monaural acoustic stimuli over hemisphere ipsilateral to healthy ear irrespective of either healthy- or affected-ear stimulation, which might be caused by disinhibition due to deafferentiation (Hsieh et al., 2002) or hyperacusis. The asymmetry in terms of ipsilateral/contralateral ratio (I/C) at acute stage was furthermore noted to be a prognosticating factor for the outcome of ISSNHL at a defined time of short-term follow-up (i.e. 1 month after the treatment) (Li et al., 2012). The aforementioned study showed not only a clinically relevant measure to predict recovery of sudden hearing loss, but also a linkage between central plasticity and cochlear lesion. However, the possible prognostication effect of the reorganization patterns for the chronic stage remained unknown.

By using MEG, auditory evoked fields (AEFs) were assessed by measuring N100m in ISSNHL (initial visit and 12 months later, respectively) and in normal-hearing subjects (once only during the study) in this study. Ipsilateral/contralateral ratio of peak dipole moment for N100m responses (Ponton et al., 2001) was applied to evaluate the extent of hemispheric asymmetry throughout follow-ups. We aimed to probe the prognostic relevance of the hemispheric asymmetry for the degree of hearing loss in the chronic stage of ISSNHL.

Materials and methods

Subjects (Table 1)

Twenty-one right-handed, previously untreated adult patients with acute unilateral left (n = 9) or right (n = 12) ISSNHL (9 males; 21–72 years of age, mean = 47) were studied. Initial MEG responses of twenty patients had been reported in our preliminary one-time point (Li et al., 2006; Po-Hung Li et al., 2003) and/or short-term (1 month) follow-up (Li et al., 2012) studies. Diagnosis criteria was a sensorineural hearing loss with a threshold of no less than 30 dB HL over three contiguous frequencies within 3 days or less (Wilson et al., 1980). No other neurological deficits or traumatic history were identified. All patients received treatments consisting of parenteral steroids and common oral rheological drugs for 5 days during the admission. Outpatient therapy with oral rheological drugs ceased by 1 month for patients with partial and no recovery at discharge. Elapsed time for the initial MEG and pure tone audiometry (PTA) exam after disease onset ranged from 4 days to 3 weeks (Murai et al., 1994). MEG and PTA exam were then repeated at about 12 months after initial exam (i.e. final stage). The average threshold of 500 Hz, 1000 Hz, and 2000 Hz (i.e. pure tone average) according to final audiograms was exploited to split patients into three prognostic subgroups: complete recovery, partial recovery, and no recovery. Hearing improvement was conventionally defined as: (1) a threshold of ≦25 dB HL in the affected ear (complete recovery), or (2) a threshold of >25 dB HL with a gain of >10 dB HL in the affected ear (partial recovery) (Mamak et al., 2005; Ochi et al., 2003).

Twenty-one right-handed healthy volunteers with normal hearing (9 males; 25–66 years of age, mean = 37) served as control. All controls were involved in our previously published studies (Li et al., 2006; Li et al., 2012; Po-Hung Li et al., 2003). The study was in compliance with national legislation and Declaration of Helsinki. Written informed consent was obtained from each participant with a protocol approved by the Institutional Ethics and Research Committee of Taipei Veterans General Hospital and Cheng Hsin General Hospital.

Audiometric and electrophysiological exam

All participants underwent PTA exam to determine both air and bone conduction threshold, using test frequencies between 250 Hz to 8000 Hz. Controls had normal PTA results (threshold ≦25 dB HL for all frequencies). A unilateral sensorineural hearing loss was confirmed in all ISSNHL patients, characterized as the cochlea being the lesion site based on results of reduced distortion-product otoacoustic emissions (DPOAEs) and within-normal-limit interaural latency differences for auditory brainstem responses (ABRs) (Gstoettner et al., 1992). Since for all patients, air and bone conduction thresholds were less than 65 dB HL at 1000 Hz (Fig. 1, Table 1), the probing auditory stimulus was set at this frequency with an intensity of 75 dB SPL for the MEG exam. This moderate intensity was chosen to avoid further acoustic damage and cross-hearing contamination.

MEG paradigm

MEG measurements were done in a magnetically shielded room using a whole-head 306-channel neuromagnetometer (Vectorview™ 4-D Neuroimaging, Helsinki, Finland). Subjects sat upright with eyes open during measurements. Tone bursts (1000 Hz, 50 ms duration with 10 ms for ramp up and down, respectively, 75 dB SPL at the exit end of the plastic tube, with an interstimulus interval of 4 s) were delivered monaurally via molded earpieces using the SoundProbe™ program on a Macintosh computer. The contralateral (i.e. non-stimulated) ear was plugged by using a molded earpiece to minimize the ear-to-ear crosstalk. Affected and healthy ears were monaurally stimulated in separate sessions separated by 2 min of rest. Trials with electro-oculographic amplitudes exceeding 150 μV were rejected. MEG signals were sampled at 400 Hz and band-pass filtered at 0.03 to 100 Hz. About 90 artifact-free trials were averaged. Digital low-pass filtering at 30 Hz and high-pass filtering at 1 Hz was performed off-line. An equivalent current dipole (ECD) model consisting of bilateral sources was used to explain the MEG signals (Hari and Makela, 1988). First, an initial guess of an independent source was done in both hemispheres respectively. Each ECD was applied to a subset of 40–60 sensors around the maximum peak in one hemisphere with a goodness-of-fit (g) larger than 90% for acceptance. The planar gradiometer can detect the maximal responses, reduce the external magnetic disturbances, and provide accurate dipolar field patterns when the activated generators are tangential to the skull (Hamalainen, 1993). It thus would be ideal in picking up auditory cortical activity (Li et al., 2006, 2012; Po-Hung Li et al., 2003), of which the source is relatively superficial as compared to other regions. Using gradiometers, even deeper response (e.g. from fusiform face area) can be detected. Since the magnetometer is sensitive to and hence easier to be contaminated by background noise, the signal collected sometimes fluctuated even after averaging in our experience. Therefore, no magnetometers were included for the analysis. Since the

Table 1
General data for all participants.

No.	Control		ISSNHL patient										Improvement
	Gender	Age (yr)	Gender	Age (yr)	Du (d)	Lesion	Th (dB)		De (dB)				
							Initial		Initial		12 m		
							Avg	1 k	Avg	1 k	Avg	1 k	
1	M*	35	M*	35	17	Rt	12	15	53	50	18	20	c
2	F*	26	F*	31	5	Rt	5	5	57	60	38	35	p
3	M*	25	M*	70	21	Lt	20	20	60	65	33	40	p
4	F*	28	M*	72	17	Lt	5	5	42	40	45	45	n
5	M*	29	M*	43	7	Lt	15	10	65	65	10	10	c
6	M*	34	M*	34	8	Rt	15	20	50	60	35	55	p
7	F*	40	M*	49	8	Rt	18	20	63	65	63	65	n
8	F*	42	F*	56	4	Rt	10	10	47	40	55	50	n
9	F*	46	F*	55	21	Rt	15	20	40	40	40	35	n
10	M*	36	F*	50	10	Rt	10	20	63	60	38	30	p
11	M*	26	F*	45	4	Rt	18	20	65	65	65	55	n
12	M*	66	F*	35	17	Rt	10	15	50	55	58	65	n
13	F*	26	F*	53	7	Lt	20	15	63	55	58	60	n
14	M*	36	F*	51	10	Lt	8	10	45	50	53	55	n
15	F*	26	M*	21	9	Lt	20	20	62	60	50	50	p
16	F*	27	F*	29	9	Lt	12	15	52	55	50	50	n
17	M*	36	F*	53	6	Lt	15	15	65	65	55	60	n
18	F*	62	F	60	16	Rt	15	10	45	45	28	25	p
19	F*	54	F*	27	21	Rt	10	5	33	35	28	30	n
20	F*	38	M*	41	10	Lt	17	15	40	40	23	25	c
21	F*	34	M*	70	20	Rt	18	20	52	60	28	30	p

No., participant number; Age, y/o; Du, time elapsed since onset of hearing loss to initial MEG exam (days); Lesion, ear of hearing loss; Lt, left ear; Rt, right ear; Th, initial hearing threshold of the healthy ear (dB HL); De, degree of hearing loss of the affected ear (dB HL); Avg, average hearing threshold of 500 Hz, 1000 Hz, and 2000 Hz; 1 k, hearing threshold at 1000 Hz; Improvement, hearing improvement defined as: (1) a threshold of ≦25 dB HL in the affected ear (complete recovery, c), or (2) a threshold of >25 dB HL with a gain of >10 dB HL in the affected ear (partial recovery, p); n, no recovery; Initial, initial PTA exam; 12 m, 12 months after initial exam (final stage); *participants who were involved in our previous studies (see Materials and methods).

accuracy of dipole localization depends on the signal-to-noise ratio (Jacobson, 1994), we included a sensor only when the peak amplitude of the signal was stronger than 2 standard deviations above the baseline. After the ECD with the highest g value was identified, all channels were taken into account for further analysis so that it explained best the recorded magnetic field globally (Hari and Makela, 1988). Peak latency was then extracted for these ECDs. T1-weighted MR images of subject brains were acquired using a 3.0 T Bruker MedSpec S300 system (Bruker, Kalsrube, Germany) for MEG-MRI co-registration. No obvious abnormality (e.g., vascular lesion, tumor growth, etc.) was found in those brain MRI-exams.

Data analysis

The epoch analyzed ranged from 50 ms before to 350 ms after stimulation onset. The prestimulus interval was used as baseline. The time window for N100m was 70–160 ms (Kanno et al., 2000; Woldorff et al., 1999). The inter-hemispheric differences of peak dipole strength and latency of N100m, observed in different hemispheres of controls and patients respectively, were evaluated using Wilcoxon's signed rank test. Two kinds of ipsilateral/contralateral ratio (I/C) were used to assess the degree of hemispheric asymmetry: (1) I/C made by reactivity of different hemispheres to monaural stimulation (I/C_a and I/C_l for N100m dipole moment amplitude and latency, respectively), i.e., ratio of N100m in ipsilateral to that in contralateral hemisphere on unilateral-ear stimulation, and (2) I/C made by reactivity of the *same* hemisphere to stimulus in two ears (I/C_{as} and I/C_{ls} for N100m dipole moment amplitude and latency, respectively), i.e., ratio of N100m in one hemisphere on ipsilateral-ear stimulation to that in the same hemisphere on contralateral-ear stimulation. The prognostic relevance of the hemispheric asymmetry as expressed in the relationship between I/C and hearing level/hearing gain in ISSNHL was evaluated using Spearman's rank correlation. Differences of I/C among prognostic subgroups (i.e., complete, partial, and no recovery) were evaluated using Kruskal–Wallis test. Statistical significance was thresholded at $p<0.05$.

Results

In all subjects, N100m dipole was identifiable over each hemisphere and was localized bilaterally on the superior temporal planum with an orientation centrifugal to the auditory cortex (Fig. 1, Table 2).

Predictive significance of ipsilateral/contralateral ratio

At the final stage, nearly half of patients achieved hearing improvement (Table 1). When ipsilateral/contralateral ratios were correlated to hearing levels, no significant correlation was revealed except for that between the initial I/C_a (i.e., the first way of calculating the ipsilateral/contralateral ratio; see Data analysis) on affected-ear stimulation and the final hearing level ($r=0.48$, $p=0.03$; Fig. 2) in ISSNHL. Averaged audiograms at the first and last measurement in ISSNHL with a depiction of the averaged audiogram in controls as a reference revealed a flat-to-descending type of hearing loss in our patients (Mamak et al., 2005) (Fig. 3). There was no correlation between hearing gain and both kinds of I/C at various stages (Fig. 2). Within-group differences in both kinds of I/C among prognostic subgroups (i.e., complete, partial, and no recovery) evaluated using Kruskal–Wallis test revealed no statistical significance (Table 3). In the initial recordings, both I/C_a and I/C_{as} were noted to be larger than 1.0 (i.e. ipsilateral dominance) on healthy-ear stimulation, in which I/C_{as} was clearly smaller. In the 12-month recordings, I/C_a was still larger than 1.0 (i.e. ipsilateral dominance) on healthy-ear stimulation, whereas I/C_{as} was revealed to be slightly smaller than 1.0 (0.99, i.e. mild degree of contralateral dominance) on healthy-ear stimulation (Table 3).

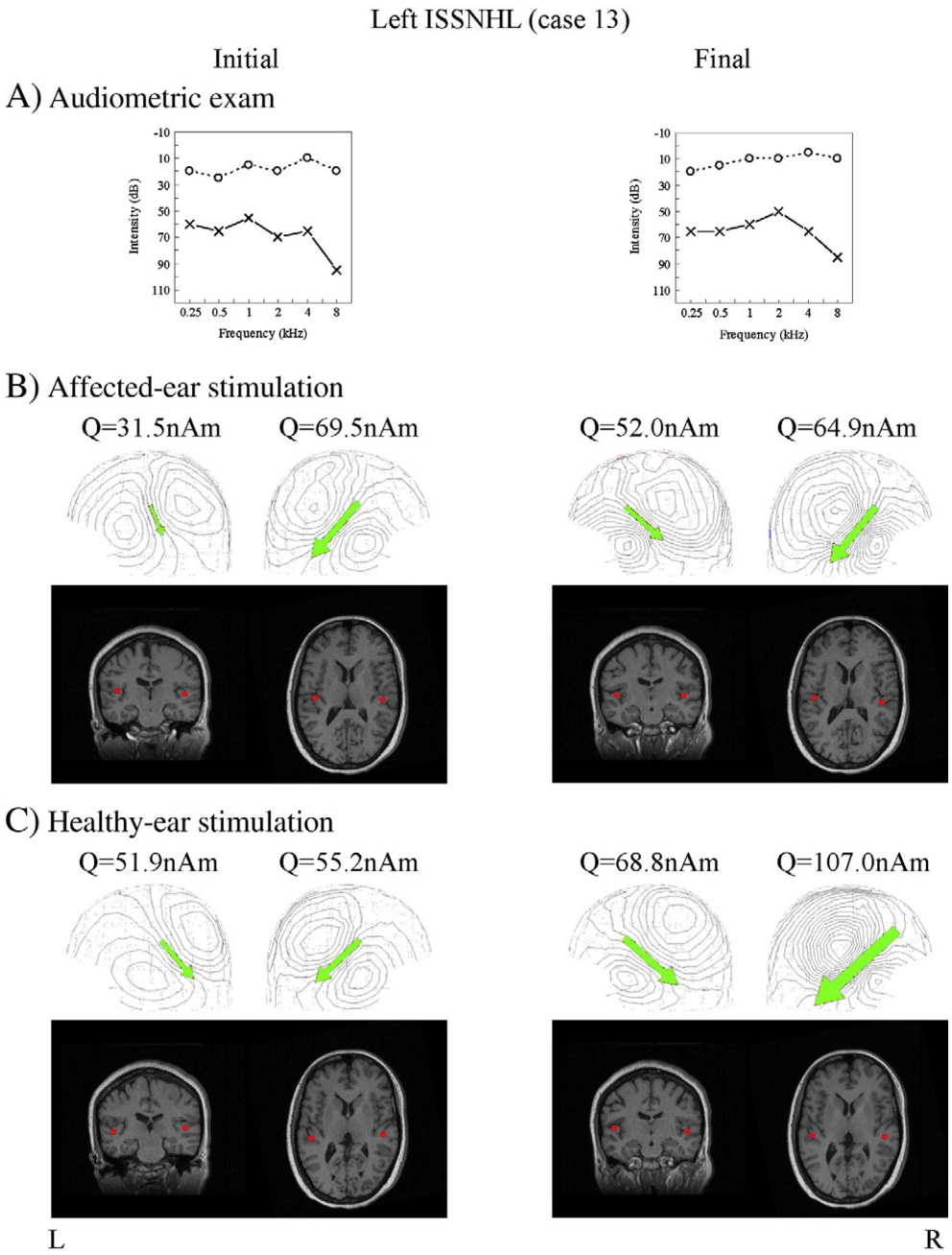

Fig. 1. Temporal dynamics of neuromagnetic responses to monaural stimulation with reference to hearing status in unilateral ISSNHL patients. Patient 13 (female, left ISSNHL) was studied initially on the seventh day after onset. (A) PTA results of air conduction exam. The patient demonstrated a sensorineural hearing loss pattern in initial exam (left column) and had no recovery 12 months later (right column). Dashed and solid lines denote right and left ear threshold, respectively. (B) and (C) Neuromagnetic field patterns and source localizations. In initial MEG exam (left column), ECDs (green arrows) revealed a pattern of healthy-side dominance. In 12-month MEG exam (right column), ECDs again showed a pattern of healthy-side dominance paralleled by worsened hearing status. Dipole sources (red dots) are localized at the auditory cortices of bilateral temporal lobes in patients' MRI images. MRI views are displayed according to neurological convention, i.e., subject's right hemisphere is on the right side of the images.

Differences of N100m between hemispheres

Normal-hearing subjects (Table 2)

When N100m activities of contralateral and ipsilateral hemispheres for all control subjects were respectively pooled from ear stimulation on both sides (42 measurements for each hemisphere), a contralateral dominance of dipole moment was noted ($p<0.001$). A faster N100m response was also noted in the contralateral hemisphere ($p<0.001$). A subset analysis ($n=21$) of peak N100m moment made according to the ear stimulated revealed a significant contralateral preponderance upon both left-ear ($p<0.001$) and right-ear stimulation ($p=0.008$). Inter-hemispheric latency differences were significant for both left-ear ($p<0.001$) and right-ear stimulation ($p=0.003$) on the subset level.

ISSNHL patients (Table 2, Fig. e-1)

On initial MEG exam of patients, the contralateral N100m was significantly shorter in response latency ($p=0.001$) as compared to that of ipsilateral hemisphere ($n=42$). Contralateral dominance was not observed ($p=0.069$) on the pooled data from stimulation of both ears (responses from the hemisphere opposite the stimulated healthy or deaf ear vs. those from the ipsilateral hemisphere; $n=42$).

Table 2
Amplitude and latency of peak dipole moment for N100m.

Hemisphere	Control				ISSNHL patient							
					Initial				12 m			
	Left		Right		Healthy		Affected		Healthy		Affected	
	a	l	a	l	a	l	a	l	a	l	a	l
Contralateral hemisphere												
1	104.1	89.7	52.1	95.3	55.3	80.5	65.9	86.0	45.1	76.8	46.5	82.4
2	47.8	104.5	76.6	108.2	41.7	80.5	102.2	89.7	81.3	99.7	83.8	99.6
3	18.0	90.8	30.6	98.9	20.7	76.8	37.4	111.9	33.1	71.2	78.0	85.9
4	36.7	102.6	49.5	104.5	22.2	84.2	79.5	80.5	27.3	97.1	58.2	95.3
5	62.4	84.2	55.1	91.6	35.5	117.4	113.5	98.9	77.9	100.8	104.6	104.5
6	113.5	97.1	49.9	106.3	66.2	82.4	16.8	138.1	76.0	88.9	58.1	103.0
7	94.7	89.7	90.6	99.5	39.7	128.5	50.3	110.1	83.4	82.2	62.6	87.9
8	66.9	80.5	55.0	81.7	87.2	84.1	54.8	114.5	127.2	96.8	81.7	96.9
9	76.3	72.4	48.1	76.1	31.8	74.3	60.0	100.0		96.8	54.2	110.1
10	35.3	76.8	59.4	87.9	54.5	75.9	35.3	121.2	72.3	79.8	28.8	103.6
11	30.7	117.4	41.7	98.9	44.2	76.1	29.2	142.2	58.3	78.6	48.6	83.4
12	62.4	89.7	55.1	121.1	50.3	72.3	76.1	84.6	84.7	72.4	103.9	81.6
13	26.7	97.1	46.8	78.5	51.9	93.9	69.5	110.0	68.8	90.8	64.9	105.5
14	31.1	77.6	37.1	111.0	48.4	78.8	35.3	78.8	28.1	76.1	68.2	76.1
15	35.1	95.1	37.3	78.9	80.1	81.6	93.8	83.4	114.1	87.1	119.4	81.6
16	57.7	79.8	40.7	85.3	30.6	87.1	76.6	74.3	80.3	98.1	61.3	94.4
17	92.5	89.7	66.5	97.1	28.0	98.1	10.4	156.8	27.7	87.1	36.7	136.6
18	35.8	74.3	63.5	81.6	34.3	75.9	66.1	71.5	21.6	81.6	68.9	82.8
19	45.2	98.1	52.1	98.1	33.7	88.9	63.3	72.4	25.5	83.4	80.4	70.6
20	65.2	74.3	89.8	81.6	36.4	74.3	96.1	76.3	95.6	79.8	88.2	79.8
21	57.2	81.6	42.6	81.6	37.6	81.6	42.3	88.9	31.3	107.3	42.8	87.1
m	56.9	88.7	54.3	93.5	44.3	85.4	60.7	99.5	63.5	87.3	68.6	92.8
SD	27.0	11.6	16.0	12.5	17.3	14.2	27.9	24.5	30.9	10.3	23.3	14.8
Ipsilateral hemisphere												
1	47.9	108.2	83.2	98.9	59.8	89.7	30.5	97.1	41.8	89.7	46.1	87.9
2	41.6	100.8	33.8	122.9	64.0	89.7	39.6	97.1	76.1	115.2	29.7	123.3
3	15.4	87.9	26.4	102.6	65.6	76.8	11.6	121.1	92.3	74.9	11.7	82.2
4	33.3	119.2	33.7	102.6	77.0	92.2	50.2	89.7	71.5	93.4	41.8	104.5
5	26.2	104.5	38.7	89.7	93.7	110.0	34.2	93.4	149.5	97.1	57.1	113.7
6	37.2	122.9	47.1	102.6	37.9	104.5	15.2	125.7	58.9	92.6	51.7	112.7
7	36.8	106.3	61.6	108.2	53.8	113.7	44.9	110.0	49.2	89.4	60.1	89.7
8	51.6	91.6	45.7	87.9	58.9	98.0	23.5	140.2	109.6	96.9	85.3	96.7
9	16.6	100.0	35.4	92.6	35.0	90.8	20.0	100.9	58.6	108.2	67.0	111.7
10	38.1	100.8	20.8	87.9	64.5	90.6	25.0	126.1	18.4	111.0	48.1	114.6
11	33.0	106.3	23.9	115.5	44.5	107.3	29.4	122.0	35.8	74.3	52.8	86.9
12	26.2	98.9	38.7	126.6	57.8	84.1	52.6	83.4	95.8	76.1	66.9	90.8
13	39.8	101.6	43.2	94.2	55.2	103.0	31.5	122.4	107.0	90.8	52.0	90.8
14	26.8	112.9	46.2	90.8	57.1	90.8	17.2	113.7	54.9	90.8	32.7	87.1
15	20.8	104.1	30.5	98.4	80.7	88.9	50.2	112.8	124.0	90.8	95.0	96.3
16	29.1	92.6	44.8	92.6	55.3	88.9	35.5	112.8	80.7	96.3	60.3	125.6
17	43.1	106.3	72.3	106.3	41.7	88.9	11.5	136.6	42.3	87.1	32.9	125.6
18	19.4	105.5	35.0	120.1	36.6	87.1	25.8	75.9	35.6	88.9	27.8	82.9
19	43.3	105.5	47.0	105.5	41.5	81.6	27.9	96.3	59.6	83.4	33.9	90.8
20	47.9	88.9	59.7	90.8	36.6	81.6	43.2	96.3	27.6	87.1	42.7	92.6
21	35.7	96.3	41.2	90.8	20.1	90.8	37.4	105.5	46.3	127.5	27.1	94.4
m	33.8	102.9	43.3	101.3	54.2	92.8	31.3	108.5	68.4	93.4	48.7	100.0
SD	10.6	8.9	15.4	11.8	17.3	9.8	12.5	17.2	34.2	13.1	20.0	14.4
	a	l	a	l	a	l	a	l	a	l	a	l
p_1	<0.001	<0.001	(Left/right pooled)		0.069	0.001	(Healthy/affected pooled)		0.101	<0.001		
p_2					<0.001	0.974	(Healthy side dominance)		0.014	0.785		
p_3	<0.001	<0.001	0.008	0.003	0.021	0.008	<0.001	0.029	0.590	0.005	0.003	0.008

Threshold for statistical significance using Wilcoxon's signed rank test was set at $p<0.05$. Left, left-ear stimulation; Right, right-ear stimulation; Healthy, healthy-ear stimulation; Affected, affected-ear stimulation; Initial, initial MEG exam; 12 m, 12 months after initial exam (final stage); a, amplitude of N100m dipole moment (Q/nAm); l, latency of N100m dipole moment (ms); m, mean; SD, standard deviation; p_1, significance of difference between pooled responses of contralateral vs. ipsilateral hemispheres on monaural stimulation to both ears in controls and patients, respectively; p_2, significance of difference between pooled responses of hemispheres ipsilateral to vs. opposite to the healthy ears on monaural stimulation to both intact and affected ears of patients; p_3, significance of difference between hemispheric responses on a subset level according to ear of stimulation (left-ear stimulation and right-ear stimulation respectively in controls, healthy-ear stimulation and affected-ear stimulation respectively in patients).

However, a healthy-side dominance was observed when responses from hemispheres ipsilateral to the healthy ears were pooled and compared with those from hemispheres ipsilateral to the deaf ears, irrespective of the ear stimulated ($p<0.001$; $n=42$). No inter-hemispheric difference in latency was observed ($p=0.974$).

On MEG exam of patients at the final stage, the contralateral N100m was significantly shorter in response latency ($p<0.001$) as compared to that of ipsilateral hemisphere ($n=42$). Contralateral dominance was not observed ($p=0.101$) on the pooled data from stimulation of both ears ($n=42$). A healthy-side dominance was

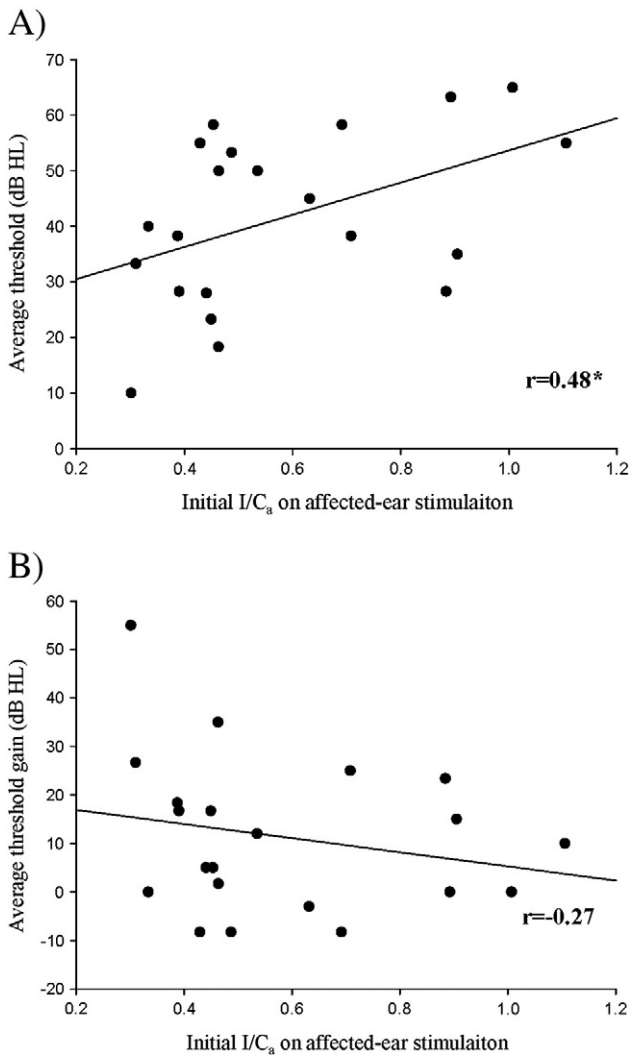

Fig. 2. Relationship between ipsilateral/contralateral (I/C) ratios and hearing levels. (A) I/C and average threshold. When ipsilateral/contralateral ratios were correlated to hearing levels, no significant correlation was revealed except for that between the initial I/C_a on affected-ear stimulation and the final average hearing level ($r = 0.48$, $p = 0.03$). (B) I/C and average threshold gain. There was no correlation between hearing gain and both kinds of I/C at various stages. For example, no significant correlation was revealed between the initial I/C_a on affected-ear stimulation and the final average threshold gain ($r = -0.27$, $p = 0.23$). r, correlation coefficient; $^*p < 0.05$.

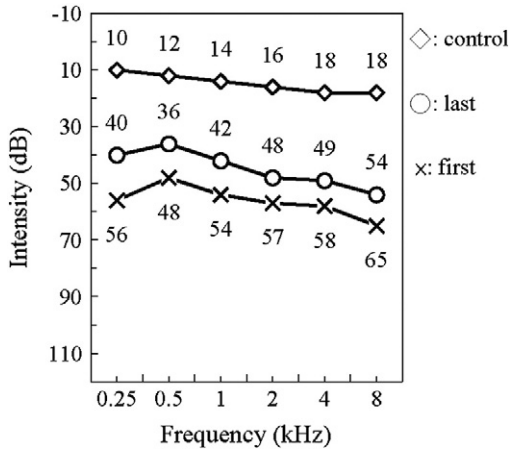

Fig. 3. Averaged audiograms at the first and last measurements in ISSNHL with a depiction of the averaged audiogram in controls as a reference. The trend revealed a flat-to-descending type of hearing loss in our patients.

observed again when responses from hemispheres ipsilateral to the healthy ears were pooled and compared with those from hemispheres ipsilateral to the deaf ears, irrespective of the ear stimulated ($p = 0.014$; $n = 42$). No inter-hemispheric difference in latency was observed ($p = 0.785$).

Discussion

Correlation between hearing level and ipsilateral/contralateral ratio of N100m dipole moment strength

One major and novel finding in the current study is the association between the hearing outcome at the final stage and the acute prototype of hemispheric asymmetry as represented by the ipsilateral/contralateral ratio for N100m responses in ISSNHL. When ipsilateral/contralateral ratios were correlated to hearing levels, no significant correlation was revealed except for that between the initial I/C_a on affected-ear stimulation and the final hearing level (positive correlation, i.e., the smaller the ratio, the lower the hearing level; Fig. 2) in ISSNHL. This type of unilateral loss is usually considered an inner ear disease in which the improvements in threshold should be caused by repair/regeneration within the cochlea, but findings here and those in one of our previous study (Li et al., 2012) showed a dynamic relationship between top- and down-levels of auditory pathway. Our finding is in line with one previous study, in which the scale of phantom limb pain was shown to be proportionately inter-correlated with the degree of cortical reorganization (Flor et al., 1995). To the best of our knowledge, the present research is the first study ever reporting on the finding of a relationship between the pattern of hemispheric asymmetry in acute ISSNHL and the long-term hearing threshold at the chronic stage (i.e. 12 months later).

The actual mechanisms of the correlation between the central auditory plasticity indexed by the ipsilateral/contralateral ratio of N100m response and both subacute (i.e. 1-mon, in our previous MEG study) (Li et al., 2012) as well as chronic (i.e. 12-month, in the present study) hearing levels of ISSNHL are currently unknown. It is somewhat unexpected that the pathological ipsilateral dominance of healthy ears at disease onset did not show a relationship with the 1-month and 12-month hearing level, but instead the contralateral dominance of affected ears did. It is also noteworthy that the dipole moment of the N100m response in the contralateral hemisphere relative to affected-ear stimulation in initial MEG exam (60.7 nAm) was about the same as that of the N100m response in the contralateral hemisphere relative to healthy-ear stimulation in 12-month MEG exam (63.5 nAm). This seems surprising given that the stimulus level used was constant. One plausible explanation is the hearing impairment itself, since inner-ear hearing loss has been revealed to cause enhanced N100m response (Morita et al., 2007). With a stimulus level of 75 dB SPL at 1000 Hz, the difference on hearing threshold translates into a pronounced disparity in sensation level (dB SL) of bilateral ears. Roughly, 65 dB HL translates to approximately 10 dB SL in the affected ear. For the healthy ear (no worse than 25 dB HL), the stimulus level is probably at least 50 dB SL. The amplitude of N100m response in the contralateral hemisphere on affected-ear stimulation at 5–10 dB SL, e.g., was almost equal to that on healthy-ear stimulation at 50–60 dB SL (Morita et al., 2007), which resulted in a seemingly "normal" contralateral dominance. It is thus reasonable to infer that the contralateral preponderance of affected ears physically reflects the degrees of auditory insults (and therefore the hearing levels), while the pathological ipsilateral dominance is a compensatory reorganization. Our finding suggested that the cochlea is the most probable lesion site of ISSNHL.

Although a smaller initial I/C_a on affected-ear stimulation (and hence a lower hearing threshold at the final stage) implied a higher possibility for the patients to recover, no statistical significance of within-group differences regarding I/C among prognostic subgroups

Table 3
Ipsilateral/contralateral ratio of N100m.

	Control								ISSNHL patient															
									Initial								12 m							
	Left				Right				Healthy				Affected				Healthy				Affected			
	I/C_a	I/C_1	I/C_{as}	I/C_{1a}	I/C_a	I/C_1	I/C_{as}	I/C_{1a}	I/C_a	I/C_1	I/C_{as}	I/C_{1a}	I/C_a	I/C_1	I/C_{as}	I/C_{1a}	I/C_a	I/C_1	I/C_{as}	I/C_{1a}	I/C_a	I/C_1	I/C_{as}	I/C_{1a}
1	0.46	1.21	0.92	1.14	1.60	1.04	0.80	1.10	1.08	1.11	0.91	1.04	0.46	1.13	0.55	1.21	0.93	1.17	0.90	1.09	0.99	1.07	1.02	1.14
2	0.87	0.96	0.54	0.93	0.44	1.14	0.71	1.18	1.53	1.11	0.63	1.00	0.39	1.08	0.95	1.21	0.94	1.16	0.91	1.16	0.35	1.24	0.37	1.24
3	0.86	0.97	0.50	0.89	0.86	1.04	1.47	1.13	3.17	1.00	1.75	0.69	0.31	1.08	0.56	1.58	2.79	1.05	1.18	0.87	0.15	0.96	0.35	1.15
4	0.91	1.16	0.67	1.14	0.68	0.98	0.92	1.00	3.47	1.10	0.97	1.15	0.63	1.11	2.26	1.07	2.62	0.96	1.23	0.98	0.72	1.10	1.53	1.08
5	0.42	1.24	0.48	1.14	0.70	0.98	0.62	1.07	2.64	0.94	0.83	1.11	0.30	0.94	0.96	0.80	1.92	0.96	1.43	0.93	0.55	1.09	0.73	1.13
6	0.33	1.27	0.75	1.16	0.94	0.97	0.41	1.06	0.57	1.27	2.26	0.76	0.90	0.91	0.23	1.53	0.78	1.04	1.01	0.90	0.89	1.09	0.68	1.27
7	0.39	1.19	0.41	1.07	0.68	1.09	0.65	1.21	1.36	0.88	1.07	1.03	0.89	1.00	1.13	0.86	0.59	1.09	0.79	1.02	0.96	1.02	0.72	1.09
8	0.77	1.14	0.94	1.12	0.83	1.08	0.68	1.09	0.68	1.17	1.07	0.86	0.43	1.22	0.27	1.67	0.86	1.00	1.34	1.00	1.04	1.00	0.67	1.00
9	0.22	1.38	0.35	1.31	0.74	1.22	0.46	1.28	1.10	1.22	0.58	0.91	0.33	1.01	0.63	1.36	0.79	1.12	1.08	0.98	1.24	1.01	0.91	1.15
10	1.08	1.31	0.64	1.15	0.35	1.00	0.59	1.14	1.18	1.19	1.83	0.75	0.71	1.04	0.46	1.66	0.25	1.39	0.64	1.07	1.67	1.11	0.67	1.44
11	1.07	0.91	0.79	1.07	0.57	1.17	0.78	0.98	1.01	1.41	1.52	0.75	1.01	0.86	0.67	1.60	0.61	0.95	0.74	0.89	1.09	1.04	0.91	1.11
12	0.42	1.10	0.48	0.82	0.70	1.05	0.62	1.41	1.15	1.16	0.76	0.99	0.69	0.99	1.05	1.15	1.13	1.05	0.92	0.93	0.64	1.11	0.79	1.25
13	1.49	1.05	0.85	1.29	0.92	1.20	1.62	0.97	1.06	1.10	0.79	0.94	0.45	1.11	0.61	1.30	1.56	1.00	1.65	0.86	0.80	0.86	0.76	1.00
14	0.86	1.45	0.72	1.02	1.25	0.82	1.49	1.17	1.18	1.15	1.62	1.15	0.49	1.44	0.36	1.44	1.95	1.19	0.80	1.19	0.48	1.14	1.16	1.14
15	0.59	1.09	0.56	1.32	0.82	1.25	0.87	1.03	1.01	1.09	0.86	1.07	0.54	1.35	0.63	1.38	1.09	1.04	1.04	1.11	0.80	1.18	0.83	1.11
16	0.50	1.16	0.71	1.09	1.10	1.09	0.78	1.16	1.81	1.02	0.72	1.20	0.46	1.52	1.16	1.30	1.00	0.98	1.32	1.02	0.98	1.33	0.75	1.28
17	0.47	1.19	0.65	1.09	1.09	1.09	0.78	1.19	1.49	0.91	4.01	0.57	1.11	0.87	0.41	1.39	1.53	1.00	1.15	0.64	0.90	0.92	1.19	1.44
18	0.54	1.42	0.31	1.29	0.55	1.47	0.98	1.62	1.07	1.15	0.55	1.22	0.39	1.06	0.75	1.00	1.65	1.09	0.52	1.07	0.40	1.00	1.29	1.02
19	0.96	1.08	0.83	1.08	0.90	1.08	1.04	1.08	1.23	0.92	0.66	1.13	0.44	1.33	0.83	1.08	2.34	1.00	0.74	1.18	0.42	1.29	1.33	1.09
20	0.73	1.20	0.53	1.09	0.66	1.11	0.92	1.22	1.01	1.10	0.38	1.07	0.45	1.26	1.19	1.30	0.29	1.09	0.31	1.09	0.48	1.16	0.45	1.16
21	0.62	1.18	0.84	1.18	0.97	1.11	0.72	1.11	0.53	1.11	0.48	1.02	0.88	1.19	0.99	1.29	1.48	1.19	1.08	1.46	0.63	1.08	0.87	0.88
m	0.69	1.17	0.64	1.11	0.83	1.09	0.85	1.15	1.40	1.10	1.15	0.97	0.58	1.12	0.79	1.29	1.29	1.07	0.99	1.02	0.77	1.09	0.86	1.15
SD	0.31	0.14	0.19	0.13	0.28	0.13	0.32	0.15	0.78	0.13	0.82	0.18	0.24	0.18	0.45	0.25	0.72	0.11	0.32	0.16	0.35	0.11	0.31	0.14
p									0.67	0.58	0.59	0.52	0.38	0.98	0.55	0.353	0.81	0.13	0.59	0.42	0.32	0.83	0.20	0.85

Threshold for statistical significance using Kruskal–Wallis test was set at $p<0.05$. Left, left-ear stimulation; Right, right-ear stimulation; Healthy, healthy-ear stimulation; Affected, affected-ear stimulation; Initial, initial MEG exam; 12 m, 12 months after initial exam (final stage); I/Ca, ipsilateral/contralateral ratio of N100m dipole moment amplitude in different hemispheres to monaural stimulation; I/Cl, ipsilateral/contralateral ratio of N100m dipole moment latency in different hemispheres to monaural stimulation; I/Cas, ipsilateral/contralateral ratio of N100m dipole moment amplitude in same hemisphere to stimulus at two ears; m, mean; SD, standard deviation; *p*, significance of difference in I/C among prognostic subgroups (i.e., complete, partial, and no recovery).

(i.e., complete, partial, and no recovery) was noted in the present study (Table 3). There was neither correlation between hearing gains and ipsilateral/contralateral ratios of various stages (Fig. 2B). The presented correlation (along with the scatter plot in Fig. 2A) might argue for a weak association which probably would not survive rigorous corrections for multiple comparisons. It is noteworthy that although efforts have been made to correlate various variables with the prognosis, no single biomarker was yet found to reliably prognosticate the eventual outcome and/or hearing level in ISSNHL at such a significant level of correlation as in the present study (Fetterman et al., 1996; Harada, 1996; Hirano et al., 1999; Mamak et al., 2005). The difficulty in prognostication probably reflected diverse etiologies of ISSNHL. In our previous MEG study (Li et al., 2012), initial ipsilateral/contralateral ratios of N100m responses have been shown to prognosticate the 1-mon hearing improvement (for definitions see Materials and methods) of ISSNHL. It is reasonable to infer that the initial pattern of hemispheric asymmetry may manifest an active compensation to facilitate hearing at the confrontation of deafness, and could thus as a potential biomarker predict the short-term result of hearing recovery. For the 12-month stage, however, our findings in the present study suggested that factors other than the initial ipsilateral/contralateral ratio must also be taken into consideration in terms of the prognostication for hearing improvement at the chronic stage of ISSNHL.

Scenario of evolution in neuromagnetic index of ISSNHL

Since the source strengths of AEFs may vary substantially between hemispheres, auditory plasticity in ISSNHL was evaluated by using two kinds of neuromagnetic index in the present study (see Data analysis and Table 3). It is noteworthy that, although some differences existed between two kinds of indices, the trend in the evolution remained basically the same. In the initial recordings, e.g., while I/C_{as} (intra-hemispheric comparison) was smaller than I/C_a (hemispheric comparison), they both presented ipsilateral dominance on healthy-ear stimulation. At the final stage (i.e. 12 months after the initial MEG exam), while the I/C_a and I/C_{as} on affected-ear stimulation approached the normal value, the I/C_a and I/C_{as} on healthy-ear stimulation remained relatively high in comparison with that of controls, although I/C_{as} was slightly smaller than 1.0 (0.99) so that there is mild degree of contralateral dominance (Fig. 1, Table 3). Accordingly, healthy-side dominance of AEFs was still observed in three final prognostic subgroups (Fig. 4). It is reasonable for such pattern to be preserved in ISSNHL patients with long-standing hearing loss (Fig. 1), which is in line with one previous MEG work showing healthy-hemisphere dominance of AEFs in the chronic phase of ISSNHL (Vasama and Makela, 1995). However, the persistence of the "healthy-side dominance" pattern in patients with hearing recovery was somewhat paradoxical. It thus seemed that a restored hearing status tended to, although not necessarily, lead toward a relatively normal functional organization in the central auditory pathway.

This could possibly be attributed to some subclinical but irreversible deterioration of neurochemical/neuroanatomical circumstances in various levels of auditory pathway. MRI evidence of ischemic changes and/or viral infection, e.g., has been reported in brainstems of ISSNHL patients with hearing recovery (Biavati et al., 1994). Diverse degrees of disorganization, with nearly normal appearance, were also revealed for regenerated hair cells in ablated cochlea of studied animals (Durham et al., 2000). Due to the subclinical nature, those minor abnormalities did not obviously compromise the behavioral threshold of pure tone perception. The neuronal architects serving auditory perception, however, are hardwired to fine-tune to subtle differences in the auditory environment (Illing and Reisch, 2006). It's therefore conceivable that chemical cues would continue

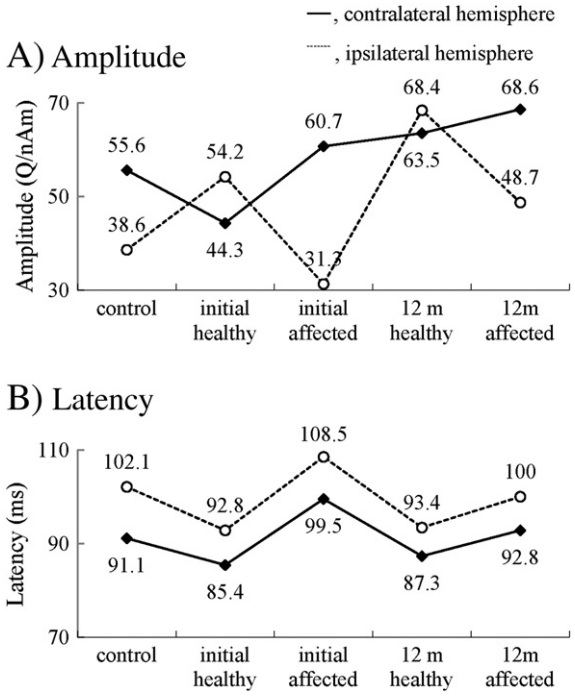

Fig. 4. Scenario of evolution in neuromagnetic fields of ISSNHL. (A) Amplitude. In the initial recordings, MEG measurements on both healthy- and affected-ear stimulation presented a trend of healthy-side dominance in terms of amplitude in ISSNHL (i.e. ipsilateral dominance on healthy-side stimulation and contralateral dominance on affected-ear stimulation). At the final stage (i.e. 12 months after the initial MEG exam), while MEG measurements on both healthy- and affected-ear stimulation became relatively more balanced, a trend of healthy-side dominance in terms of amplitude was still observed in ISSNHL. (B) Latency. In the initial and final recordings, MEG measurements on both healthy- and affected-ear stimulation in terms of latency presented a trend of faster N100m response over the contralateral hemisphere in ISSNHL as in controls. Initial healthy, initial MEG measurements on healthy-ear stimulation; initial affected, initial MEG measurements on affected-ear stimulation; 12 m healthy, final MEG measurements on healthy-ear stimulation; 12 m affected, final MEG measurements on affected-ear stimulation.

to be released from those injured/disorganized sites, leading to a lasting process of reorganization in the central auditory pathway. The dynamics of hemispheric asymmetry thus might not mirror the degree to which the essential circuits for intensity perception recovered, but rather all the reorganizing strategies taken by the central auditory pathway in compensation for the clinical/subclinical insults from ISSNHL (Illing and Reisch, 2006; Reale and Kettner, 1986; Reale et al., 1987). The pattern in turn may connote a central signature which implicates previous insults. Our finding suggested that brain activation patterns can be more sensitive than behavioral measurements to reflect the pathophysiological process in ISSNHL (Hwang et al., 2008; Shaywitz et al., 1999).

In summary, the ipsilateral/contralateral ratio of N100m amplitude on affected-ear stimulation at acute stage positively correlated with the hearing threshold at chronic stage of ISSNHL. However, there was no prognostic effect of hemispheric asymmetry pattern for the 12-month hearing improvement. Nevertheless, this finding suggests a new perspective, and perhaps new interventions, to diagnose and treat unilateral ISSNHL. The heterogeneity between neuromagnetic index and hearing recovery possibly echoed different pathogeneses of ISSNHL. Since a restored hearing status did not necessarily lead toward a relatively normal functional organization in ISSNHL, the dynamics of hemispheric asymmetry could actually be a signature of a central resilient reorganization indexing long-term rewiring of the neural network in the brain for sound processing. Our research invites studies on a larger group of patients to see if the predictive effect can be generated to common hearing loss. Further studies addressing other behavioral changes such as sound localization, suprathreshold psychophysical measures, and speech perception are also needed to get better psychoacoustic correlates associated with the observed peripheral and central changes and of the pathological ipsilateral dominance.

Acknowledgments

This work was supported by grants from the National Science Council (NSC97-2314-B-075-025 and NSC101-2314-B-350-002), Cheng Hsin General Hospital (100F117CY14 and 9943), and the Taipei Veterans General Hospital (V101C-177) of Taiwan. Special thanks to Dr. Tao-Hsin Tung and Ms Tai-Ying Liu for statistical consultation. We declare that we have no conflict of interest or financial relationships with this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2012.09.002.

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