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Healthy-side dominance of middle- and long-latency neuromagnetic fields in idiopathic sudden sensorineural hearing loss

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Abstract

Any lesion along the neural axis may induce a subsequent functional reorganization at the level above. The present study used magnetoencephalography to investigate auditory-evoked magnetic fields [a component of the middle-latency auditory evoked fields peaking at ~50 ms (P50m) and a component of the long-latency auditory evoked fields peaking at ~100 ms (N100m)] on stimulation of both healthy and affected ears in patients with acute unilateral idiopathic sudden sensorineural hearing loss (ISSNHL) of moderate degree in order to elucidate the functional plasticity of the auditory system. Sixteen right-handed, previously untreated adult patients with acute unilateral left ($n = 8$) or right ($n = 8$) ISSNHL of moderate degree were studied. Sixteen right-handed healthy volunteers with normal hearing served as control. Auditory neuromagnetic responses, measured by a whole-head 306-channel neuromagnetometer, were detected by monaural tone stimulation applied to affected and healthy ears, respectively, in different sessions. Intragroup and intergroup interhemispheric differences of peak dipole strengths and latencies of P50m and N100m, respectively, to monaural tones were evaluated. Healthy-side amplitude dominance of both P50m and N100m was found in ISSNHL, i.e. contralateral dominance was preserved on affected-ear stimulation but ipsilateral dominance was seen on healthy-ear stimulation. The phenomena could be attributed to the combined contralateral attenuation and ipsilateral enhancement of P50m and N100m activity in response to healthy-ear stimulation. Our findings confirmed that functional modulation can occur within the first few tens of milliseconds of evoked response at the auditory cortex in ISSNHL. The mechanisms of healthy-side dominance might be ascribed to a functional retune of auditory pathways, i.e. conjoined contralateral inhibition and ipsilateral excitation of the auditory pathway in response to healthy-ear stimulation. The effect could be registered in cortical responses.

Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is one of the few inner ear hearing disorders for which recovery can be observed. The incidence of ISSNHL increases from 4.6/100 000 per year in the second decade to 47.2/100 000 in the seventh decade (Byl, 1984). Suspected aetiologies include viral infection, small vessel thrombosis or basilar membrane rupture of the cochlea (Byl, 1984). About one-third of affected persons achieve complete recovery of hearing either spontaneously or after appropriate interventions (Byl, 1984). However, the precise localization of the ISSNHL lesion(s) and the functional modulation of the auditory pathway after insult remain unresolved. Although it is possible that the neural deficit(s) lies at a higher level of the auditory pathway, the cochlea has generally been considered the most probable lesion site of ISSNHL. Results from auditory evoked potentials (AEPs) and auditory evoked fields (AEFs) studies suggest that any lesion along the axis may induce a subsequent functional reorganization at the level above (Wang *et al.*, 1996; Morita *et al.*, 2003).

A normal AEF or AEP relies upon the integrity of both transmission of the auditory signal along the auditory pathway and processing in the

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cortex. It is conceivable that the site(s) of auditory neuroplasticity may not necessarily be the primary lesion site and the reorganization as expressed in the auditory cortex might originate from more peripheral loci along the auditory pathway. The long-latency N100 (peak latency at ~100 ms) component of AEPs, for example, may reflect 'lower-level' sensory processing in the cortex (Oates *et al.*, 2002). Amplitude reduction of N100 may indicate compromised cortical processing of the auditory signal in patients with mild-to-severe hearing loss of peripheral origin (Oates *et al.*, 2002). Magnetoencephalographic (MEG) studies of long-latency AEFs (LLAEFs), e.g. a component of the LLAEFs peaking at ~100 ms (N100m), in patients with acute ISSNHL or chronic unilateral deafness of various aetiologies show a dynamic plasticity in the central auditory pathway (Vasama & Makela, 1995; Fujiki *et al.*, 1998; Vasama *et al.*, 1998; Dietrich *et al.*, 2001; Li *et al.*, 2003). Most of these MEG studies were limited to the investigation of cerebral responses to auditory stimulation of the healthy ear owing to the profound degree of hearing loss of the affected ear (Vasama & Makela, 1995; Fujiki *et al.*, 1998; Vasama *et al.*, 1998; Dietrich *et al.*, 2001).

Components of middle-latency AEFs (MLAEFs) and middle-latency AEPs, e.g. P30m/P50m and P30/P50, are critical for the initial cortical representations of perceived transient sounds (Kanno *et al.*, 2000) and may mirror the neurophysiological correlates for auditory recognition (Ozdamar *et al.*, 1982). Studies in patients with temporal lobe lesions have shown that the P30 amplitude decreases on the lesion side regardless of the side of auditory stimulation (Kaseda *et al.*, 1991), in contrast to the 'contralateral dominance' of MLAEFs to monaural stimulation in subjects with normal hearing (Ackermann *et al.*, 2001). Nevertheless, it is unclear whether there is altered responsiveness antecedent to LLAEFs after ISSNHL or hearing impairment in general.

The present study seeks to investigate both MLAEFs [a component of the MLAEFs peaking at ~50 ms (P50m)] and LLAEFs (N100m) using MEG tests of a group of 16 patients with acute unilateral ISSNHL. P50m is the magnetic counterpart of the P50 component of middle-latency AEPs, peaking at ~50 ms, emanating from an area different from that of the N100m in the auditory cortex (Kanno *et al.*, 2000). P50m represents the cortical event for pure tone processing just ahead of N100m (Pekkonen *et al.*, 2004). Patients with ISSNHL with mild-to-moderate hearing impairment were chosen for the study so that P50m and N100m were concurrently detectable on either affected- or healthy-ear stimulation, which in turn promised the possibility of delving into the temporal scenario of functional plasticity in the primary auditory cortex.

Materials and methods

Subjects

Sixteen right-handed, previously untreated adult patients with acute unilateral left ($n = 8$) or right ($n = 8$) ISSNHL (eight males; 21–72 years of age, mean 44 years) were studied (Table 1). Patients were normal for age in hearing in the opposite ear (Table 1). Sixteen right-handed healthy volunteers with normal hearing (eight males; 21–66 years of age, mean 39 years) served as controls (Table 1). Two patients (nos 1 and 2) and four controls (nos 1–4) were involved in our previously reported preliminary study (Li *et al.*, 2003). The diagnosis criterion was a sensorineural hearing loss with a threshold of not less than 30-dB hearing level over three contiguous frequencies in an octave within 3 days or less (Wilson *et al.*, 1980). No other neurological deficits or traumatic history were identified. The elapsed time until MEG examination after disease onset ranged from 3 days to 3 weeks (Table 1). The study conformed to the 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.

TABLE 1. General data for all participants

	Normal control group		Patients with ISSNHL				
Participant number	Gender	Age (years)	Gender	Age (years)	Du (days)	Th (dB)	De (dB)
1	M	35	M	35	17	15	50
2	F	26	M	72	17	5	40
3	M	33	M	34	8	20	60
4	M	29	M	49	8	20	60
5	F	34	F	46	21	15	50
6	F	46	M	48	8	20	60
7	M	21	F	50	10	20	60
8	M	66	F	29	9	15	55
9	M	51	F	35	17	15	55
10	M	25	F	53	7	15	55
11	F	41	F	50	20	10	50
12	F	22	M	55	3	10	45
13	M	46	M	21	9	20	60
14	F	62	F	60	16	10	45
15	F	54	M	35	12	20	55
16	F	38	F	27	21	5	35

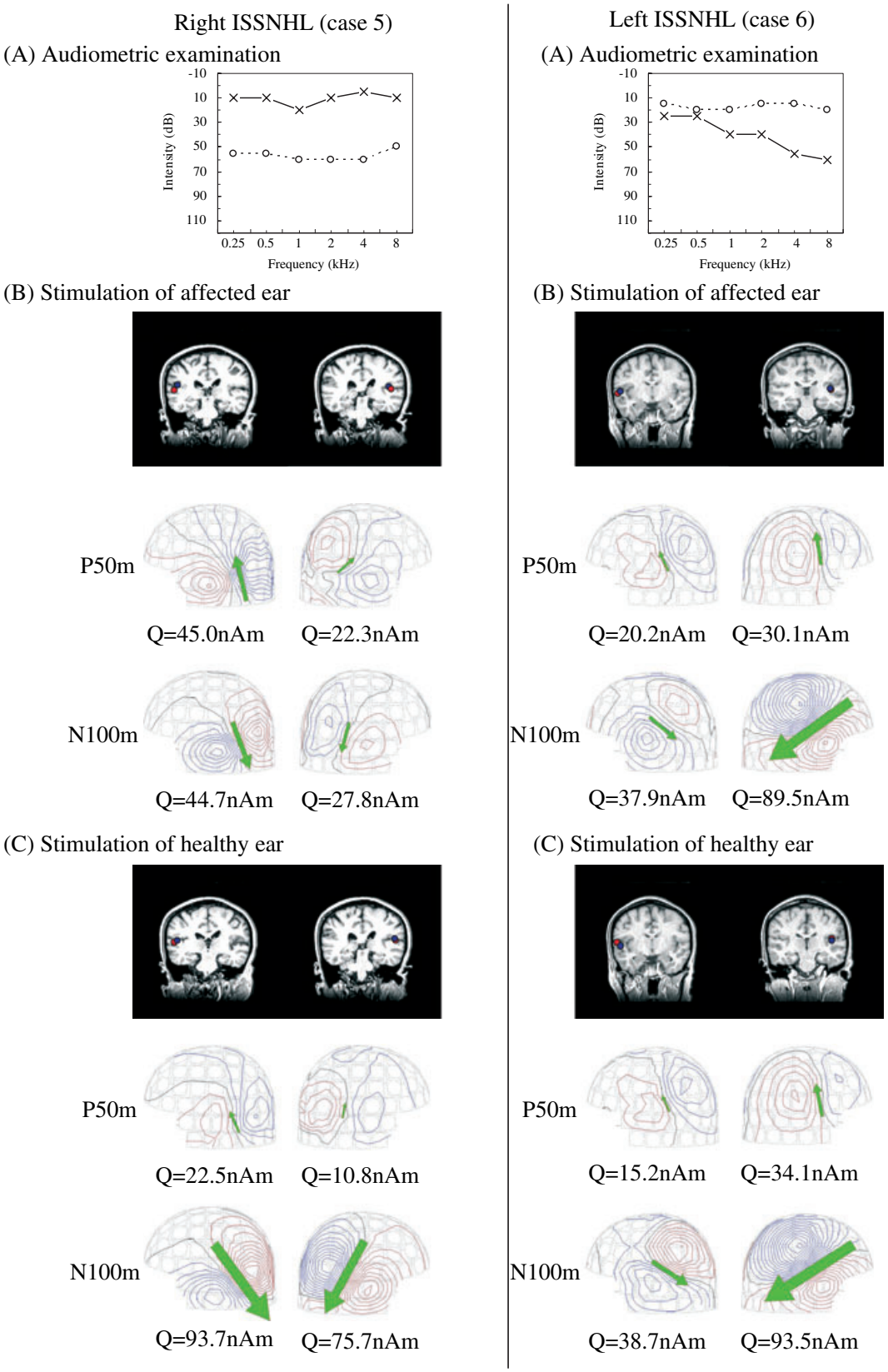
No., participant number; Du, duration from onset of hearing loss to magnetoencephalographic test; Th, hearing threshold of healthy ear (dB hearing level) at 1000 Hz; De, degree of hearing loss (dB hearing level) at 1000 Hz. ISSNHL, idiopathic sudden sensorineural hearing loss.

Audiometric and electrophysiological examinations

All participants underwent pure tone audiometry examination to determine both air and bone conduction thresholds, using test frequencies between 250 and 8000 Hz. Controls had normal pure tone audiometry results (threshold <20-dB hearing level for all frequencies). A unilateral sensorineural hearing level was noted in all patients with ISSNHL, characterized as cochlear in lesion site based on

FIG. 1. Healthy-side dominance of neuromagnetic responses on monaural stimulation in patients with unilateral idiopathic sudden sensorineural hearing loss (ISSNHL). Patient 5 (left column, female, right ISSNHL) was studied on the 15th day and patient 6 (right column, male, left ISSNHL) on the fourth day post-onset. (A) Pure tone audiometry results of air conduction examination. Both cases demonstrated a sensorineural hearing loss pattern. Dashed line, right ear threshold; solid line, left ear threshold. (B) Source localization and magnetic field pattern respective to monaural stimulation of the affected ears. Equivalent current dipoles (ECDs) (green arrows) are stronger over the hemisphere contralateral to affected ears for both a component of the middle-latency auditory evoked fields peaking at ~50 ms (P50m) (upper panel) and a component of the long-latency auditory evoked fields peaking at ~100 ms (N100m) (lower panel). (C) Source localization and magnetic field pattern respective to monaural stimulation of the healthy ears. ECDs (green arrows) are stronger over the hemispheres ipsilateral to the healthy ears for both P50m (upper panel) and N100m (lower panel). Dipole sources (red dots for N100m and blue spots for P50m) are localized at the auditory cortices of bilateral temporal lobes in magnetic resonance imaging (MRI) images of patients. MRI views are displayed according to neurological convention, i.e. subject's right hemisphere is on the right side of the images.

the results of reduced distortion-product otoacoustic emissions and within-normal-limit age-adjusted interaural latency differences for auditory brainstem responses (Gstoettner *et al.*, 1992; Foster & Luebke, 2002). As for all patients, air and bone conduction thresholds were less than 60-dB hearing level at 1000 Hz (Fig. 1, Table 1) and the probing auditory stimulus was set at this frequency at 70-dB SPL for the MEG experiment. This moderate intensity was chosen to avoid further acoustic damage and cross-hearing contamination.



Magnetoencephalographic paradigm

The MEG measurements were performed in a magnetically shielded room using a whole-head 306-channel neuromagnetometer (Vectorview(tm), 4-D Neuroimaging, Helsinki, Finland). Subjects were seated upright with eyes open and were instructed to pay attention to the auditory stimulation during measurements. Simple tones (1000 Hz, 50-ms duration with 10 ms for ramp up and down, respectively; 70-dB SPL at the exit end of the plastic tube, with an interstimulus interval of about 4 s) were delivered monaurally via moulded earpieces using the SoundProbe(tm) program on a Macintosh computer. 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 0.03–100 Hz. About 90 artifact-free trials were averaged. An equivalent current dipole (ECD) modelling consisting of bilateral sources was used to explain the MEG signals (Hari & Makela, 1988; Kanno *et al.*, 2000). Each ECD was fitted to a subset of 40–60 sensors around the maximum peak in one hemisphere with a goodness-of-fit larger than 80% for acceptance. As the accuracy of dipole localization depended largely on the signal-to-noise ratio (Jacobson, 1994), we included a sensor only when the peak amplitude of the signal was stronger than 2 SDs above the baseline. After the ECD with the highest goodness-of-fit value was identified, all channels were taken into account for further analysis so that it best explained the recorded magnetic field globally (Kanno *et al.*, 2000). The peak latency was then extracted for these ECDs. T1-weighted magnetic resonance images of subject brains were acquired using a 3.0-T MedSpec S300 system (Bruker, Kalsrube, Germany) for MEG/magnetic resonance imaging coregistration. No obvious abnormality (e.g. vascular lesion, tumour growth, etc.) was found in those brain magnetic resonance imaging examinations.

Data analysis

The epoch analysed ranged from 50 ms before to 350 ms after stimulation onset. The interval between −50 ms and 0 ms (trigger onset) was used as baseline. The time windows for P50m and N100m measurements were 20–70 and 70–160 ms, respectively (Woldorff *et al.*, 1999; Kanno *et al.*, 2000). If two or more identifiable peaks were observed within the defined P50m interval, the one nearest the N100m peak was designated as the P50m (Onitsuka *et al.*, 2000). Within-group interhemispheric differences of peak dipole strength and latency of P50m and N100m observed in different hemispheres were evaluated using the Wilcoxon signed rank tests (threshold at $P < 0.05$).

Differences in peak dipole strength and latency for P50m and N100m between controls and patients on the same side of the brain (i.e. contralateral or ipsilateral hemisphere with reference to the ear stimulated) were analysed using ANOVA with a post-hoc test of Games-Howell (threshold at $P < 0.05$). The peak dipole moments and latencies for P50m and N100m were grouped into three sets for statistical analysis: either (i.e. left or right) ear stimulation in subjects with normal hearing ($n = 32$) and affected-ear ($n = 16$) as well as healthy-ear ($n = 16$) stimulation in patients with ISSNHL, respectively (i.e. ear × hemisphere).

Results

In all subjects, a P50m and an N100m dipole were identifiable over each hemisphere. Sources for P50m and N100m were localized bilaterally on the superior temporal plane with the orientations of P50m and N100m ECDs opposite to each other, i.e. centripetal and centrifugal to the auditory cortex, respectively (Fig. 1). The relative position of the peak dipole of P50m and N100m was expressed in terms of Talairach's nomenclature (Talairach & Tournoux, 1988) (Table 2). The threshold for statistical significance in dipole location between P50m and P100m (x, y and z coordinates, respectively) using the Wilcoxon signed rank test was set at $P < 0.05$. The differences between the location of N100m and P50m sources were minimal (Table 2). This result is compatible with those of previous studies (Pekkonen *et al.*, 1995; Onitsuka *et al.*, 2000), in which the P50m and N100m sources were suggested to be colocated in an extended area of the cortex.

Within-group differences (comparisons of responses between both hemispheres of an individual participant of the respective group)

Component of the middle-latency auditory evoked fields peaking at ~50 ms

When the P50m activity for contralateral and ipsilateral hemispheres across all control subjects was, respectively, pooled from ear

TABLE 2. Relative position of peak dipole of a component of the middle-latency auditory evoked fields peaking at ~50 ms (P50m) and a component of the long-latency auditory evoked fields peaking at ~100 ms (N100m)

	Talairach coordinates (*x*, *y* and *z* in mm)			
	Normal control		Patient with ISSNHL	
Parameters	Left ($n = 16$)	Right ($n = 16$)	Left ($n = 16$)	Right ($n = 16$)
Contralateral hemisphere				
x				
P50m	47.6 ± 3.5	−51.4 ± 1.8	49.7 ± 7.1	−47.1 ± 4.8
N100m	48.9 ± 3.7	−51.8 ± 2.5	50.3 ± 5.8	−49.5 ± 5.3
(*P*-value)	(0.285)	(0.285)	(0.612)	(0.128)
y				
P50m	−13.1 ± 1.4	−13.9 ± 4.0	−13.3 ± 4.4	−18.0 ± 8.8
N100m	−14.5 ± 3.8	−12.2 ± 2.5	−17.3 ± 3.4	−16.5 ± 5.5
(*P*-value)	(0.593)	(0.593)	(0.018)*	(0.128)
z				
P50m	11.3 ± 3.2	4.7 ± 2.8	13.5 ± 3.9	9.5 ± 6.6
N100m	11.0 ± 2.3	8.4 ± 4.8	14.6 ± 4.0	10.5 ± 3.3
(*P*-value)	(0.593)	(0.285)	(0.398)	(0.237)
Ipsilateral hemisphere				
x				
P50m	−54.4 ± 4.8	48.6 ± 5.2	−50.6 ± 3.8	47.4 ± 5.3
N100m	−55.5 ± 1.7	49.0 ± 2.7	−55.1 ± 5.9	49.8 ± 4.4
(*P*-value)	(0.513)	(0.109)	(0.128)	(0.018)*
y				
P50m	−14.3 ± 2.4	−12.8 ± 3.3	−18.6 ± 3.1	−16.6 ± 7.5
N100m	−13.8 ± 2.6	−13.2 ± 4.4	−20.0 ± 7.6	−14.1 ± 2.6
(*P*-value)	(0.710)	(0.827)	(0.398)	(0.672)
z				
P50m	10.9 ± 2.6	11.2 ± 6.2	10.1 ± 2.2	13.6 ± 1.4
N100m	7.3 ± 1.9	11.6 ± 2.9	11.3 ± 2.7	15.1 ± 4.2
(*P*-value)	(0.042)*	(0.827)	(0.108)	(0.237)

Data presented as mean ± SD. Threshold for statistical significance using Wilcoxon signed rank test was set at $P < 0.05$. Left, left-ear stimulation; Right, right-ear stimulation; *P*-value, significance of difference between dipole location of P50m and P100m (their *x*, *y* and *z* coordinates); *$P < 0.05$; *x*, medial/lateral position relative to midline (right, positive); *y*, anterior/posterior position relative to the anterior commissure (anterior , positive); *z*, superior/inferior position relative to the commissural line (superior , positive). ISSNHL, idiopathic sudden sensorineural hearing loss.

TABLE 3. Peak dipole moment and latency of a component of the middle-latency auditory evoked fields peaking at ~50 ms (P50m) and a component of the long-latency auditory evoked fields peaking at ~100 ms (N100m) for all participants

	Normal controls				Patients with ISSNHL			
	Left-ear stimulation		Right-ear stimulation		Healthy-ear stimulation		Affected-ear stimulation	
	Dipole moment (Q/nAm)	Latency (ms)	Dipole moment (Q/nAm)	Latency (ms)	Dipole moment (Q/nAm)	Latency (ms)	Dipole moment (Q/nAm)	Latency (ms)
Contralateral hemisphere								
P50m	23.3 ± 11.1	47.1 ± 8.5	17.3 ± 6.4	44.4 ± 8.6	13.8 ± 4.7	44.9 ± 8.7	21.1 ± 10.9	49.1 ± 13.8
N100m	62.8 ± 24.2	89.1 ± 13.0	60.8 ± 16.5	94.0 ± 15.2	47.0 ± 19.1	87.6 ± 10.7	60.4 ± 22.1	96.6 ± 19.7
Ipsilateral hemisphere								
P50m	18.3 ± 9.5	55.5 ± 9.5	12.6 ± 8.4	52.5 ± 7.7	25.4 ± 8.3	51.5 ± 10.2	13.5 ± 5.9	55.3 ± 11.3
N100m	36.2 ± 14.8	101.9 ± 11.8	48.5 ± 26.0	106.6 ± 16.6	61.6 ± 18.9	96.3 ± 11.3	33.5 ± 10.3	108.2 ± 13.2
P50m								
P1	< 0.001	< 0.001	(Left and right pooled)		0.379	< 0.001		(Healthy and affected pooled)
P2	–	–	–	–	< 0.001	0.517		(Healthy side dominance)
P3	0.007	0.016	0.013	0.001	< 0.001	0.002	0.004	0.012
N100m								
P1	< 0.001	< 0.001	(Left and right pooled)		0.204	< 0.001		(Healthy and affected pooled)
P2	–	–	–	–	< 0.001	0.970		(Healthy side dominance)
P3	0.001	0.001	0.034	0.001	0.004	< 0.001	< 0.001	0.014

Data are presented as mean ± SD. Threshold for statistical significance using Wilcoxon signed rank test was set at $P < 0.05$. P1, significant *P*-values comparing pooled responses of contralateral vs. ipsilateral hemispheres on monaural stimulation to both ears in controls and patients, respectively; P2, significant *P*-values comparing pooled responses of hemispheres ipsilateral to vs. opposite to the healthy ears on monaural stimulation to both healthy and affected ears of patients; P3, significant *P*-values comparing hemispheric responses on a subset level according to ear of stimulation. ISSNHL, idiopathic sudden sensorineural hearing loss.

stimulation on both sides (32 measurements for each hemisphere), a contralateral dominance (amplitude) was noted ($P < 0.001$; Table 3). A faster P50m response was also noted in the contralateral hemisphere ($P < 0.001$; Table 3). A subset analysis ($n = 16$) of the peak P50m moment made according to the ear stimulated revealed a significant contralateral preponderance upon left-ear ($P = 0.007$; Table 3) and right-ear ($P = 0.013$; Table 3) stimulation. Interhemispheric latency differences (contralateral responses faster than ipsilateral responses) were significant for both left-ear ($P = 0.016$; Table 3) and right-ear ($P = 0.001$; Table 3) stimulation at the subset level.

In the ISSNHL patient group, a significantly shorter response latency in the contralateral hemisphere was observed ($P < 0.001$; Table 3) at P50m as compared with that in the ipsilateral hemisphere; no pattern of contralateral dominance (amplitude) was seen ($P = 0.379$; Table 3) on the pooled data set from stimulation of both ears (responses from the hemisphere opposite the stimulated healthy or deaf ear vs. those from the ipsilateral hemisphere, 32 measurements). However, healthy-side dominance of the dipole moment was observed when responses from hemispheres ipsilateral to the healthy ears were pooled (32 measurements) and compared with those from hemispheres ipsilateral to the deaf ears, irrespective of the ear stimulated ($P < 0.001$; Table 3, Fig. 1). No interhemispheric difference in latency was observed ($P = 0.517$; Table 3). On a subset level ($n = 16$), P50m dipoles were significantly stronger over the ipsilateral hemisphere but faster over the contralateral hemisphere upon healthy-ear stimulation ($P < 0.001$ for dipole moment and $P = 0.002$ for latency; Table 3). On deaf-ear stimulation, P50m dipoles were both significantly faster and stronger over the contralateral hemisphere ($P = 0.004$ for dipole moment and $P = 0.012$ for latency; Table 3).

Component of the long-latency auditory evoked fields peaking at ~100 ms

When N100m activity for contralateral and ipsilateral hemispheres of all control subjects was, respectively, pooled from ear stimulation on both sides (32 measurements for each hemisphere), a contralateral dominance was noted ($P < 0.001$; Table 3). A faster N100m response was also noted in the contralateral hemisphere ($P < 0.001$; Table 3). A subset analysis ($n = 16$) of the peak N100m moment made according to the ear stimulated revealed a significant contralateral preponderance upon left-ear ($P = 0.001$; Table 3) and right-ear ($P = 0.034$; Table 3) stimulation. Interhemispheric latency differences were significant for both left-ear ($P = 0.001$; Table 3) and right-ear ($P = 0.001$; Table 3) stimulation on the subset level.

In the ISSNHL patient group, the contralateral hemisphere showed significantly shorter response latency ($P < 0.001$; Table 3) at N100m as compared with the ipsilateral hemisphere but no pattern of contralateral dominance was seen ($P = 0.204$; Table 3) on a pooled data set from stimulation of both ears (32 measurements). However, a healthy-side dominance of the dipole moment was observed when responses from hemispheres ipsilateral to the healthy ears were pooled (32 measurements) and compared with those from hemispheres ipsilateral to the deaf ears, irrespective of the ear stimulated ($P < 0.001$; Table 3, Fig. 1). No interhemispheric difference in latency was observed ($P = 0.970$; Table 3). On a subset level ($n = 16$), N100m dipoles were significantly stronger over the ipsilateral hemisphere but faster over the contralateral hemisphere upon healthy-ear stimulation ($P = 0.004$ for dipole moment and $P < 0.001$ for latency; Table 3). On deaf-ear stimulation, N100m

dipoles were both significantly faster and stronger over the contralateral hemisphere ($P < 0.001$ for dipole moment and $P = 0.014$ for latency; Table 3).

Between-group differences (comparisons of responses among either-ear stimulation in subjects with normal hearing, affected-ear stimulation in patients with idiopathic sudden sensorineural hearing loss and healthy-ear stimulation in patients with idiopathic sudden sensorineural hearing loss)

Hemispheres contralateral to ears of stimulation

The P50m peak dipole amplitudes were significantly different over contralateral hemispheres ($F_{2,61} = 3.500$, $P = 0.036$). Post-hoc analysis revealed that P50m peak dipoles were significantly weaker over contralateral hemispheres on healthy-ear stimulation in patients with ISSNHL (mean 13.79 nAm) than on stimulation of either ear in subjects with normal hearing (mean 20.31 nAm; $P = 0.007$) (Fig. 2). Although P50m peak dipoles on healthy-ear stimulation seemed to be weaker than on affected-ear stimulation in patients with ISSNHL (mean 21.13 nAm; $P = 0.056$), the effect was borderline. There was no significant difference between the conditions of either-ear stimulation in subjects with normal hearing and affected-ear stimulation in patients with ISSNHL ($P = 0.965$).

There were differences in amplitudes of N100m peak dipoles over contralateral hemispheres but the effect was borderline ($F_{2,61} = 2.952$, $P = 0.060$). Post-hoc analysis showed that N100m peak dipoles were significantly weaker on healthy-ear stimulation in patients with ISSNHL (mean 46.97 nAm) than on stimulation of either ear in subjects with normal hearing (mean 61.78 nAm; $P = 0.049$) (Fig. 2). Although N100m peak dipoles on healthy-ear stimulation seemed to be weaker than on affected-ear stimulation in patients with ISSNHL (mean 60.40 nAm), the effect was insignificant ($P = 0.175$). There was no difference between the conditions of either-ear stimulation in subjects with normal hearing and affected-ear stimulation in patients with ISSNHL ($P = 0.976$).

Peak latencies for P50m and N100m dipoles over contralateral hemispheres were not significantly different ($F_{2,61} = 0.803$, $P = 0.453$ for P50m; $F_{2,61} = 1.428$, $P = 0.248$ for N100m) (Fig. 3).

Hemispheres ipsilateral to stimulated ear

The P50m and N100m peak dipole amplitudes were significantly different over ipsilateral hemispheres ($F_{2,61} = 10.116$, $P < 0.001$ for P50m; $F_{2,61} = 9.570$, $P < 0.001$ for N100m). Post-hoc analysis revealed that P50m and N100m peak dipoles were significantly stronger over ipsilateral hemispheres on healthy-ear stimulation in patients with ISSNHL (mean 25.43 nAm for P50m, 61.64 nAm for N100m) than on affected-ear stimulation in patients with ISSNHL (mean 13.48 nAm, $P < 0.001$ for P50m; mean 33.50 nAm, $P < 0.001$ for N100m) and on stimulation of either ear in subjects with normal hearing (mean 15.45 nAm, $P = 0.002$ for P50m; mean 42.34 nAm, $P = 0.009$ for N100m) (Fig. 2). There was no significant difference between the conditions of either-ear stimulation in subjects with normal hearing and affected-ear stimulation in patients with ISSNHL ($P = 0.648$ for P50m; $P = 0.147$ for N100m).

Peak latencies for P50m dipoles over ipsilateral hemispheres were not significantly different ($F_{2,61} = 0.679$, $P = 0.511$) (Fig. 3) but N100m peak latencies were significantly different over ipsilateral hemispheres ($F_{2,61} = 3.361$, $P = 0.041$) (Fig. 3). Post-hoc analysis revealed that the effect resulted mainly from the difference between the conditions of healthy-ear stimulation in patients with ISSNHL (mean 96.26 ms) and of affected-ear stimulation in patients with ISSNHL (mean 108.17 ms; $P = 0.027$) (Fig. 3). There was no significant difference between the conditions of either-ear stimulation in subjects with normal hearing (mean 104.25 ms) and affected-ear stimulation in patients with ISSNHL ($P = 0.618$) or between the conditions of either-ear stimulation in subjects with normal hearing and healthy-ear stimulation in patients with ISSNHL ($P = 0.103$) (Fig. 3).

Discussion

Contralateral dominance of a component of the middle-latency auditory evoked fields peaking at ~50 ms and a component of the long-latency auditory evoked fields peaking at ~100 ms in subjects with normal hearing

The finding of a contralateral dominance of both P50m and N100m in terms of peak dipole strength by monaural stimulation on normal subjects in the present study is congruent with previous MEG and functional magnetic resonance imaging reports (Ackermann *et al.*, 2001; Suzuki *et al.*, 2002) (Table 3). This hemispheric lateralization can be attributed to the prevailing cross-hemispheric projections in the auditory pathway and has been suggested to subserve in part the function of sound localization (Moore, 1991). In fact, this pattern of contralateral dominance can be observed at levels as low as the inferior colliculus (Moore, 1991), which is upstream of the auditory pathway receiving cross-hemispheric projections from cochlear nuclei in the brainstem (Hausler & Levine, 2000). At the cortical level, there are additional crossings from the ipsilateral to contralateral auditory cortex via the posterior corpus callosum (Woldorff *et al.*, 1999; Hausler & Levine, 2000). It is reasonable to infer that the number of neurone subpopulations might also be greater in the contralateral hemisphere (Rojas *et al.*, 2001). Such anatomical architecture may underlie the enhanced P50m and N100m neuromagnetic activity (amplitude) of the contralateral auditory cortex upon monaural acoustic stimulation.

Faster component of the middle-latency auditory evoked fields peaking at ~50 ms and a component of the long-latency auditory evoked fields peaking at ~100 ms responses over contralateral hemispheres in subjects with normal hearing and patients with idiopathic sudden sensorineural hearing loss

The latencies of ipsilateral auditory brainstem responses, MLAEFs and LLAEFs are known to be longer than the homologous auditory brainstem responses, MLAEFs and LLAEFs of the contralateral hemisphere upon monaural stimulation in subjects with normal hearing (Quaranta *et al.*, 1986; Makela *et al.*, 1994). These longer peak latencies of ipsilateral AEPs/AEFs can be attributed in part to the aforementioned delayed transcallosal activation in the ipsilateral auditory cortex (Woldorff *et al.*, 1999; Ackermann *et al.*, 2001).

Abnormally prolonged peak latencies for components of auditory brainstem responses may indicate a central conduction defect (Hansen *et al.*, 1989) implying an organic lesion, e.g. acoustic neuroma or an inflammatory process. Ipsilaterally localized central lesions may result in a significant delayed middle-latency auditory-evoked cortical response (Kaseda *et al.*, 1991). All of our patients with ISSNHL had within-normal-limit interhemispheric latency differences (Table 3). Nonetheless, prolongation of peak dipole latencies over hemispheres ipsilateral to the affected ears was noted only for N100m (but not P50m) in patients with ISSNHL (Fig. 3). The observations may imply that the latency alone may be not as sensitive a parameter as amplitude to index for the subtle functional modulation/plasticity in the ISSNHL

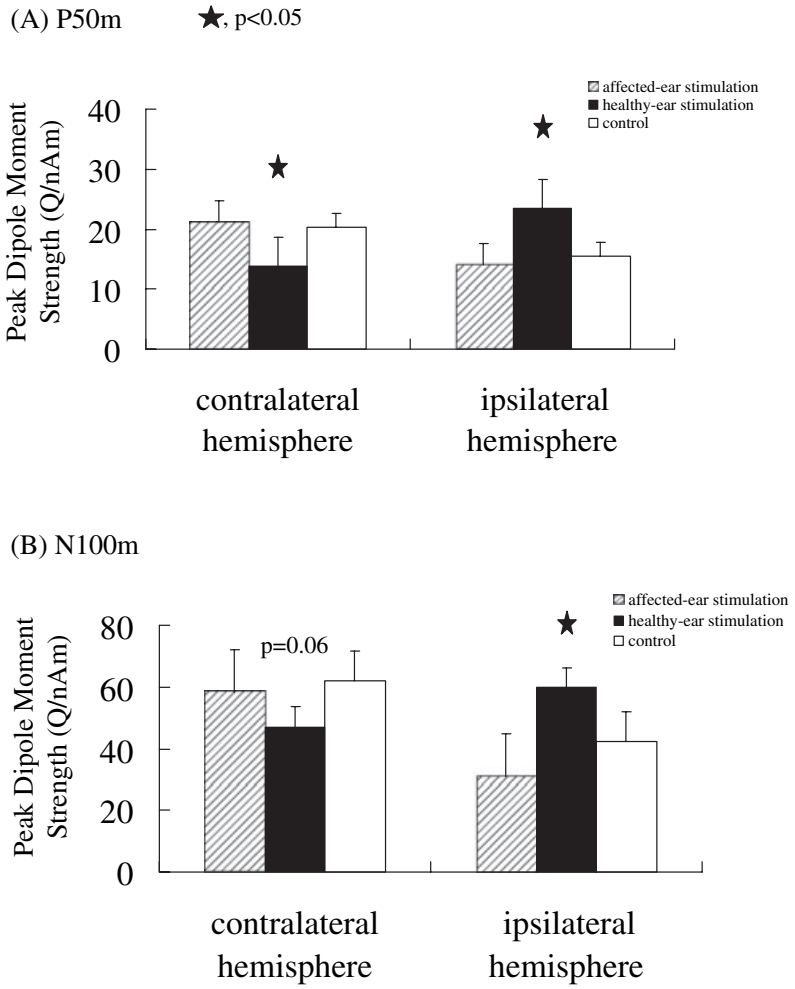


FIG. 2. Comparisons of peak dipole strength between patients with idiopathic sudden sensorineural hearing loss (ISSNHL) and controls. (A) ANOVA analysis revealed that a component of the middle-latency auditory evoked fields peaking at ~50 ms (P50m) peak dipole amplitudes were significantly different among three ear-stimulation conditions over both contralateral and ipsilateral hemispheres. Post-hoc analysis revealed that P50m peak dipoles were significantly weaker over contralateral hemispheres and significantly stronger over ipsilateral hemispheres on healthy-ear stimulation in patients with ISSNHL than on affected-ear stimulation in patients with ISSNHL and on stimulation of either ear in subjects with normal hearing (control). There was no significant difference between the conditions of either-ear stimulation in subjects with normal hearing and affected-ear stimulation in patients with ISSNHL. (B) The differences in amplitudes of a component of the long-latency auditory evoked fields peaking at ~100 ms (N100m) peak dipoles among three ear-stimulation conditions over contralateral hemispheres achieve borderline significance (ANOVA, $P = 0.06$). Post-hoc analysis showed that N100m peak dipoles were significantly weaker on healthy-ear stimulation in patients with ISSNHL than on stimulation of either ear in subjects with normal hearing. N100m peak dipoles on healthy-ear stimulation were weaker (borderline significance, $P = 0.069$) than those on affected-ear stimulation in patients with ISSNHL. There was no difference between the conditions of either-ear stimulation in subjects with normal hearing and affected-ear stimulation in patients with ISSNHL. N100m peak dipole amplitudes were significantly different among three ear-stimulation conditions over ipsilateral hemispheres. Post-hoc analysis revealed that N100m peak dipoles were significantly stronger over ipsilateral hemispheres on healthy-ear stimulation in patients with ISSNHL than on affected-ear stimulation in patients with ISSNHL and on stimulation of either ear in subjects with normal hearing. Findings imply contralateral inhibition and enhanced ipsilateral activation of cortical neuromagnetic activities on healthy-ear but not on affected-ear stimulation in ISSNHL. *$P < 0.05$.

of slight to moderate degree, despite the possibility of structural changes at different levels in auditory pathways.

Healthy-side dominance of a component of the middle-latency auditory evoked fields peaking at ~50 ms and a component of the long-latency auditory evoked fields peaking at ~100 ms in patients with idiopathic sudden sensorineural hearing loss

One major and novel finding in the present study is the healthy-side dominance for P50m in the patients with ISSNHL studied (Table 3, Fig. 1). This is the first MEG study to report such an observation of middle-latency neuromagnetic responses to monaural stimulation on both the healthy and affected ears in patients with acute unilateral ISSNHL. P50m dipoles were significantly stronger in the hemisphere ipsilateral to the healthy ear irrespective of the side of monaural stimulation, i.e. the healthy or the affected ear (Table 3, Fig. 1). P50m functionally indexes automatic auditory processing underlying stimulus detection (Pekkonen *et al.*, 2004) and is one of the initial cortical representations of transient sounds (Rupp *et al.*, 2002). Our finding thus confirms that functional modulation of the central auditory pathway, i.e. the loss of contralateral dominance on healthy-ear stimulation, can occur within the first few tens of milliseconds as transient sound arrives at the auditory cortex in patients with acute unilateral ISSNHL.

The emergence of the 'healthy-side dominance' of N100m in a smaller group of patients with acute unilateral ISSNHL was previously

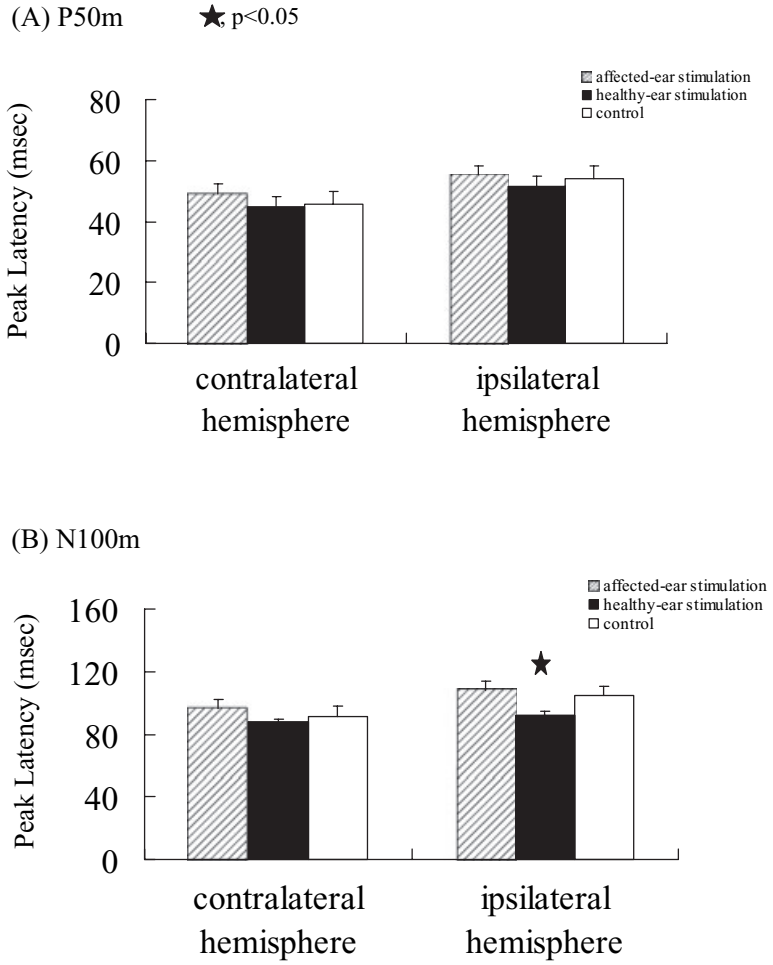


FIG. 3. Comparisons of peak latency between patients with idiopathic sudden sensorineural hearing loss (ISSNHL) and controls. Peak latencies for (A) a component of the middle-latency auditory evoked fields peaking at ~50 ms (P50m) and (B) a component of the long-latency auditory evoked fields peaking at ~100 ms (N100m) dipoles over contralateral hemispheres were not significantly different. Prolongation of peak dipole latencies over hemispheres ipsilateral to the affected ears was noted only for N100m (but not P50m) in patients with ISSNHL. Findings imply that the latency alone may be not as sensitive a parameter as amplitude to indicate the subtle functional modulation/plasticity in the ISSNHL of slight to moderate degree.

reported in our recent preliminary MEG study (Li *et al.*, 2003) and is verified here with a larger sample size. N100m dipoles were significantly stronger over hemispheres ipsilateral to healthy ears irrespective of the side stimulated (Table 3, Fig. 1). Patients in other related MEG studies were all chronic in disease course and were either deaf or had profound hearing loss (Vasama & Makela, 1995; Fujiki *et al.*, 1998). The severity of the hearing deficit (and structural insult) was neurophysiologically confirmed by compromise to N100m responses to affected-ear stimulation, as the presence of N100m implies the cortical detection and processing of sound (Oates *et al.*, 2002). Therefore, only the stronger response over the hemisphere ipsilateral to the stimulation of the healthy ear was reported. On the contrary, patients studied in the current study had mild to moderate hearing loss (threshold of affected ears at 1000 Hz, ⩽60-dB hearing level), providing an opportunity to study cortical reactions in response to the stimulation of the affected ear. The intensity of the stimuli used (70-dB SPL at 1000 Hz) was about 10 dB above the hearing threshold of our patients with ISSNHL. Stimuli approximately 10 dB above the hearing threshold were clearly audible to patients with a moderate degree of hearing loss, as indexed by the auditory evoked responses (Oates *et al.*, 2002). N100m responses to affected-ear stimulation were clearly identified in all patients in our study. It should be kept in mind that the AEFs measured by MEG stand for the final representations of the activity along the auditory pathway. Without segmental information of the entire pathway, it can be difficult to posit precisely where the origin of plasticity occurs, e.g. at the cortical or subcortical levels.

Although the mean age of our controls is less than that of the patients, the observations cannot be ascribed to the ageing effect (Pekkonen *et al.*, 1995) or to the influence of dipole location (Table 2). One possible explanation of the loss of contralateral dominance in AEFs upon stimulation of the healthy ear, in the absence of cortical and/or cochlear lesions, is that the effect of a cochlear lesion(s) might be bilateral through retrocochlear crossing fibres, influencing the function of the auditory pathway ipsilateral to the healthy ear. Chemical 'cues' signalling auditory plasticity, probably in terms of changes in neurotransmission/neuromodulation generated by the cochlear nuclei on the affected side, can be carried to neuronal substrates in the healthy side of the central auditory pathway through direct and/or indirect fibre projections within 2 days after insult (Potashner *et al.*, 2000; Smith *et al.*, 2002). This provides the auditory system with a synaptic fine-tuning capacity for optimization of processing requirements and to react/adapt to changes of input (Sato *et al.*, 2000).

Another possible explanation of the loss of contralateral dominance in patients with ISSNHL in response to healthy-ear stimulation is the involvement of the corticofugal auditory pathway (Suga *et al.*, 2002). This descending auditory pathway encompasses bilateral fibres coming from the auditory cortices and mediates physiological feedback to fine-tune subcortical neurones (Yan & Suga, 1999). By redistributing the information processed in the auditory cortex to subcortical centres, the corticofugal auditory pathway may in turn modulate the hearing function in the presence of a peripheral lesion (Khalfa *et al.*, 2001; Morand *et al.*, 2001). The modulation may affect auditory processing at levels as low as the hair cell of the cochlea (Xiao & Suga, 2002). This descending influence may be either transient or permanent (Suga *et al.*, 2002).

The observation of ipsilateral dominance for healthy-ear stimulation for both P50m and N100m dipole strength (Table 3) could possibly be ascribed to conjoined contralateral inhibition (or loss of excitation) and enhanced ipsilateral excitation (or loss of inhibition) in response to healthy-ear stimulation (Hsieh *et al.*, 2002) (Fig. 2). In an operational context, such readjustment could be one facet of the overall ISSNHL adaptive process and mirror the functional status of the patients. Animal studies have revealed a down-regulation of both ipsilateral excitatory receptor expression/binding (loss of excitation) (Sato *et al.*, 2000) and contralateral inhibitory neurotransmitter synthesis (loss of inhibition) (Mossop *et al.*, 2000) with respect to the affected ear in the central auditory pathway. The deafness-related changes after cochlear ablation can emerge along the auditory pathway up to the level of the inferior colliculus and can occur within minutes after cochlear damage (Mossop *et al.*, 2000). In turn, the effect of these changes might affect subcortical and/or cortical auditory neuronal substrates through projecting fibres from the inferior colliculus (Hausler & Levine, 2000). The above changes may contribute to alterations in auditory processing following sensory deprivation (Vale & Sanes, 2002). It is noteworthy that multiunit recordings of responses to stimulation of healthy ears also showed a greater excitation in neurones of the ipsilateral central auditory pathway after contralateral cochlear ablation (Mossop *et al.*, 2000). Functionally, this enhanced ipsilateral excitation might be a compensatory mechanism operating between the cortex and cochlea, meant to increase the gain of the system and partially correct for reduced cochlear input (Salvi *et al.*, 2000). As contralateral dominance in normal subjects services, in part, sound localization, this specific pattern of plasticity might have some relevance in preventing the neural network for locating sounds in the environment from delivering erroneous signals central-ward (Michler & Illing, 2002).

Although the audiometry results in the present study point toward a possible cochlear lesion, auditory plasticity might be coupled with anatomical changes at different levels of the auditory pathway. Decreased afferent inputs, e.g. due to cochlear destruction, can cause dramatic adverse molecular effects on neurones in the central auditory pathway within hours of cochlear damage, with some dying or shrinking in size within days (Born & Rubel, 1985; Durham *et al.*, 2000). Moreover, increased activity may reflect the formation of new synapses and even the emergence of additional afferent fibres in the ipsilateral pathway (Salvi *et al.*, 2000). These may be triggered by the increased synthesis of growth factors in response to the damage (Smith *et al.*, 2002).

In conclusion, our data show that central auditory plasticity can be induced by peripheral lesions. The neurophysiological evidence of functional reorganization of the central auditory pathway in patients with acute unilateral ISSNHL can be found in the very early central processing of transient sounds arriving at the auditory cortex. The wide ranges of neuroanatomical and neurochemical changes observed in the central auditory pathway following peripheral hearing loss might underpin the neuromagnetic changes. The convergence of neurochemical, neuroanatomical and electromagnetophysiological studies at all levels of the auditory pathway could be a promising approach to thoroughly explore the mechanisms of functional neuroplasticity in ISSNHL. Further longitudinal studies are required to determine whether the temporal changes of dominance expression can serve as a prognostic indicator in clinical settings.

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Abbreviations

AEF, auditory evoked field; AEP, auditory evoked potential; ECD, equivalent current dipole; ISSNHL, idiopathic sudden sensorineural hearing loss; LLAEF, long-latency auditory evoked field; MEG, magnetoencephalographic; MLAEF, middle-latency auditory evoked field; N100m, a component of the long-latency auditory evoked fields peaking at ~100 ms; P50m, a component of the middle-latency auditory evoked fields peaking at ~50 ms.

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