Healthy-Side Dominance of Cortical Neuromagnetic Responses in Sudden Hearing Loss

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Previous brain imaging and mapping studies have reported findings indicating functional reorganization in the central auditory pathways of patients with profound unilateral hearing loss. This study reports for the first time to our knowledge, using a whole-head neuromagnetometer with monaural stimulation of both intact and affected ears, a pattern of healthy-side dominance for cortical neuromagnetic responses in adult patients in the early stage of idiopathic sudden sensorineural hearing loss, and a pattern of contralateral dominance is verified in controls.


Idiopathic sudden sensorineural hearing loss (ISSNHL), a disease of unknown pathogenesis, is widely varied in presenting signs and prognoses. Incidence increases from 4.6 of 100,000 per year in the second decade to 47.2 of 100,000 in the seventh decade; approximately one third of patients experience complete recovery of hearing after treatment. Localization of neural deficits in ISSNHL by audiometric examination/neuroradiology...
logical investigation and functional modulation of the auditory cortex by ISSNHL remains unclear.2,3

Recent functional magnetic resonance imaging (fMRI) studies have shown an altered auditory cortical response upon auditory stimulation in patients with acute unilateral ISSNHL4 and in those with sudden hearing loss caused by surgical complications.5 Magnetoencephalographic (MEG) studies also have shown that abrupt or chronic unilateral deafness of various causes can cause immediate and protracted changes in the function of auditory pathways in adult humans.6–9 The few reports characterizing auditory brain activation in patients with profound unilateral hearing loss or deafness suggest a dynamic plasticity of central auditory pathways. However, the aforementioned studies were limited to investigation of the cerebral responses invoked by auditory stimulation of the intact ear.

This MEG study investigates auditory-evoked magnetic fields on stimulation of both intact and affected ears in patients with acute unilateral ISSNHL of moderate degree. In the control group, a pattern of contralateral dominance was verified,4,10,11 whereas in the patient group a pattern of healthy-side dominance in the activity of auditory cortex is reported, regardless of the ear stimulated.

Subjects and Methods

Subjects

Nine right-handed adult patients with acute unilateral left (n = 5) or right (n = 4) ISSNHL (five men, four women; 27–72 years of age; mean, 43) were studied. Nine right-handed healthy volunteers with normal hearing (five men, four women; 25–42 years of age; mean, 32) served as controls. Diagnosis criteria were a sensorineural hearing loss of not less than 30dB HL over three contiguous frequencies in 3 days or less.12 No other neurological deficits or traumatic history were identified. Elapsed time for MEG examination after disease onset ranged from 3 days to 3 weeks. Written informed consent was obtained from each participant with a protocol approved by the Institutional Ethics and Research Committee of Taipei Veterans General Hospital.

Audiometric and Electrophysiological Examinations

All participants underwent pure tone audiometry examination to determine both air and bone conduction threshold, using test frequencies between 250 and 8kHz, and sensorineural hearing loss was impress. Because for all ISSNHL patients air and bone conduction thresholds were less than 65dB HL at 1kHz, the probing auditory stimulus was set at this frequency with an intensity of 70dB Sound Pressure Level (SPL) for the MEG experiment (Fig. a). This intensity was chosen to avoid further acoustic damage and cross-hearing contamination. Controls had normal pure tone audiometry results (<20dB HL for all frequencies). In addition, all ISSNHL patients had normal auditory brainstem responses for age-adjusted interaural latency difference; eight ISSNHL patients had reduced responses of distortion product otoacoustic emissions.

Magnetoencephalographic Paradigm

MEG measurements were performed in a magnetically shielded room using a whole-head 306-channel neuromagnetometer (Vectorview 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 (1kHz, 50-millisecond duration with 10 milliseconds for ramp up and down, respectively, 70dB SPL at the exit end of the plastic tube, and interstimulus interval of approximately 4 seconds) were delivered monaurally via molded earpieces using the SoundProbe program on a McIntosh computer. Affected and intact ears were monaurally stimulated in separate sessions separated by 2 minutes of rest. Trials with electrooculographic amplitudes exceeding 150µV were rejected. MEG signals were sampled at 400Hz and band-pass filtered at 0.03 to 100Hz. Approximately 90 artifact-free trials were averaged. An equivalent current dipole model was applied for fitting the MEG sources.10 Only dipoles with goodness of fit greater than 80% were accepted. T1-weighted MR images of subject brains were acquired using a 3.0T Bruker Medspec S300 system (Bruker, Kalsruhe, Germany) for MEG-MRI coregistration.

Data Analysis

The epoch analyzed ranged from 50 milliseconds before to 350 milliseconds after stimulation onset. The interval between –50 milliseconds and 0 milliseconds (trigger onset) was used as baseline. Differences in N100m dipole moments and latencies observed in different hemispheres were evaluated using the Wilcoxon signed rank test (threshold at p < 0.05).

Results

All participants, both controls and patients, had a detectable N100m dipole in the primary auditory cortex of each hemisphere (Table). When N100m activities for contralateral and ipsilateral hemispheres of all control subjects were pooled, respectively, from ear stimulation on both sides (18 measurements for each hemisphere), a contralateral dominance was noted (p = 0.008). A faster N100m response also was noted in the contralateral hemisphere (p = 0.006). A subset analysis (n = 9) of peak N100m moment made according to the ear stimulated showed a significant contralateral preponderance upon left ear stimulation (p = 0.008) but not upon right ear stimulation (p = 0.441). Interhemispheric latency differences were significant for left ear stimulation (p = 0.021) but insignificant for right ear stimulation (p = 0.161) on the subset level.

In ISSNHL patients, we noted that the contralateral hemisphere was significantly shorter in response latency (p = 0.019) at N100m as compared with that of ipsilateral hemisphere but did not observe a pattern of contralateral dominance (p = 0.744 for dipole moment) on a pooled data set from stimulation of both ears (responses from the hemisphere opposite the stimulated healthy or affected ear vs those from the ipsilateral hemisphere, 18 measurements). How-
Fig. Healthy-side dominance of neuromagnetic responses on monaural stimulation in unilateral idiopathic sudden sensorineural hearing loss (ISSNHL) patients. Patient 3 (left column, female, right ISSNHL) was studied on the seventh day and Patient 6 (right column, male, left ISSNHL) was studied on the fifth day after onset. (a) Pure tone audiometry results of air conduction examination. Both cases demonstrated a sensorineural hearing loss pattern. Dashed line denotes right ear threshold; the solid line indicates the left ear threshold. (b) Magnetic field pattern and source localization for monaural stimulation of the affected ear. Equivalent current dipoles (green arrows) are stronger over the hemisphere contralateral to the affected ear. (c) Magnetic field pattern and source localization for monaural stimulation of the healthy ears. Equivalent current dipoles (green arrows) are stronger over the hemispheres ipsilateral to the healthy ears. Dipole sources (red dots) are localized at the auditory cortices of bilateral temporal lobes in patients’ magnetic resonance images (MRIs). MRI views are displayed according to neurological convention; that is, subject’s right hemisphere is on the right side of the images.
ever, a healthy-side dominance of dipole moment was observed when responses from hemispheres ipsilateral to the healthy ears were pooled (18 measurements) and compared with that from hemispheres ipsilateral to the affected ears, regardless of the ear stimulated ($p < 0.001$; see Table; Fig). No interhemispheric difference in latency was observed ($p = 0.102$). On a subset level ($n = 9$), N100m dipoles were significantly stronger over the ipsilateral hemisphere upon healthy ear stimulation ($p = 0.008$). No interhemispheric latency difference was noted ($p = 0.361$). On affected ear stimulation, N100m dipoles were both significantly faster and stronger over the contralateral hemisphere ($p = 0.011$ for dipole moment; $p = 0.015$ for latency).

### Discussion

Our finding of contralateral dominance in auditory-evoked MEG response for peak dipole moment on monaural stimulation on the controls is in line with previous MEG and fMRI reports.\cite{1,2,3} This hemispheric lateralization can be attributed to the prevailing cross-hemispheric projections in the auditory pathway and has been suggested to service in part the function of sound localization.\cite{4} Contralateral N100m activities have been reported to occur 4 to 10 milliseconds earlier than ipsilateral ones on monaural stimulation.\cite{5} In this study, N100m peaked, on average, 3.3 milliseconds earlier on right ear stimulation over the contralateral hemisphere. The lack of a significant interhemispheric latency difference in the current study further suggests that auditory perception and sound localization primarily rely on a predominant contralateral mechanism.
spheric latency difference can be ascribed to the small sample size with mixed genders and different ages.\textsuperscript{15}

Contralateral dominance in response to stimulation of the intact ear was lost in patients with acute unilateral ISSNHL and was replaced by a pattern of healthy-side dominance. To our knowledge, this is the first MEG study reporting such neuromagnetic responses to monaural stimulation of both healthy and affected ears of patients with acute unilateral ISSNHL. N100m dipoles were significantly stronger over the hemisphere ipsilateral to the healthy ear regardless of whether the intact or the affected ear received monaural stimulation (see Table; Fig). Because the patients studied in previous literature had mainly chronic disease and either were deaf or had profound hearing loss, previous MEG studies investigated the brain responses to healthy ear stimulation only and reported a response preponderance over the ipsilateral hemisphere.\textsuperscript{7,8} Our novel MEG findings are corroborated by a recent fMRI study in which a loss of contralateral dominance on healthy ear stimulation in patients with unilateral deafness was reported.\textsuperscript{4} Furthermore, fMRI evidence of healthy-side dominance can be noted for spatial extent (significant voxels) as activated by auditory stimulation.\textsuperscript{4} The lesion site in ISSNHL patients may be of cochlear origin because auditory brainstem response results of these patients are all within normal limits and eight of them have reduced distortion product otoacoustic emission response. Our MEG findings are in line with the observations from animal studies in which an increased excitability of auditory cortex emerges after cochlear ablation on the opposite side.\textsuperscript{16,17} These converging findings indicate that unilateral sensorineural hearing loss may modify information processing in the central auditory pathways in the early stage.

Despite a normal auditory brainstem response result, neuroplastic changes can occur to the higher auditory pathway.\textsuperscript{6} The actual mechanisms of functional reorganization and the significance underlying the pattern of “healthy-side dominance” (ie, preservation of contralateral dominance on stimulation of the affected ear but ipsilateral dominance on stimulation of the healthy ear) are currently unknown. The observations cannot be ascribed to the aging effect.\textsuperscript{11} One possibility is a reduction of interhemispheric inhibition,\textsuperscript{18} which could be one facet of overall adaptive plasticity in ISSNHL, mirroring the functional status of the patients in an operational context. A more plausible explanation is that a functional neuroplasticity occurs in the hemisphere opposite the affected ear where the AI neurons with equidominance or ipsilateral aural dominance become more responsive to ipsilateral aural input in compensation for loss of optimal binaural interaction for effective information processing.\textsuperscript{16,19} This plasticity can be coupled with structural changes because damage to the peripheral receptor organ in animal studies has been demonstrated to induce cellular changes in the central auditory pathway and auditory cortex.\textsuperscript{20}

Our preliminary report invites further studies on a larger group of patients to correlate neuromagnetic changes with the time from onset, severity of functional impairment, and psychoacoustics. A longitudinal study is also needed to show whether such neuromagnetic responses change with recovery of function or persist in patients with long-standing hearing loss.

This study was funded by the National Science Council (902314B075124, 902314B075115, 902511S010001, 912314B0-75069 J.-C.H.), Taipei Veterans General Hospital (90400, 90443, 91361, 91380 J.-C.H.), and the Ministry of Education of Taiwan (89BFA21401 J.-C.H., L.-F. C., D.-M.N., L.-P.H.L.).

We thank C.-M. Cheng and C.-Y. Lin for MEG technical aid, and Drs Ing-T. Kuo and W.-J. Kuo for statistical assistance.

References

N19S, a New SOD1 Mutation in Sporadic Amyotrophic Lateral Sclerosis: No Evidence for Disease Causation

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In a group of 331 sporadic amyotrophic lateral sclerosis (ALS) cases, we identified a new Cu/Zn superoxide dismutase single base substitution, N19S, in two patients. In the first case, seven healthy family members of 15 carried the substitution. Controls (n = 268) and familial ALS index cases (n = 180) were screened and one control subject with N19S was identified. Our data show that, despite a possible role of susceptibility factor for ALS, N19S alone cannot be considered as a direct cause for the disease.

Ann Neurol 2003;53:815–818

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder leading to motoneuron loss in spinal cord and motor cortex. The age of disease onset is approximately 55 years old, and death usually occurs between 3 to 5 years after onset. Familial inheritance has been shown in 10 to 20% of ALS cases among which 20% have a mutation in the Cu/Zn superoxide dismutase (SOD1) gene.

To date, more than 90 SOD1 mutations have been reported. SOD1 mutations are thought to be responsible for an increased toxicity resulting in motor neuron damage. They are found in all five exons, but exon 4 has the most mutations (37%). Most of the mutations have a dominant inheritance, except for the Scan-