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Changes of auditory evoked magnetic fields in patients after acute cerebral infarction using magnetoencephalography☆

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Abstract
Auditory evoked magnetic fields were recorded from 15 patients with acute cerebral infarction and 11 healthy volunteers using magnetoencephalography. The auditory stimuli of 2 kHz pure tone were binaurally presented with an interstimulus interval of 1 second. The intensity of stimuli was 90 dB and the stimulus duration was 8 ms. The results showed that the M100 was the prominent response, peaking approximately 100 ms after stimulus onset in all subjects. It originated from the area close to Heschl's gyrus. In the patient group, the peak latency of M100 responses was significantly prolonged, and the mean strength of equivalent current dipole was significantly smaller in the affected hemisphere. The three-dimensional inter-hemispheric difference of the M100 positions was increased in the patient group. Our experimental findings suggested that impairment of cerebral function in patients with acute ischemic stroke can be detected using magnetoencephalography with the higher spatial resolution and temporal resolution. Magnetoencephalography could provide objective and sensitive indices to estimate auditory cortex function in patients with acute cerebral infarction.

Key Words
acute cerebral infarction; cerebral ischemia; magnetoencephalography; auditory evoked magnetic fields; equivalent current dipole; Heschl's gyrus; brain functional impairment; nerve injury; regeneration; neural regeneration

Research Highlights
(1) Auditory evoked magnetic fields were detected using magnetic source imaging, which combines magnetoencephalography and MRI.
(2) This study provides the first confirmation that the primary auditory cortex is located in Heschl's gyrus in normal adults, using a biomagnetism method.
(3) Irregular waveform of auditory evoked magnetic fields, decreased equivalent current dipole strength in the affected hemisphere, delayed latency of M100, and asymmetric spatial equivalent current dipole position were found in patients with acute cerebral infarction. Clear asymmetry of bilateral auditory cortical areas was apparent.

Abbreviations
MSI, magnetic source imaging; ECD: equivalent current dipole

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INTRODUCTION

With developments in neuroscience, particularly the clinical application of neuroimaging techniques such as CT and MRI, the volume and location of an infarct can be identified at an early stage. However, the degree of impairment in brain function cannot be directly assessed[1-3]. Magnetoencephalography primarily reflects intracellular current flow, thus providing relatively direct information concerning the living neural tissue[4-5]. This method combines the anatomical superiority of MRI with magnetoencephalography to enable anatomic localization of magnetoencephalography dipoles on the subject's own MRI scan, a procedure known as magnetic source imaging (MSI). Auditory fibers pass through the brainstem at the level of the inferior cerebellar peduncle, ascending through the cochlear nuclei, lateral lemniscus, inferior colliculus, and medial geniculate body, and finally reach the posterior transverse gyrus (Heschl's gyrus) in the superotemporal cortex, the primary auditory area, *via* the auditory radiations. Lesions anywhere in this pathway can cause auditory dysfunction[6]. Magnetoencephalography can reveal impaired function of the auditory cortex that is not observable with MRI, using auditory evoked magnetic field responses in stroke patients[7-8].

In humans, auditory evoked magnetic fields can be elicited by auditory stimuli[9-10]. Magnetoencephalography enables mapping of the auditory cortex accurately and non-invasively based on auditory evoked magnetic fields[11]. The current flow in activated neurons of the auditory cortex can create extremely weak magnetic fields, which are detectable outside the head using super-conducting quantum interference device sensors[12]. The field strength of auditory evoked magnetic fields is maximal at both ends of the sylvian fissure[13]. This field distribution resembles that generated by a current dipole located 30–40 mm below the scalp and oriented almost perpendicular to the sylvian fissure[14].

Previous studies of auditory evoked magnetic fields have mainly examined cortical responses to different auditory stimuli in patients with Parkinson's disease, schizophrenia, epilepsy and normal subjects[15-18]. There are few studies of changes in auditory evoked magnetic fields in acute cerebral infarction patients[19]. Further investigation is needed to extend knowledge of this issue.

In the current study, magnetoencephalography was used to examine auditory evoked magnetic field characteristics in the primary auditory cortex, including peak latencies, waveforms and strength, comparing between patients with ischemic stroke and control subjects. In addition, we used MSI to explore the interhemispheric symmetry among the investigated parameters, as well as spatial position differences of auditory evoked magnetic fields.

RESULTS

Quantitative analysis and clinical information of subjects

A total of 15 patients with acute unilateral cerebral infarction, aged between 37 and 70 years, were recruited in this study (three female, 12 male). In addition, another 11 healthy volunteers, who matched the patients in age and gender, were also involved in the study. All participants were included in the final analysis. Subjects' clinical information is shown in Table 1.

Table 1 Baseline information for participants

Patients No.	Gender	Age (year)	Magnetoencephalography examination (days after onset)	Lesions
1	M	38	9	Left temporal, occipital lobe
2	M	53	6	Left suv-parietal, occipital lobe
3	M	40	20	Pontine
4	M	45	15	Right parietal lobe
5	M	74	22	Right sub-parietal basal ganglia region thalamus
6	M	73	10	Left basal ganglia region, sub-parietal
7	F	61	10	Right basal ganglia region
8	F	74	22	Left occipital lobe, basal ganglia region
9	M	53	9	Right internal capsule
10	M	66	4	Right sub-parietal, basal ganglia region
11	M	78	7	Left sub-frontal lobe, pontine
12	F	48	13	Left frontal, parietal lobe, basal ganglia region
13	M	62	1	Right occipital lobe
14	M	66	10	Right temporal lobe, basal ganglia region
15	M	76	13	Right frontal, sub-parietal lobes, basal ganglia region

M: Male; F: female.

Delayed latency and abnormal waveforms in patients with cerebral infarction

The two earliest components M50, M100 (*i.e.* around 50 ms and 100 ms after the tone burst stimulus, respectively) were identified. Previous auditory evoked magnetic field studies from healthy volunteers focused on the M100, which is the largest and most commonly observed peak in the waveforms[20]. As such, auditory evoked magnetic fields were evaluated using the M100 in the current study.

The mean latency of the M100 in the patient group was 97.0 ± 6.0 ms, longer than that in the control group (89.3 ± 7.9 ms, $P < 0.05$). In auditory evoked magnetic fields of cerebral infarction patients, the waveform was irregular, the latency of the M100 was delayed, and the peak was attenuated (Figure 1).

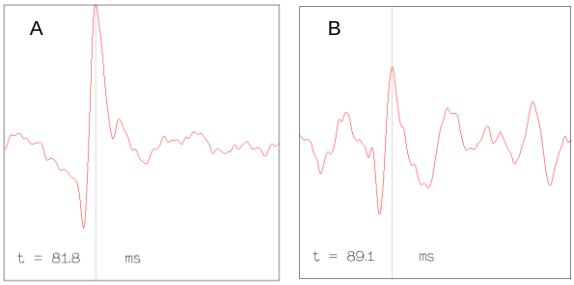

Figure 1 The response of the AEF M100 latency and waveform from a healthy subject (A, male, 63 years old) and a patient (B, female, 61 years old, infarct site: right basal ganglia region), at the primary auditory cortex individually.

The AEF waveform from the healthy subject shows a typical M100, with a peak at 81.8 ms. In contrast, an irregular M100 waveform was exhibited by the patient; a delayed and attenuated peak shift is seen at 89.1 ms on the affected hemisphere. Test unit: ms. Dash line represents the position of wave peak. AEFs: Auditory evoked magnetic fields.

Equivalent current dipole (ECD) strength abnormalities in patients with cerebral infarction

The mean strength of ECD was 17.2 ± 4.8 nA in the affected hemisphere of patients, which was significantly smaller than in the control subjects (24.7 ± 9.6 nA, $P < 0.01$) and the unaffected hemisphere (30.5 ± 5.9 nA, $P < 0.01$). The mean strength of ECD in the unaffected hemisphere of patients was larger than that in the control subjects ($P < 0.01$).

As shown in Figure 2, the dipole moments were 34.6 nA in the unaffected hemisphere and 17.9 nA in the affected hemisphere in patient 7. The strength of ECD in the affected hemisphere was significantly smaller than that in the unaffected hemisphere in this patient. The M100 strength of ECD in the unaffected hemisphere was much greater than that in control subjects 10 (24.8 nA).

ECD spatial position abnormalities in patients with cerebral infarction

Table 2 shows the contrast of M100 ECD spatial inter-hemisphere symmetry among the patient and control groups. ΔX, ΔY, and ΔZ respectively represent the absolute value of the coordinate variations on the X, Y, and Z axes. Three-dimensional inter-hemisphere spatial symmetry of the M100 ECD position is represented by $(\Delta X^2 + \Delta Y^2 + \Delta Z^2)^{1/2}$.

The mean distance variations of M100 ECD on X, Y, and Z coordinates (ΔX, ΔY, and ΔZ) were 11.1 ± 0.1, 3.7 ± 2.1, and 3.2 ± 2.3 in the patient group and 1.2 ± 1.0, 0.2 ± 1.0, and 0.4 ± 0.1 in the control group. This was significantly higher in the patient group with a mean variation of 18.6 ± 3.3 mm, compared with the control group for the Heschl's gyrus ECD position ($P < 0.01$). These findings indicate that the bilateral M100 ECD spatial positions were largely symmetrical in the control group, but exhibited abnormal asymmetry in the patient group.

The M100 ECD positions were superimposed on the subject's brain MRI with the aid of anatomical reference points in magnetoencephalography and MRI examinations, to form the MSI. The inter-hemispheric asymmetry of ECD position in the patients is significantly larger than in the healthy subjects (Figure 3).

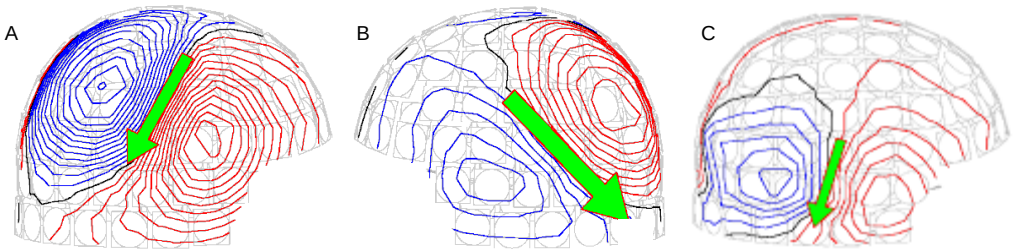

Figure 2 The isofield contour map shows the M100 strength of an equivalent current dipole on the right hemisphere in healthy volunteer (A; male, 63 years old) and bilateral hemispheres in patients (B, C; female, 61 years old, infarct site: right basal ganglia region), in the primary auditory cortex.

The green arrows represent the position, orientation and strength of the corresponding equivalent current dipole projected on the head surface for each peak. The blue concentric circles show magnetic flux entering the head and red concentric circles show flux exiting the head, respectively. Green arrows indicate dipole moments, which show the strength of the M100 response.

Table 2 The comparison of asymmetry values (mm) of inter-hemispheric differences of the M100 ECD positions between patients and healthy controls

Group	*n*	LH ECD			RH ECD			IHDV ECD $(\Delta X^2+\Delta Y^2+\Delta Z^2)^{1/2}$
		X	Y	Z	X	Y	Z	
Patient	15	−46.6±2.5	3.8±10.1	50.2±6.8	57.7±2.6	7.5±8.0	53.4±9.1	18.6±3.3
Healthy	11	−52.1±6.0	9.8±9.0	49.0±8.5	53.3±5.0	9.6±8.0	48.6±8.4	11.8±5.6
t		2.85	1.56	0.38	2.63	0.68	1.37	3.89
P		0.01	0.13	0.71	0.02	0.51	0.18	0.00

Data are expressed as mean ± SD and analyzed with a two-sample *t*-test. ECD: Equivalent current dipole; LH ECD: the M100 ECD positions in the left hemisphere; RH ECD: the M100 ECD positions in the right hemisphere; IHDV ECD: the M100 ECD difference values inter-hemispherically; ΔX, ΔY, and ΔZ represented the absolute value of the coordinate variations on the X, Y, and Z axes, respectively. $(\Delta X^2+\Delta Y^2+\Delta Z^2)^{1/2}$: The spatial symmetry of the M100 ECD positions inter-hemispherically.

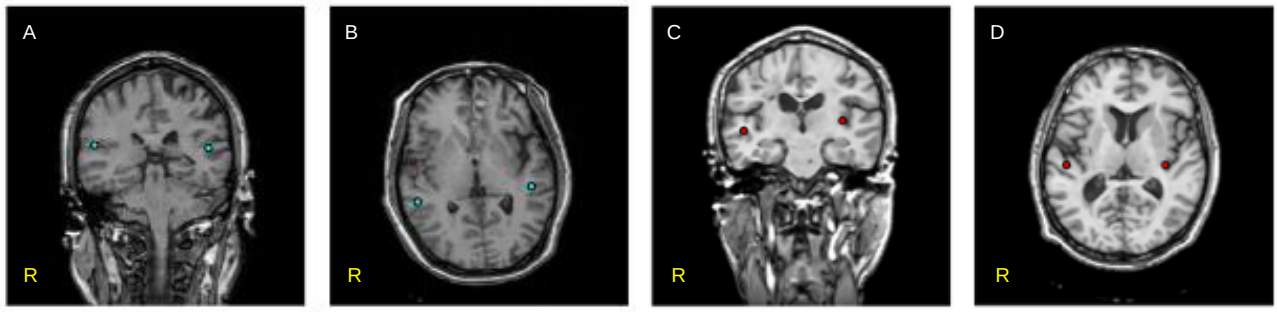

Figure 3 Comparison of magnetic source imaging between a patient and a healthy volunteer.

The coronal and axial T1WI MRI demonstrate the positions of the M100 equivalent current dipole of bilateral hemispheres in a healthy volunteer (A, B; male, 63 years old, labeled as blue spot) and in a patient (C, D; female, 61 years old, infarct site: right basal ganglia region, labeled as red spot). R: Right.

DISCUSSION

Magnetoencephalography is a non-invasive technique for detecting magnetic signals in the brain, and has recently been used for examining brain functions. Using a super-conducting quantum interference device and magnetically shielded systems, magnetoencephalography can detect the weak magnetic fields that are produced by neuronal electrical activity precisely to 50–500 fT[21]. Magnetoencephalography permits detection of the exact generator areas of these components[22]. The heterogeneity of head conductivity or interference of skin potentials can affect electrically evoked potentials, but not magnetic fields. Mathematical procedures based on simplified assumptions about the biophysical nature of neural activity; the shape and electrical conductivity properties of the brain, skull, and scalp allow magnetoencephalography data to be used to infer the three-dimensional spatial position of neuronal regions that generate normal or pathological neuromagnetic activity patterns. The temporal resolution and spatial resolution of magnetoencephalography can reach 1 ms and 1 mm, respectively[23].

Changes in latency, waveform and ECD strength in the affected hemisphere

The present study revealed abnormal M100 auditory evoked magnetic field responses to stimuli in the Heschl's gyrus of the affected hemisphere in patients with acute cerebral infarction. Delayed M100 peak latencies, abnormal waveforms, and diminished ECD strengths were observed.

What is the cause of these abnormalities? Nagata *et al* [24] observed that the rhythmical electrophysiological activities measured by quantitative electroencephalography appear to correlate well with positron emission tomography indices. Toyoda *et al* [8] reported that cerebral hemodynamic disorders in and around the superotemporal cortex also cause abnormal auditory evoked magnetic field responses. Significant correlations between auditory evoked magnetic fields and hemispheric regional cerebral blood flow suggest that hemodynamic disorders in areas surrounding the auditory cortex, including the medial geniculate body and auditory radiations, also affect auditory evoked magnetic fields. Bundo *et al* [25] reported a marked decrease of somatosensory evoked magnetic field M20 strength in the affected hemisphere of patients with neurological impairment. Furthermore, there was a significant correlation between resting regional cerebral blood flow and the strength of

the M20, indicating that the extent of the M20 reduction correlated with the severity of cortical ischemia. On the other hand, it has been reported that a metabolic depression occurs in the thalamus and basal ganglia in the presence of cortical ischemia, and similar subcortical ischemic lesions induce cortical metabolic depression, which is known as cerebral diaschisis[26]. The reduction of the M20 of the SEF in the affected hemisphere might reflect not only the severity of cortical damage but also the cerebral diaschisis caused by cortical ischemia[25]. Therefore, the changes observed in the present study may reflect a partial or total auditory cortex deafferentation. One possible explanation for this phenomenon is the activities of cortical neurons decrease due to the hypoxic-ischemic impairment. Another possibility is that this pattern results from damage to the subcortical fibers projecting to Heschl's gyri caused by cerebral ischemia.

Increased ECD strength in the unaffected hemisphere

The increased ECD strength in the unaffected hemisphere observed in the present study is in accord with previous reports. Several somatosensory evoked potential studies have found enhanced responses in the unaffected hemisphere of stroke patients[27]. In animal experiments, hemispheric lesions have been found to reduce neuronal inhibition in areas remote from the lesion, including the opposite hemisphere[28]. Furthermore, Netz *et al* [29] applied transcranial magnetic stimulation to patients with stroke-induced motor hemiparesis and observed increased excitability in the non-affected hemisphere. This phenomenon appears to be related to cortical lesions in the affected hemisphere[30]. Neocortical infarction could lead to hyperexcitability of the contralateral hemisphere, an action largely mediated by transcallosal fibers[31]. Meanwhile, cortical involvement appears to play a key role in unaffected hemisphere "disinhibition", because all patients with an increased unaffected hemisphere response exhibited evidence of cortical infarction. The silence of cortical interneurons in the affected hemisphere has been proposed as the common neural mechanism explaining these findings[32].

The asymmetrical spatial positions of ECD

In the present study, the M100 auditory evoked magnetic field ECD spatial positions were significantly asymmetrical based on coordinates, as shown by the MSI results in the patient group. This change was likely to have been caused by the shift of cerebral infarct tissue due to edema, especially in the anatomical Heschl's gyrus[33]. In summary, using magnetoencephalography we demonstrated that cerebral infarction can result in delayed peak latency, decreased ECD strength in the affected hemisphere and increased inter-hemispheric asymmetry of M100 ECD positions in the auditory evoked magnetic field. Magnetoencephalography can provide objective and sensitive indices to estimate auditory cortex function in patients with acute cerebral infarction.

SUBJECTS AND METHODS

Design

A controlled clinical neuroimaging study.

Time and setting

The study was performed from March 2009 to July 2010 at Hebei General Hospital in Shijiazhuang, China.

Subjects

A total of 15 adult patients with acute unilateral cerebral infarction (mean age 59.4 ± 5.9 years, three females, 12 males) were recruited through the Department of Neurology, Heibei General Hospital, China. Patients were excluded from the study if they met the following criteria: history of psychiatric disorders or previous neurological diseases, and presence of pace makers or metallic material in the skull. Patients with hearing difficulties and those unable to tolerate magnetoencephalography studies were also excluded. Among the included groups, there were nine cases with hypertension, and five cases with diabetes in their medical history. Evidence of atherosclerosis was found in 12 patients. Cerebral infarcts were diagnosed based on clinical history and evidence of motor and/or sensory deficit. All diagnoses were confirmed by cranial MRI. A lesion was classified as "cortical" when mainly cortical areas were involved; and classified as "subcortical" when there was no visible cortical involvement, and the basal ganglia, thalamus, or internal capsule were affected[34]. According to these methods, there were three confirmed cases of subcortical infarcts, seven cases of basal ganglia region infarcts, and five cases of subcortical combined with cortical infarcts.

Healthy volunteers were recruited among members of the hospital staff and their relatives. Eleven healthy volunteers aged from 46 to 73 years (mean age 56.3 ± 3.59 years, four females, seven males) with no history of stroke, hypertension, diabetes mellitus or other neurological disorders served as controls. All subjects exhibited normal cranial MRI scan results.

Informed consent was obtained from all patients and control subjects before magnetoencephalography studies.

Methods

All patients were examined within 1 month of acute unilateral cerebral infarction course.

Placement of electrooculogram electrodes and coils

Electrooculogram electrodes were placed on the right infraorbital foramen and left pterion. To decrease the electrical resistance between the electrodes and skin, the skin was cleaned with alcohol and paste was applied to the electrodes before placement. Coils were placed in both frontal regions and both parietal regions to determine the position of the head[35-36].

Adjustment of head position

Subjects were asked to sit on a custom-made chair and to wear special spectacles connected to a head-position indicator. The positions of the stylus tip (connected to the head-position indicator) at the bilateral preauricular points and nasion were recorded by clicking the corresponding button in the head-position indicator dialog[37-38]. If the distance between the two preauriculars exceeded 5 mm, this procedure was repeated. The head coordinate system was defined by the head-position indicator as follows: The X-axis passed through the preauricular points with positive values on the right, the Y-axis was perpendicular to the X-axis, passing through the nasion and the positive axis pointing towards the nose, and the Z-axis pointed up, perpendicular to the X, Y-plane[39-40].

Sound stimuli

Subjects quietly sat under the helmet, and were instructed to position their head in the center of the helmet. The positions of both preauricular points and the nasion, as well as the head shape, were measured for each subject using a three-dimensional digitizer, and a sensor position indicator system. Each subject was instructed to remain awake and to avoid moving their head during measurement. They were instructed to keep their eyes open, to minimize eye movements and eye blinks, and to silently count the number of stimuli. Subjects were monitored using a video camera.

Tone bursts of 2 kHz and 90 dB sound pressure level at the ear with 8 ms duration were presented to the patient's ear, contralateral to the brain lesion, or the right ear of control subjects, through a 5 m long plastic tube of 15 mm inner diameter terminating in an inserted earphone. The interstimulus interval was 1 000 ms. Magnetoencephalography was recorded from 150 ms before the stimuli to 750 ms after the stimuli. The sound stimulation system was constructed by Neuroscan, El Paso, USA, Stim Audio System 1105.

Magnetoencephalography data acquisition and data analysis

Magnetoencephalography was conducted in a magnetically shielded room with a 306-channel whole-head biomagnetometer (VectorView 306 whole-head biomagnetometer, Neuromag, Helsinki, Finland). MRI scanning was performed using a 1.5 Tesla MRI system (Signa, GE, USA). A spoiled gradient recalled sequence was used during the process, consisting of 124 sequential sagittal slices of 1.5 mm thickness, no space, flip angle 30° with a resolution of 256 × 192 points on a field of view of 300 × 300 mm, time of repetition = 17 ms, time of echo = 3 ms. Before MRI scanning, 2 mm-diameter markers were used to indicate fiducial locations. The locations of the fiducial markers were used for acquisition of both magnetoencephalography and MRI and to superimpose magnetoencephalography data and MRI data in the same coordinate frame.

The signals of the brain were band pass filtered at 0.03–300 Hz on line and digitized at 1 000 Hz. Electrooculography was measured during magnetoencephalography data acquisition. Signals above 150 μV were automatically removed to eliminate artifacts caused by eye movement. The data acquisition computer automatically averaged readings according to the pure tone. Brain activity with double dipolar patterns was modeled with ECD. An ECD is the dipole that best explains the field pattern at a given instant in time. The shape of the brain was modeled using the boundary element model. Once neuroanatomical data were available from magnetic resonance images, the functional magnetoencephalography data were integrated with structural brain data to produce MSI[41-42].

The data were analyzed off-line with a band pass of 0.5–30 Hz, to prohibit the effects of low frequency and high frequency environmental noise. Three-dimensional MRI reconstruction was performed using magnetoencephalography-Segmentation software (Neuromag Company, Helsinki, Finland).

Statistical analysis

Data are expressed as mean ± SD. The data were analyzed using a two-sample *t*-test, using SPSS 10.0 for windows software package (SPSS, Chicago, IL, USA). $P < 0.05$ was used to indicate statistically significant differences.

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Author contributions: Peiyuan Lv was in charge of funds. Peiyuan Lv and Zhanyong Sun conceived and designed this study. Jilin Sun, Jie Wu and Yujin Wu provided and integrated data. Chunfeng Song, Ling Li, Wenzhu Cui and Yanhong Dong

collected and analyzed data. Zhanyong Sun and Chunfeng Song wrote and revised the manuscript. Jianhua Wang contributed to statistical analysis.

Conflicts of interest: None declared.

Ethical approval: The study was approved by Ethics Committee, Hebei General Hospital, China.

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