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Authors

Huang, M
Davis, LE
Aine, C
et al.

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MEG response to median nerve stimulation correlates with recovery of sensory and motor function after stroke

M. Huang[a,b,*], L.E. Davis[a,c], C. Aine[a,b,c], M. Weisend[a,b], D. Harrington[a,c], R. Christner[a], J. Stephen[a,b], J.C. Edgar[a], M. Herman[a], J. Meyer[a], K. Paulson[a], K. Martin[a], R.R. Lee[a,b]

[a]*Center for Functional Brain Imaging, Building 49 (114M), New Mexico VA Health Care System, 1501 San Pedro Drive, SE, Albuquerque, NM 87108, USA*
[b]*Department of Radiology, School of Medicine, Health Sciences Center, University of New Mexico, Albuquerque, NM 87131, USA*
[c]*Department of Neurology, School of Medicine, Health Sciences Center, University of New Mexico, Albuquerque, NM 87131, USA*

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Abstract

Objective: Hemiparesis due to damage by stroke in primary motor cortex (MI) or its underlying projections presents a problem for functional neuroimaging technologies that attempt to evaluate the neurophysiological basis for restoration of motor function. Traditional assessments of MI function require patients to move their fingers, hands, or limbs, which can be either impossible or markedly compromised after stroke. We recently demonstrated in normal subjects that magnetoencephalography (MEG), a non-invasive neuromagnetic functional imaging technique, detects neuronal response elicited by electrical median nerve stimulation in MI, as well as primary somatosensory cortex (SI). In the present study, we used the MEG response from median nerve stimulation to investigate the recovery of primary motor and somatosensory in acute ischemic stroke patients.

Methods: Twelve patients with unilateral ischemic strokes that affected sensorimotor functions of their hand were studied in the acute stage (4.4 ± 1.2 days, mean ± SD) and during a 1-month follow-up (38.6 ± 5.6 days, except for one patient's follow-up done 6 month after stroke).

Results: Among the multiple cortical sources localized after median nerve stimulation, one source localized to SI and another localized to the vicinity of MI. Changes in the source strengths of the first component post-stimulus of MI and SI correlated with the extent of recovery of sensorimotor functions as determined by neurological exams.

Conclusions: This study provides a novel way of indirectly assessing MI function using MEG during the acute stroke phase, when many patients often cannot perform motor tasks due to paralysis.

Keywords: Stroke; Magnetoencephalography; Motor; Somatosensory; Median nerve

1. Introduction

In the present study, functional changes in motor and somatosensory systems in ischemic stroke patients were studied longitudinally using magnetoencephalography (MEG) measurements. Previous somatosensory studies using MEG and somatosensory evoked potential (SEP) on stroke patients have revealed abnormalities in the 20 ms component with an absent, weak, or delayed response (La Joie et al., 1982; Reisecker et al., 1986; Knecht et al., 1996; Franssen et al., 1992; Maclin et al., 1994; Kalita and Misra, 1997, 1998; Hijosa et al., 1998; Wikström et al., 1999; Forss et al., 1999; Bundo et al., 2002). Other MEG work has also found that some chronic stroke patients showed abnormal inter-hemispheric asymmetries for the primary somatosensory sources (Rossini et al., 2001), particularly patients with subcortical damages. Still, it has been difficult to use MEG to study motor function in acute stroke patients with motor deficits, because motor responses in acute sensorimotor stroke patients are generally weak. Consequently, a large number of trials are needed in order to generate averaged responses with a sufficient signal to noise ratio (SNR). To generate good SNR for the MEG motor responses, the patient needs to lift his/her finger quickly, with a large displacement, for hundreds of repetitions in

* Corresponding author. Tel.: +1-505-265-1711x4855; fax: +1-505-256-5708.
E-mail address: mhuang@unm.edu (M. Huang).

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a time-locked fashion. In reality, however, finger movements of many stroke patients are slow, weak, and not time-locked.

A solution to this problem was first suggested by findings showing that pyramidal tract neurons in primary motor cortex (MI) receive strong topographically organized afferent input from sensory receptors in the periphery (Rosen and Asanuma, 1972; Lemon and Porter, 1976; Wong et al., 1978; Huang et al., 1989; Davidoff, 1990; Baldissera and Leocani, 1995). The peripheral sensory input to MI is through two paths. The first is a path that involves direct input to MI from the thalamus, through ventro-posterior lateralis par oralis (VPLo) and ventro-posterior lateralis par caudalis (VPLc) (Asanuma et al., 1980; Jones et al., 1979; Lemon and van der Burg, 1979; Lemon, 1981; Leichnetz, 1986; Davidoff, 1990; Darian-Smith et al., 1990; Padel and Relova, 1991; Zarzecki, 1991; Mauguiere and Desmedt, 1991; Butler et al., 1992; Hirashima and Yokota, 1997). The second path involves cortico-cortical inputs from the primary somatosensory cortex (Brooks et al., 1961; Pandya and Kuypers, 1969; Jones et al., 1978; Huerta and Pons, 1990; Zarzecki, 1991; Darian-Smith et al., 1993). Thus, sensory input, which activates the sensory cortex, is very effective in altering pyramidal tract activity (Asanuma and Arissian, 1984), though it is debatable by which pathway the early signal arrives at MI after sensory stimulation.

These results guided investigations into whether somatosensory input produced by median nerve stimulation, a task traditionally used for testing the viability of primary somatosensory (SI) cortex, generated an MI signal strong enough to be measured by electromagnetic techniques in the macro scale. Earlier studies of median nerve stimulation using MEG, scalp EEG, and electrocorticography reported contradictory results (Allison et al., 1991a,b; Kawamura et al., 1996). Recently, we demonstrated in healthy adults that MEG can reliably identify a source on the anterior bank of the central sulcus, in addition to the primary somatosensory source on the posterior bank of the central sulcus, contralateral to the site of median nerve stimulation (Huang et al., 2000). We also showed that this anterior central sulcus source was approximately at the same location as the MI source obtained by MEG during a finger-lifting task (Huang et al., 2000). Both sources showed two peaks of near opposite polarities, the first peaked around 20 ms and the second peaked around 30 ms, although the latter was not always distinguishable from later activities occurring around 40 ms in all subjects. For most individuals, activity of the posterior central sulcus sources slightly preceded (1–2 ms) the anterior central sulcus sources. These findings showed that median nerve stimulation can provide reliable spatial and temporal information about MI and SI functions.

In the present study, acute stroke patients received median nerve stimulation during MEG recordings to assess the viability of both MI and SI function and monitor of recovery. MEG, instead of EEG, was used because MEG is much less affected by problems associated with estimating the conductivity profile which results in MEG's better source localization accuracy than EEG in the cortex (Leahy et al., 1998). Patients were tested within 1 week of stroke onset and then tested again at least 1 month later. We chose 1 month as the follow-up time to detect early changes of the sensorimotor function during stroke recovery. In the sensorimotor system, recovery from stroke occurs predominantly in the initial a few weeks, but may last to 3 months, and in same cases, recovery can continue at a much slower pace throughout the first year (Kotila et al., 1984; Kelly-Hayes et al., 1989). A number of mechanisms are thought to explain the recovery: (1) resolution of edema or reperfusion of the ischemic penumbra; (2) unmasking of existing but functionally inactive pathways, particularly, unmasking of latent synapses involving modulation of GABAergic inhibition; (3) redundancy of brain circuitry allowing alternative pathways to take over functions; and (4) sprouting of fibers from surviving neurons and formation of new synapses (Lee and van Donkelaar, 1995; Chen et al., 2002). Having a follow-up testing at 1 month rather than later may allow us ultimately to study the physiological mechanism(s) that are actually contributing to most of a patient's recovery.

We hypothesized that changes in locations and/or temporal dynamics (source strength, peak latency) of neuronal activity due to stroke recovery would be detected in MI and SI. Specifically, recovery of function was expected to be associated with (1) increased dipole strength and (2) presence of a 20 ms peak component. Furthermore, if the location of a source(s) changed with recovery, this might be suggestive of reorganization of function. We also predicted that the change in dipole strength would correlate with the results from neurological exams of motor and sensory function.

2. Patients and methods

2.1. Neurological and magnetic resonance imaging (MRI) examinations

Study participants included 12 patients (11 male, age: 41–81, mean 61.1 years) diagnosed with first-ever acute ischemic stroke affecting primary sensorimotor functions of the hand, as determined by neurological exam and MRI. Consent forms approved by the Human Research Review Committee at the University of New Mexico and the Research Committee at the New Mexico VA Health Care System were signed by the patients or their spouses. The graphesthesia testing was used as the neurological exam to measure the sensory function of the stroke-affected hand. During this test, graphesthesia was determined by writing numbers on both palms with the eyes closed and noting how many were correctly perceived. The scores were converted to 6 points with 0 for 'no sensation,' 1–2 for 'severe sensory loss,' 3 for 'moderate sensory loss,' 4 for 'mild sensory

Table 1
Neurological, MRI, and MEG assessments

Patient	Age (years)	Gender	Acute neurological exam (days)	Acute MEG exam (days)	Acute MRI exam (days)	Follow-up neurological and MEG exam (days)
1	73	M	5	6	1	41
2	46	M	3	4	5	185
3	73	M	5	5	8	33
4	54	M	5	7	4	48
5	41	M	4	4	1	42
6	81	M	3	4	2	39
7	46	F	4	5	2	32
8	58	M	3	5	2	37
9	72	M	3	3	2	31
10	72	M	2	3	2	37
11	59	M	2	4	2	47
12	58	M	1	3	2	38

loss,' and 5 for 'normal sensory function.' Functional capacity of hand movement of the stroke-affected side was assessed using the Medical Research Council scale (Medical Research Council, 1982) wherein 0 for 'absence of any movement or contraction,' 1 for 'flicker of movement or visible muscle contraction,' 2 for 'active movement, though unable to overcome gravity,' 3 for 'active movement: move joint against gravity only,' 4 for 'active movement: decreased power, moves joint against load greater than gravity alone,' and 5 for 'full movement strength.' Neurological exams were performed during the acute stage (the first week) on each patient. Table 1 lists the number of days post-stroke in which the acute neurological exam and MEG testing was conducted for the acute and follow-up phases of the study. The follow-up MEG exam was performed on the same day as the patients' follow-up neurological exam. Follow-up testing was conducted within 4–6 weeks after the stroke in 11 patients and 6 months after stroke in one patient (#2). MR diffusion-weighted images (Warach et al., 1995; Sorensen et al., 1996), fluid-attenuated inversion recovery (FLAIR) images (Rydberg et al., 1994; De Coene et al., 1992; Hajnal et al., 1992), sagittal T1-weighted images, axial proton-density and T2-weighted spin-echo images were collected on a 1.5 T scanner for acute stroke diagnoses within 8 days of ictus. All patients underwent daily intensive neuro-rehabilitation by certified physical and occupational therapists until maximum possible recovery occurred.

2.2. MEG median nerve and finger-lifting examinations

During an MEG median nerve test, left and right median nerves of each patient were stimulated with a bipolar Grass constant current stimulator. Three hundred square-wave electric pulses (0.2 ms duration) were delivered at 2 Hz. The intensity of the stimulation was adjusted until robust thumb twitches were observed; the left and right sides were stimulated in random order. A simultaneous trigger from the stimulator was sent to the MEG acquisition system for signal averaging. Magnetic fields evoked by median nerve stimulation were measured using a Neuromag whole-head MEG system (Helsinki, Finland), with 122 planar gradiometers in a magnetically shielded room (IMEDCO-AG, Switzerland). An interval of 400 ms post-stimulus signal was recorded, with 100 ms pre-stimulus data for noise measurement. The baseline of the MEG data was adjusted by setting the mean of the pre-stimulus data for each channel to zero. The sampling frequency of the data was 1000 Hz, and the data were run through a bandpass filter with 0.1–300 Hz bandpass (or 2–300 Hz in data contaminated with strong low frequency artifacts, usually due to dental work), and through a notch filter (58–62 Hz) to remove 60 Hz power-line noise. The MEG responses were averaged with respect to the stimulus trigger to increase the SNR. Selective attention studies (e.g. Mima et al., 1998) have shown that later components (40 ms, 70 ms, etc.) associated with primary somatosensory area activity and the 125 ms component associated with secondary somatosensory area activity are sensitive to alterations in attention. Although this is not a problem for the early 20 ms component in our study, we asked the subjects to relax and 'empty their mind' which reduced subjects' attention to the stimulation.

For comparison purposes, patients who were able to perform an MEG finger-lifting motor task were also asked to place their hands on a table and lift their right/left index finger following a visual cue (ISI 2000 ± 200 ms). These data were obtained whenever possible to determine if the MI source evoked by median nerve stimulation was in or near the MI area determined by finger-lifting. Interruption of a laser beam by the finger-lift generated a trigger for stimulus averaging. Three hundred trials were averaged with respect to the onset of the finger movement. The pre-stimulus and post-stimulus intervals of the recording were 1000 and 500 ms, respectively. The interval of −250 to −50 ms was used to localize the MI source. The same sampling rate and filter-setup used in the median nerve task were also employed in the acquisition of the finger-lifting task.

To detect abnormalities in MI and SI sources, we used two types of control conditions. In the first, a control group of 8 aged-matched normal subjects were studied (5 male, age: 45–76, mean 58 years). Across all 16 hemispheres, the source parameters (i.e. dipole location, peak latency, and peak dipole strength) of the early component near 20 ms for SI and MI sources evoked by median nerve stimulation were obtained. In addition, interhemispheric peak latency asymmetry (lat_asy) and dipole peak strength asymmetry ratio (str_asy_ratio) measured as log(str_left/str_right) were calculated based on the study by Rossini et al. (2001) who showed that these measurements were sensitive in detecting hemispheric asymmetry abnormalities abnormality in stroke patients. A source parameter in a stroke patient is considered

abnormal if it differs from the mean value of normal control subjects by more than 2.33 SD (or 98% confidence level).

The peak strength of the initial component for the dipole time-course is defined as the first identifiable peak during the 15–28 ms interval. A peak in dipole time-course is considered identifiable for the SI or MI source if the dipole strength is greater than 2.33 SD of the baseline dipole time-course, as determined by fitting the pre-stimulus (−100 to 0 ms) baseline data using the same dipole locations obtained from the post-stimulus interval. The peak latency is the time associated with the peak dipole strength. In some stroke patients, the peak in the dipole time-course could not be identified from background noise.

The second control condition involves a within-subject, cross-measurement comparison. This approach used the longitudinal measurements in the stroke-unaffected side. Namely, the SI and MI locations in the stroke-unaffected hemisphere were obtained in stroke patients from the acute and follow-up MEG exams. Then, the source location deviation from these two sequential measurements was used as a control to detect potential shifts in source location in the stroke-affected hemisphere. A source location shift in the affected hemisphere is considered significant if the location difference between acute and follow-up measurement exceeds 2.33 SD of the corresponding source in the unaffected hemisphere.

2.3. MEG data analysis

In the present study, a spherical MEG head model was adopted (Sarvas, 1987). In this approach, a sphere is fitted to the inner surface of the skull overlying the central sulcus (obtained from the subject's MR images). Using a human skull phantom, we showed that, for the region at the central sulcus, the spherical model and the real-shape head model based on boundary element method (BEM, cf. Mejis et al., 1987; Hämäläinen and Sarvas, 1989; Ferguson et al., 1994; Schlitt et al., 1995) yielded very similar results (Leahy et al., 1998), due to the high spherical symmetry of the skull in this region. The equivalent current dipole model, which assumes brain activations are focal and can be modeled by a few point current dipoles, was applied in the present study. The physiological validity of the dipole model for somatosensory responses has been well documented (Okada et al., 1996; Jenkins and Merzenich, 1987).

The dipole locations, orientations, and moments (strengths) are determined by the non-linear dipole fitting procedure. In traditional fitting algorithms, the investigator is required to make initial guesses about the locations of sources in order to fit data that contains multiple sources (Berg and Scherg, 1994; Neuromag Ltd, 1996). In the present study, the Multi-Start Spatio-Temporal (MSST) modeling technique (Huang et al., 1998) was used to obtain the locations of neuronal sources and their time courses (temporal dynamics of the sources). MSST has been tested in computer simulations, phantom studies, and human studies (Huang et al., 1998; Aine et al., 2000), and has been shown to be a significant improvement over traditional inverse techniques. In this approach, multiple sets of initial dipole locations are automatically selected by randomly sampling a given brain volume. Upon completion of the multiple searches, the sets of best-fitting solutions, which form clusters in space, are averaged to obtain the multiple dipole locations. Unlike traditional approaches, MSST does not require users to provide initial guesses for dipole locations, hence the fitting procedure is more objective and user-friendly.

Cartesian coordinates were used to describe the dipole locations. The x axis is defined as the direction from left preauricula (PA) to right PA, with positive x to the right direction. The y axis is defined as a line through the nasion (NA) intersecting and perpendicular to the left-right PA line, with positive y in the anterior direction. The z axis is perpendicular to the x-y plane, with positive z in the superior direction. The locations of the sources provided by MEG were then superimposed on 3-dimensional volumetric GRE T1-weighted anatomical MR images of the patients collected on a 1.5 T Picker/Phillips scanner. To co-register the MEG result with anatomical MRIs, we used the 3 anatomical landmarks (i.e. NA, left and right PA) measured for each subject using a Head Position Identification system included with the Neuromag whole-head MEG system. By identifying the same 3 points on a subject's MRI, a transformation matrix involving both rotation and translation between the MEG and MRI coordinate systems was generated to provide accurate co-registration of the functional and anatomical data.

3. Results

3.1. Control data

Table 2 lists dipole location, peak latency, peak strength, interhemispheric latency asymmetry, and dipole strength asymmetry ratio for the 20 ms component of SI and MI sources evoked by median nerve stimulation in the 8 control subjects. Also listed in Table 2 are MI dipole locations calculated from index finger-lifting task. These values were used to determine between group abnormalities in SI and MI sources. The variability in source locations in healthy adults is relatively large (ranging from 6.8 to 9.6 mm), due to the variations in head size and head shape. However, these values are similar to those reported by Rossini et al. (2001).

Table 3 shows the mean SI and MI location deviations between acute and follow-up measurements for the unaffected hemispheres in the 12 stroke patients. The within-patient across-measurement deviations in source locations were rather small (~ 3 mm). These values were used to detect small shifts in source location in the stroke-affected hemisphere between acute and follow-up measurements.

Table 2
Control condition one: SI and MI dipole location, peak latency, peak strength, interhemispheric peak latency asymmetry (lat_asy), and interhemispheric peak strength asymmetry ratio (str_asy_ratio) in normal control subjects

	x (mm)	*y* (mm)	*z* (mm)	Latency (ms)	Strength (nAm)	Inter-hemi lat_asy SD (ms)	inter-hemi str_asy_ratio SD
SI: median nerve	39.3 ± 6.8	2.1 ± 7.9	83.0 ± 8.1	20.4 ± 1.6	19.8 ± 7.2	0.0 ± 1.0	0.05 ± 0.79
MI: median nerve	34.8 ± 8.8	4.4 ± 6.9	88.4 ± 9.6	21.1 ± 1.9	10.4 ± 3.8	0.2 ± 1.4	0.04 ± 0.66
MI: finger-lifting	32.3 ± 9.2	4.1 ± 7.3	89.9 ± 9.1	–	–	–	–

For each parameter, the upper normal limit is chosen to be 2.33 times the listed SD.

3.2. MRI findings and neurological scores

Table 4 describes the acute MRI findings and the scores on neurological exams during the acute and follow-up phases for the stroke patients. The acute MRI findings showed that 9 patients (#1, 2, 4, 5, 6, 8, 10, 11, and 12) had cortical infarcts involving, but not limited to, primary sensorimotor cortex. Three patients (#3, 7, and 9) had acute infarcts primarily involving the posterior limb of the internal capsule (corticospinal tract). Two of them (#3 and 9) also had marked chronic periventricular white matter hypertensive changes. The NIH stroke scores are also included in the Table 4 (0 = normal, 42 = maximum impairment). Three patients (#2, 5, and 7) had Broca's aphasia and one of them (#2) had additional mild comprehension deficit, in addition to their abnormal sensorimotor functions, as reflected in their high NIH stroke scores. All except one internal-capsule stroke patient (#3) showed recovery of their sensorimotor functions as determined by the improvement on the neurological sensory and motor scales at the time of their follow-ups compared with the scales during the acute neurological exams. Patient 3 experienced slight improvement of hand motor function but his hand sensory function was worse during the follow-up testing relative to the acute stage.

3.3. MEG source location: median nerve exam

It took 6–7 dipoles (contralateral SI and MI, bilateral secondary somatosensory and superior-parietal sources, supplementary motor area source, etc) to fit the MEG responses during the 15–135 ms post-stimulus interval following unilateral median nerve stimulation of the stroke-affected side. The percent-variance explained by the best fitting solutions exceeded 85% and reduced chi-square values (Supek and Aine, 1993; Huang et al., 1998) were less than 1.2 for the entire interval. The focus of the present study is the SI and MI sources in the stroke-affected hemisphere evoked by stimulation at the contralateral hand. The MEG findings for SI and MI sources of the 12 stroke patients are summarized in Table 5 for both the acute and follow-up measurements.

In Table 5, coordinates for the SI and MI sources of the stroke-affected hemispheres are listed for the acute and follow-up MEG median nerve measurements (acute values are listed above follow-up values). One subcortical stroke patient (#9) showed abnormal MI location (>2.33 SD) in the anterior direction in both acute and follow-up testing. No cortical stroke patients showed source locations that exceeded 2.33 SD of the mean locations obtained in the normal subjects.

The within-patient longitudinal changes for SI and MI source locations of the stroke-affected hemisphere were also studied using two MEG median nerve responses during the acute stage and at follow-up. With the unaffected hemisphere data as a control (Table 3), we found that 22% of the cortical stroke patients' (#1 and 4) showed a significant lateral shift (>2.33 deviation) in the MI source at the follow-up MEG assessment, compared with the acute assessment, i.e., 9.6 mm shift for patient #1 and 10.4 mm shi'ft for patient #4 (Table 5).

3.4. MEG source peak latency: median nerve exam

The peak latencies and latency asymmetry of the SI and MI sources in the stroke-affected hemisphere were also listed in Table 5 for both the acute and follow-up MEG median nerve tests. During the acute MEG exams, 33% of the 9 cortical stroke patients (# 1, 5, and 6) showed abnormal SI/MI peak latency with either an absent 20 ms peak (#1 and 5) or an abnormal latency asymmetry (#6).

Table 3
Control condition two: deviation in source location in the unaffected hemisphere of the 12 stroke patients between acute and follow-up measurements

Loc diff follow-up vs. acute	*x* (mm)	*y* (mm)	*z* (mm)
SI: median verve (12 patients)	3.0	2.6	2.9
MI: median verve (12 patients)	3.3	3.2	3.1
MI: finger lifting (8 patients)	3.2	3.0	3.7

For each coordinate, the deviation is calculated as the difference between the values in acute and follow-up MEG exams, averaging across patients.

Table 4
Neurological examination results and MRI readings

Patient	Acute MRI findings	Acute neurological exams			Follow-up neurological exams		
		Sensory score (0–5)	Motor score (0–5)	NIH stroke score (0–42)	Sensory score (0–5)	Motor score (0–5)	NIH stroke score (0–42)
1	Multiple small focal acute cortical infarcts in the medial left occipital lobe, left postcentral gyrus, left middle frontal gyrus, and most marked in the left precentral gyrus (including left motor strip).	3	2.0	7	5.0	4.0	5
2	Large acute infarct involving the lateral left frontal and temporal lobes including Broca's area; insula; superior basal ganglia; and small portion of left parietal lobe. Left motor strip has only mild focal involvement supralaterally.	4	4.0	7	5.0	5.0	5
3	New small focal infarcts in the left posterior limb internal capsule and in the anterior left putamen. Old severe periventricular white matter hypertensive changes (also involving the pons). Small infarct in posterior right occipital lobe.	5	2.0	11	4.0	3.0	9
4	New small acute infarct involving the right frontal lobe anterior watershed distribution, involving the right middle and superior frontal gyri, extending back to the right motor strip. Old right centrum semiovale watershed ischemic changes.	4	3.0	6	4.5	4.0	4
5	New small acute infarct involving the right frontal lobe anterior watershed distribution, involving the right middle and superior frontal gyri, extending back to the right motor strip. Old right centrum semiovale watershed ischemic changes.	1	1.0	17	5.0	5.0	3
6	Small punctate acute infarct in medial left motor strip; and 2 smaller punctate acute infarcts in anterolateral right frontal lobe. Chronic infarcts involving regions of the left middle and superior frontal gyri, and the left motor strip. Chronic periventricular white matter ischemic changes.	5	4.5	2	5.0	5.0	1
7	Small acute infarct involving the left uncus and left posterior limb internal capsule.	4	4.0	13	5.0	5.0	1
8	Acute small focal infarct in the right temporoparietal junction in the region of the supramarginal gyrus and subjacent white matter, extending to the lateral ventricle; and a small acute punctate infarct in the more posterior right parietal gray-white junction.	5	4.0	5	5.0	5.0	1
9	Small focal acute infarct in right posterior limb internal capsule/lateral right thalamus. Chronic marked diffuse white matter ischemic changes.	5	4.0	2	5.0	5.0	0
10	Small patchy acute infarcts in the inferolateral right precentral gyrus/motor strip, extending down to right centrum semiovale.	5	4.0	5	5.0	5.0	2
11	Multiple punctate acute infarcts along the right superior frontal sulcus, right motor/sensory cortices, and especially around the right postcentral sulcus. Old mild pons ischemia.	3	5.0	2	5.0	5.0	0
12	Multiple punctate acute infarcts in the right middle frontal gyrus, right motor strip, and vicinity of right intraparietal sulcus. Focal old right posterior watershed white matter gliosis	5	4.0	5	5.0	5.0	0

The normal values for sensory, motor and NIH stroke score are 5, 5 and 0, respectively.

During the follow-up MEG exams, the two patients with absent 20 ms peaks in the acute MEG exams, had identifiable 20 ms peaks and their peak latencies were within normal limits. The other patient's MI peak latency also became normal in the follow-up exam. However, another patient (#2), whose peak latency was within the normal range during the acute MEG exam, showed an abnormal MI peak latency at the follow-up assessment. For the subcortical stroke patients, 67% of the 3 patients (#9 and 3) showed either an absent MI peak (#9) or an absent MI source (#3) during the acute MEG exam. During the follow-up exam, one patient's (#9) MI peak became identifiable, but its peak latency was late and exceeded the normal asymmetry range. The other patient (#3), with an absent MI source in the acute exam, had a localizable MI source during the follow-up median nerve exam, but the peak latency was not identifiable due to a weak strength. So, despite some improvements peak latency in both subcortical patients remained abnormal in the follow-up exams.

Table 5
MEG results for median nerve and finger-lifting tasks

Patient	SI: median nerve			MI: median nerve			MI: finger lifting
	Location (mm):	Peak Lat & lat_asy (ms)	Peak Str (nAm) & str_asy_ratio	Location (mm)	Peak Lat & Lat_asy (ms)	Peak Str (nAm) & str_asy_ratio	Location (mm)
1	[−28.5 −11.9 84.1]	21.0 (0.0)	5.8 (0.87)	[−33.8 −1.4 76.7]	Unidentified[a]	1.2 (2.50)[a]	Unable to do
	[−31.9 −11.2 85.9]	22.0 (1.0)	13.3 (0.14)	[−43.4 −0.2 73.5][b]	24.0 (2.0)	6.9 (0.19)	Strong artifacts
2	[−40.5 12.6 82.8]	22.0 (0.0)	5.9 (1.17)	[−22.4 −1.0 85.6]	24.0 (2.0)	4.4 (1.12)	Unable to do
	[−43.1 14.6 84.9]	24.0 (2.0)	14.5 (0.53)	[−27.0 0.1 87.8]	26.0 (4.0)[a]	14.2 (0.46)	Unable, aphasia
3	[−46.5 7.5 68.0]	22.0 (1.0)	23.5 (0.31)	Source absent[a]	Source absent[a]	Source absent[a]	Unable to do
	[−49.9 7.7 65.4]	22.0 (1.0)	11.2 (0.91)	[−47.3 18.8 67.7]	Unidentified[a]	1.5 (2.22)[a]	Unable to do
4	[36.3 −0.6 73.2]	22.0 (1.0)	9.5 (0.70)	[27.2 8.2 76.5]	24.0 (1.0)	4.6 (0.73)	[25.8 6.9 77.7]
	[33.0 2.9 76.0]	23.0 (2.0)	12.3 (0.66)	[37.5 4.5 71.6][b]	23.0 (0.0)	7.7 (0.30)	[35.5 6.6 72.2][b]
5	[−35.6 −1.7 91.3]	Unidentified[a]	2.4 (2.39)[a]	[−26.1 2.6 89.2]	Unidentified[a]	1.6 (1.66)[a]	Unable to do
	[−32.0 1.9 88.8]	20.0 (1.0)	15.1 (0.71)	[−20.8 4.2 84.7]	23.0 (1.0)	18.9 (0.56)	[−22.6 6.5 82.2]
6	[−35.5 −1.0 86.3]	22.0 (1.0)	30.1 (0.47)	[−23.8 −1.0 86.3]	26.0 (5.0)[a]	8.8 (0.54)	Unable to do
	[−36.9 −5.5 82.8]	23.0 (2.0)	35.3 (0.45)	[−28.4 1.6 90.6]	24.0 (3.0)	13.9 (0.22)	[−25.1 2.6 89.8]
7	[−48.3 1.5 80.2]	18.0 (1.0)	6.6 (0.98)	[−32.9 4.6 83.7]	18.0 (2.0)	3.7 (0.93)	[−30.6 6.2 85.3]
	[−44.5 −1.2 84.5]	18.0 (1.0)	15.5 (0.13)	[−30.5 1.7 87.3]	18.0 (2.0)	9.1 (0.06)	[−28.8 3.2 85.5]
8	[38.2 8.5 95.9]	21.0 (1.0)	8.1 (0.60)	[28.8 14.3 97.6]	23.0 (0.0)	3.3 (1.63)[a]	Unable to do.
	[41.4 5.9 92.0]	23.0 (2.0)	12.8 (0.40)	[33.5 10.0 94.6]	24.0 (1.0)	12.3 (0.15)	[32.5 11.8 93.1]
9	[43.2 13.2 86.4]	23.0 (2.0)	10.7 (0.65)	[26.1 22.1 87.7][a]	Unidentified[a]	2.1 (1.77)[a]	[30.0 23.6 83.9][a]
	[39.4 11.6 90.2]	23.0 (2.0)	8.7 (1.03)	[22.1 21.2 83.7][a]	26.0 (4.0)[a]	7.3 (0.30)	Strong artifacts
10	[25.5 −11.2 86.6]	22.0 (1.0)	10.1 (0.81)	[40.2 16.7 85.3]	24.0 (1.0)	3.9 (1.11)	Strong artifacts
	[24.2 −9.0 83.7]	22.0 (1.0)	9.8 (0.88)	[36.5 18.6 87.7]	24.0 (1.0)	6.0 (0.32)	[38.8 16.8 88.6]
11	[41.8 −5.3 94.6]	20.0 (0.0)	12.0 (0.67)	[44.7 4.1 93.7]	23.0 (1.0)	11.3 (0.03)	[43.9 8.2 94.4]
	[46.8 −3.5 89.3]	20.0 (0.0)	17.7 (0.46)	[49.5 3.5 90.8]	24.0 (2.0)	14.5 (0.41)	Strong artifacts
12	[41.2 18.1 87.8]	22.0 (2.0)	12.5 (0.89)	[35.4 17.5 83.2]	25.0 (3.0)	6.4 (0.06)	[37.3 13.0 87.9]
	[39.3 16.9 83.8]	22.0 (2.0)	19.8 (0.01)	[32.3 18.9 80.3]	25.0 (3.0)	15.8 (0.28)	[35.7 16.1 83.8]

Location, peak latency, latency asymmetry (sign ignored), peak strength, and peak strength asymmetry (sign ignored) of SI and MI sources obtained by median-nerve task for the early component. The parameters for the acute measurement are above those for the follow-up.

[a] Abnormal with respect to the control subjects.

[b] Significant location shift in the follow-up measurement with respect to the acute measurement, using the unaffected hemisphere as control. MI source locations from finger-lifting task are also listed. An explanation is provided if MI finger-lifting data is not available or analyzable.

3.5. MEG source strength: correlation of neurological scores with median nerve response

The peak strength and interhemispheric of peak strength asymmetry ratio of SI and MI sources in the affected hemispheres for the 20 ms component were examined for the 12 stroke patients and the values are listed in Table 5. If peak was not identifiable from the MEG dipole source time-course during the [15–28] ms interval, an averaged value of the dipole strength during that interval was calculated and this value was listed in the table. During the acute MEG exams, 6 out of the 9 cortical stroke patients (67%) and 2 out of 3 subcortical stroke patients (67%) showed significant abnormal strength asymmetry (>2.33 SD) or an absent source (#3) for either SI or MI. For the follow-up MEG exams, only one subcortical stroke patient (#3) showed abnormal MI strength asymmetry.

Next we examined the relationship between the source strength from the MEG median nerve responses and neurological scores from clinical exam of sensorimotor functions. Fig. 1 plots the relative change in dipole strength between the acute and the follow-up exams as a function of the corresponding neurological change. The relative MEG change for the SI (MI) source is defined as (Pf − Pa)/Pf, where Pa and Pf were the peak dipole strengths of the SI (MI) source around 20 ms during the acute and follow-up MEG median nerve exams, respectively. The same computation was used to obtain the relative changes for the neurological measurements of the hand sensation and motor functions.

In Fig. 1, the circles represent the 9 cortical stroke patients and the squares represent the 3 internal capsule subcortical stroke patients. Fig. 1A shows that SI dipole strength in the stroke-affected hemisphere and neurological sensory function scores were positively correlated ($r = 0.82$, df = 10, $P < 0.01$, Spearman's rank correlation analysis) for the group of 12 stroke patients. When the 3 subcortical stroke patients were excluded from the analysis, the correlation was still significant ($r = 0.74$, df = 7, $P < 0.05$) for the 9 cortical stroke patients. Fig. 1B shows that MI dipole strength due to median nerve stimulation of the stroke-affected hand positively correlated with neurological motor function scores ($r = 0.76$, df = 10, $P < 0.01$ for all 12 patients; $r = 0.78$, df = 7, $P < 0.05$ for the 9 cortical stroke patients only).

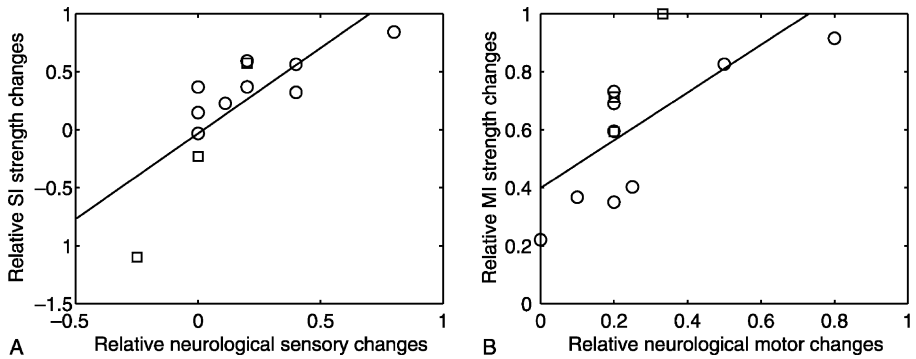

Fig. 1. Spearman's rank correlation between median nerve MEG results and neurological measurements during stroke recovery period. The circles represent the data from 9 cortical stroke patients and the squares represent data from 3 internal capsule stroke patients. (A) Relative changes in SI dipole strength around 20 ms between acute and follow-up median nerve MEG responses are plotted as a function of the relative changes in hand sensory scores between the acute and follow-up neurological exam. (B) Relative changes in MI dipole strength around 20 ms between acute and follow-up median nerve MEG responses are plotted as a function of the relative to changes in hand motor scores between the acute and follow-up neurological exams. The regression lines were obtained using a least-square fit.

For the acute exams alone, we also found that the SI dipole strengths from MEG median nerve responses strongly correlated with neurological scores for all 12 stroke patients ($r = 0.73$, df $= 10$, $P < 0.01$) and for 9 cortical stroke patients ($r = 0.71$, df $= 7$, $P < 0.05$). Similar results were found for the MI sources ($r = 0.78$, df $= 10$, $P < 0.01$ for all 12 patients, and $r = 0.81$, df $= 7$, $P < 0.01$ for 9 cortical patients). However, in the follow-up exams, there were only non-significant trends for a relationship between SI dipole strength and neurological scores ($r = 0.56$, df $= 10$, $P = 0.058$ for all 12 patients, and $r = 0.63$, df $= 7$, $P = 0.064$ for 9 cortical stroke patients). In contrast, the MI dipole strength correlated significantly with neurological motor scores for the follow-up exams ($r = 0.59$, df $= 10$, $P < 0.05$ for all 12 patients, and $r = 0.68$, df $= 7$, $P < 0.05$ for 9 cortical stroke patients), but the correlations were markedly smaller than those in the acute exams.

3.6. MEG finger-lifting exam

Table 5 also lists the MEG results from the finger-lifting motor task. Six out of 12 patients were unable to perform this active motor test due to impaired motor function in the acute stroke phase. Another patient's (#1) acute MEG finger-lifting response was contaminated by strong low-frequency artifacts due to dental work and thus, was not analyzable. In the remaining 5 patients, one patient's (#9) MI source location showed abnormal interhemispheric asymmetry, which was consistent with this patient's abnormal MI location evoked by the median nerve exam.

During the follow-up MEG finger-lifting exams, one patient (#3) was still unable to perform the task due to persistent motor function deficit. Another patient (#2) was unable to follow the visual cue to perform the finger-lifting MEG task in the follow-up exam, not because of his motor deficit (his motor score 5/5) but perhaps due to the patient's aphasia. Three other patients (#1, 9, and 11) were able to perform the task, however, their data could not be analyzed due to strong contamination of low-frequency artifacts. In only 25% (#4, 7, and 12) of the 12 patients, we were able to obtain MI locations in both acute and follow-up finger-lifting MEG exams. One patient (#4) showed a significant lateral shift in the MI source during recovery, with the longitudinal data in unaffected hemisphere used as a control (Table 3). This result was also consistent with the lateral shift of his MI source evoked by median nerve stimulation shown previously.

3.7. A typical case

To further illustrate the utility of using MEG median nerve response to monitor recovery of sensorimotor functions in stroke patients, it is worthwhile to consider the case history for a representative patient (#1). This patient was a 73 year-old man who developed a small left middle cerebral artery (MCA) territory stroke. Acutely, the patient had a moderately severe right-sided hemiparesis and hemisensory loss, and was unable to perform the right finger-lifting task during the acute MEG test due to the paralysis of the hand. His NIH stroke score was 7. Fig. 2A shows the acute diffusion-weighted MR images of this patient, acquired on the day of the stroke, which shows small acute infarcts involving the pre- and post-central gyri. The MEG right median nerve responses, recorded in the first week of the stroke, show a weak signal at about 20 ms (see asterisk in Fig. 2B). Acutely, SI and MI sources in the contralateral hemisphere were localized in the 15–135 ms interval and their locations are shown in T1-weighted MR image Fig. 2C as black and white dots, respectively. The location of this T1-weighted image is about the same level as the left diffusion-weighted image in Fig. 2A. The region of stroke infarct that was immediately medial to the MI source is also highlighted in Fig. 2C. The time-course of the SI source peaked at 21 ms with a peak-amplitude of 5.8 nAm (black line in Fig. 2D), while the MI source did not show

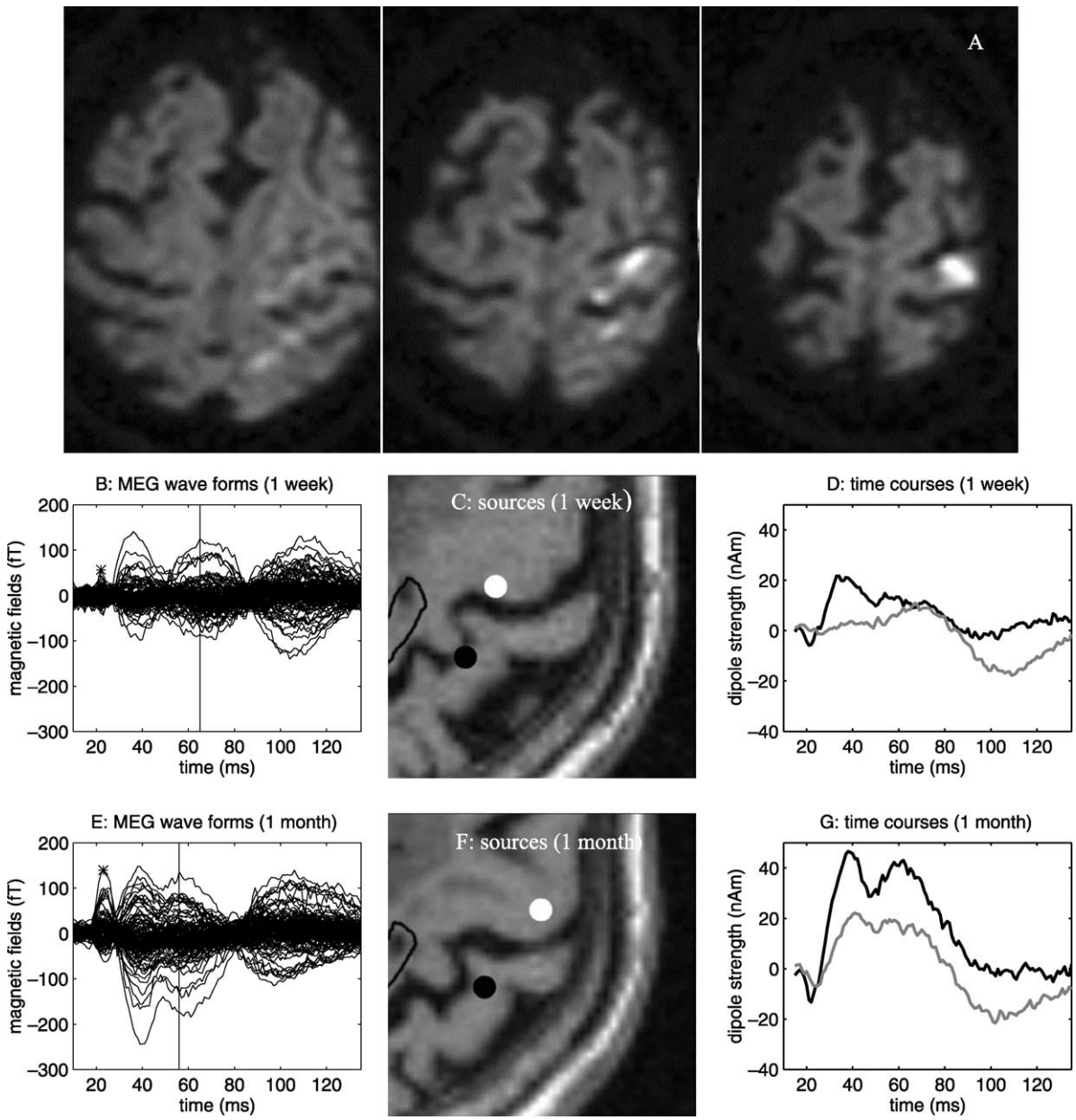

Fig. 2. Patient 1. (A) Diffusion-weighted MR images of a stroke patient shows small acute infarcts in the pre- and postcentral gyri. Radiological convention was adopted where the left side of the MR images represents the right hemisphere. (B) MEG averaged signals evoked by median nerve stimulation during the first week of the stroke are superimposed for all 122 channels. (C) SI (black dot) and MI (white dot) sources localized from the first week's median nerve responses are shown in the T1-weighted MR image. (D) The temporal dynamics of the SI (black line) and MI (gray line) sources during the acute stage. Notice that the MI in the first week does not reveal early activity. (E), (F) and (G) show the MEG signal, locations and temporal dynamics, respectively, of the SI and MI sources for the 1-month follow-up. In B and E, the asterisks indicate the peak amplitudes around 20 ms. The boundary of the stroke infarct medial to the MI source is highlighted in C and F.

evidence of activity until much later (peaking at about 65 ms, gray line in Fig. 2D). One month later, the patient showed mild hemiparesis and no hemisensory loss. He could use his right hand (affected side) to feed and dress himself, however, the SNR of his MEG right finger-lifting responses was too poor for source localization. On the other hand, the MEG responses from right median nerve stimulation showed markedly increased signals for the first three peaks (Fig. 2E) when compared with the first week's data. This is especially true for the first peak at about 20 ms (see asterisk). Another marked change was a decrease in the latency of the third peak to 55 ms (compare waveforms in Fig. 2B and E at the vertical lines). The MI source was shifted laterally by 9.6 mm in the 1-month follow-up (Fig. 2F), compared with the first week's measurement (Fig. 2C). The time-course of the SI source showed stronger activity than that of the 1-week measurement with a peak-amplitude of 13.3 nAm at 22 ms (Fig. 2G).

Furthermore, the time-course of the MI source (Fig. 2G) showed a peak at 24 ms, which was not observable in the first week. The strength of the 24 ms peak was 6.9 nAm. In addition, the time-course of the MI source tended to follow that of the SI source, a pattern seen in our normal subjects (Huang et al., 2000). This case study demonstrates that median nerve stimulation evoked a response in the hand area of MI (in addition to SI) at a time when the hand was paralyzed. The changes in strengths of MI and SI were consistent with the recovery of the patient's hand sensorimotor function at 1 month.

4. Discussion

The results of the present study show that the integrity of MI, in addition to SI, can be assessed using median nerve stimulation in acute stroke patients. The relative changes in MEG source strengths for both SI and MI dipoles significantly correlated with the relative changes in neurological scores, between acute and follow-up exams. This finding has significant clinical value since it provides an indirect way to assess primary motor function in acute stroke patients who are initially unable to perform motor tasks. We believe that such primary motor activation is through afferent input similar to the afferent input to the primary somatosensory area. Our study also demonstrates that performing an active motor task can be difficult for stroke patients in the acute phase. In order to generate efferent MEG motor responses with enough SNR for analysis, the patient needs to lift his/her finger quickly with a large displacement for hundreds of repetitions in a time-locked fashion. In reality, however, this was not possible for 50% of our stroke patients, especially in the acute phase. Moreover, some patients were unable to do the task due to severe aphasia or other reasons. For example, patient 2 showed normal motor function in the follow-up neurological exam. However, he was unable to follow the visual cue to perform finger-lifting MEG task. This may be explained by his mild comprehension deficit. Alternatively, difficulties in finger-lifting may be due to his basal ganglia damage, which disrupts paced-finger tapping (Harrington et al., 1998). Median nerve stimulation, on the other hand, is a passive task with no requirement for patient participation with the exception of sitting still. As was demonstrated in the present study, the source in the integrity of primary motor area from such a passive task can be used to monitor the recovery of function in MI.

Many results in the present study are consistent with previous stroke studies using MEG. For example, the location and uncertainty range of the SI source in normal control subjects are quite similar to the values presented by Rossini et al. (2001). We also confirm that inter-hemispheric asymmetry of the dipole peak latency and strength are sensitive measurements of source abnormality in stroke patients, as was reported in Rossini et al. (2001). Furthermore, the present study showed that more patients had abnormal inter-hemispheric asymmetry in the acute exams than in their follow-up exams. The SI abnormalities observed in the present study (e.g. absent, weak, or delayed 20 ms response) were also consistent with previous MEG and SEP studies (La Joie et al., 1982; Reisecker et al., 1986; Knecht et al., 1996; Franssen et al., 1992; Maclin et al., 1994; Kalita and Misra, 1997, 1998; Hijosa et al., 1998; Wikström et al., 1999; Forss et al., 1999; Bundo et al., 2002). In addition, SI dipole strength correlated with neurological score during the acute exam. However, only a non-significant trend was found for the follow-up data. The latter was consistent with recent SEP findings by Park et al. (2003) showing a weak correlation between SI SEP and clinical measurements in chronic stroke patients. One reason for this weak correlation could be the relatively large inter-subject variations observed for dipole strength and less variability in clinical scores. Another reason could be that clinical scales used to quantify sensory and motor functions are coarse and my not be sensitive enough to subtle sensorimotor impairments that persist especially in the follow-up. Nevertheless, our results showed strong correlations between clinical neurological rating and changes in SI and MI MEG responses, which validate the clinical utility of these scales.

We found only one abnormal source location in 1 out of 3 patients (33%) with subcortical stroke and in none of the patients with cortical stroke based on the normal control data. Our result contrast with Rossini and colleagues' cross-sectional study of chronic stroke patients (>6 months after stroke), in which they reported that 32% of their subcortical and 25% of their cortical stroke patients showed abnormal locations with respect to the normal control data. One potential explanation for such a difference may be the substantial difference in the patient population. In Rossini et al.'s study, the majority of patients suffered from subcortical stroke (13 subcortical vs. 4 cortical) while in the present study the majority of patients suffered from cortical stroke (9 cortical vs. 3 subcortical). Still, the large variability in source locations in normal control subjects in both study due to the differences in head size and head shape may limit the utility of normal control data for detecting small abnormalities in source location in patients. An alternative way is to transfer the individual brain into Talairach space (Talairach et al., 1967; Talairach and Tournoux, 1988) using linear and nonlinear transformations (for review see Woods, 1996) to minimize cross-subject difference in head size and shape. This approach is a common practice in analyzing functional MRI and positron emission tomography data, but has not been widely applied to MEG.

On the other hand, we showed that deviation in the location of the SI and MI sources in the unaffected hemisphere between acute and follow-up assessments was much smaller (~3 mm). Using the unaffected hemisphere as a control, we were able to detect relatively small location

changes in two cortical stroke patients between the acute and follow-up measurements. It was also reported in Rossini et al. (2001) that the inter-hemispheric difference of the hand representation, measured as the Euclidean distance separating the 1st from the 5th digit SI dipole, is another sensitive measurement of abnormality in stroke patients. In the present study, we only stimulated median-nerve and did not have the data for 1st and 5th digit, so we were unable to calculate such hand representation asymmetry.

The results also showed that MEG measurements following median nerve stimulation permitted the characterization of neurophysiological changes that occur following sensorimotor ischemic stroke. Changes in neuronal activities, including source locations, strengths, and the absence/presence of the early 20 ms component, provide more complete information regarding functional changes within the brain that occur during the recovery process, than clinical MRI alone. In particular, the SI and MI sources and consequent changes in their source strengths of the early component evoked by median nerve stimulation during the acute stage of sensorimotor ischemic stroke and at follow-up, correlate well with the recovery of sensorimotor functions as determined from the neurological exam. Such functional changes cannot be obtained from clinical MRI. On the other hand, MEG cannot directly distinguish a lesion at the cortical level from the lesion in the underlying corticospinal pathway. This information is readily available from clinical MRI. Therefore, the combination of functional imaging techniques, such as MEG, and clinical MRI is clearly a better way to characterize the stroke recovery.

It is still unclear, however, by which pathway the early signal arrives at MI following median nerve stimulation. In our normal control subjects, the peak strengths of SI and MI sources were significant correlated ($r = 0.56$, $df = 14$, $P < 0.05$). Still, we cannot conclude that this is the result of cortico-cortical projection. Specifically, if the thalamus sends signal to both SI and MI through thalamo-cortical connections, significant SI-MI correlation might be expected as well (both SI and MI activities are dependent variables controlled by thalamus). If the signal to MI arrives via cortico-cortical connections, one would expect some delay in the time-courses between the SI source (in area 3b) and MI source (in area 4). Given the findings from a monkey study by Darian-Smith et al. (1993) using a dye-tracing technique, which reported that direct connections between 3b and 4 are rare in the macaque monkey, and concluded that the signals most likely relay to area 4 through other areas (e.g. areas 2 and/or 5) via cortico-cortical projections. Cortico-cortical projections from other areas should cause a latency delay of about 10–20 ms (depend on which pathways were used: 3b-2-4, or 3b-5-4). This estimate is markedly larger than what we have seen in normal subjects (Huang et al., 2000 and in the present study), in which a 1–2 ms latency difference for the 20 ms peaks between the SI and MI sources was observed. Based on findings from our normal subjects, we suggested that the early median nerve signal (about 20 ms) reaches the anterior bank of the central sulcus through a direct thalamo-cortical projection, rather than relaying from SI (Huang et al., 2000). The current study provides some supporting evidence for this proposal in stroke patients. We found that the SI source peak latency around 20 ms preceded that of the MI source by only a few ms (Table 5). Furthermore, patient 3 had an acute infarct in the left posterior limb internal capsule and anterior left putamen, but no acute cortical infarct in the left primary sensorimotor cortex. This patient's acute MEG responses due to right median nerve stimulation showed a normal SI source with a normal time-course. However, we were unable to localize the source in the vicinity of MI. Since the primary motor cortex did not appear to be affected by the stroke in this patient, it is unlikely that the MI source would be absent if the signal arrived at MI through cortico-cortical connections. A more parsimonious explanation for this finding would be that activity caused by median nerve stimulation reached the anterior bank of the central sulcus by a direct thalamo-cortical projection. The infarct in the posterior limb internal capsule directly affected the transmission of the signal in the thalamo-cortical pathway; therefore, the signal was unable to reach the MI. An ideal way to study the thalamo-cortical pathway is to measure the activation from thalamus directly. However, the MEG system used in the present study (planar gradiometer configuration) is not sensitive enough to pick-up signal from the thalamus under the existing experimental conditions. Therefore, this issue remains unresolved.

The present study also revealed different patterns of recovery, which likely depend on the location of infarct, lesion, size, and other unknown factors. The MI source of two cortical patients (#1 and 4) showed significant shifts in location (9.6 and 10.3 mm, respectively), in the lateral direction during the MEG follow-up median nerve exams, compared with the acute measurements. The MR images of these patients showed that the infarct was immediately medial to the MI (e.g. Fig. 2C and F) and the shifts in location were in the direction away from the stroke infarct. We believe that this lateral shift is evidence of functional reorganization due to neuroplasticity of the motor cortex. A shift in hand motor representation has been associated with cortical lesions and may be medial (Rouiller et al., 1998), anterior-lateral (Nudo et al., 1996), ventral-lateral (Weiller et al., 1993), or posterior direction (Rossini et al., 1998; Cramer et al., 1997). We believe that the lateral shifts in patients 1 and 4 were due to the location of the lesion relative to the hand motor area. In these patients, the lesions were immediately medial to MI suggesting that functional reorganization shifted to an area away from the lesion (in the lateral direction), which is more likely than occurring closer to the lesion (in the medial direction). In other words, if only part of MI receiving hand sensory input is damaged, then the brain would unmask a pathway to the undamaged tissue, which would appear as a shift in source representation towards undamaged cortex that received input normally

(Lee and van Donkelaar, 1995; Chen et al., 2002). Another possibility could be that such shifts in source location were due to two other mechanisms: resolving of the perilesional edema and loss of tissue. However, the infarcts in our patients were small, and there was no significant perilesional edema or mass effect initially, nor on follow-up MRI (obtained in 7 patients). Another interesting finding is that, unlike many other patients who showed full recovery, these two patients who showed a lateral shift in location experienced good, but not full recovery, as reflected by their clinical motor scores. Clearly, more patients are needed in future studies to further investigate the relation between neuroplasticity associated with location changes and functional recovery.

One sub-cortical (posterior limb of internal capsule) stroke patient's MI sources showed abnormal MI location in the premotor region in both acute and follow-up MEG measurements. However, the location difference between acute and follow-up measurements was not significant, indicating that the abnormal location change must have happened during the first few days after stroke (before the acute MEG exam was done 3 days after the stroke). This case may be explained by redundancy in the motor system, which allows alternative pathways (premotor) to take over the damaged MI function (Lee and van Donkelaar, 1995; Chen et al., 2002). This proposal is further supported by the abnormally late MI latency in the follow-up assessment. The mechanism of recovery in other patients is not as clear. Since these patients did not show significant source location changes, it is likely that the recovery was due to resolution of edema or reperfusion of the ischemic penumbra. It is also possible that the location changes were subtle and a better control is needed to detect such changes.

It is notable that all patients in the present study had moderate to mild stroke. All except one had good or excellent recovery. The only patient (#3) who had poor motor function recovery also had a missing MI source in the acute MEG median nerve exam. This result is consistent with the findings by Schwarz et al. (2000) using transcranial magnetic stimulation (TMS). Namely, the absence of motor evoked potentials after TMS correlated strongly with the presence of persisting motor deficits. To study potential prognostic value of certain parameters of SI and MI sources, more severe stroke patients with poor outcome are needed. However, in practice, it is extremely difficult to acquire acute MEG data in severe stroke patients since they are often on life-support equipment and unable to participate in research studies. In two severe stroke cases where we were able to collect acute MEG data, both patients died within a month of stroke.

In the present study, the graphesthesia test and Medical Research Council motor scale were used as clinical scales to measure the somatosensory and motor functions, respectively. These scales are commonly used for clinical assessment of stroke patients and the strong correlations between changes of these clinical neurological scores and changes MEG responses validate the clinical utility of these scales. However, it is likely that these scales were probably too coarse for revealing more details in our study. In our future studies, more detailed and valid neurological scaling systems will be explored to more accurately measure the clinical sensorimotor status of stroke patients.

In summary, longitudinal MEG studies using median nerve stimulation can advance our understanding of the neuro-physiological changes accompanying recovery of sensorimotor function. In particular, the present study showed that the viability of tissue in primary motor area, in addition to the adjacent primary somatosensory area, can be assessed by the passive median nerve MEG exam. The changes in MEG source strength of primary motor and primary somatosensory sources significantly correlated with the changes in neurological scores of sensorimotor functions, which demonstrates the potential clinical value of MEG in studying the recovery of sensorimotor functions in stroke patients.

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