Title:

Muscle afferent projection to the sensorimotor cortex after voluntary movement and motor point stimulation: An MEG study

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Abstract

OBJECTIVE: To investigate the projection of muscle afferents to the sensorimotor cortex after voluntary finger movement by using magnetoencephalography (MEG).

METHODS: The movement-evoked magnetic fields (MEFs) after voluntary index finger extension were recorded by a 204-channel whole-head MEG system. Somatosensory-evoked magnetic fields (SEFs) were recorded after motor point stimulation was applied to the right extensor indicis muscle by using a pair of wire electrodes.

RESULTS: The MEF waveforms were observed at 35.8 ± 9.7 ms after movement onset (MEF1). The most concentrated SEFs were identified at 78.7 ± 5.6 ms (M70), and the onset latency of M70 was 39.0 ± 5.5 ms after motor point stimulation. The mean locations of the equivalent current dipoles (ECDs) of MEF1 and M70 were significantly medial and superior to that of N20m elicited by median nerve stimulation. The ECD locations and directions of both MEF1 and M70 were concordant in the axial, coronal, and sagittal planes.

CONCLUSIONS: MEF1 and M70 might be elicited by muscle afferent feedback following muscle contraction. In addition, these ECDs may be located in area 4.

SIGNIFICANCE: Motor point stimulation is a useful tool for confirming the projection of muscle afferent feedback to the sensorimotor cortex after voluntary movement.

1. Introduction

Several cortical imaging tools such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), functional near-infrared spectroscopy (fNIRS), transcranial magnetic stimulation (TMS), electroencephalography (EEG), and magnetoencephalography (MEG) have provided unequivocal evidence of the brain activity in sensorimotor integration (Kawashima et al., 1996, 1999; Ball et al., 1999; Rossi et al., 2000; Kristeva-Feige et al., 2002; Stefan et al., 2000, 2002; Suzuki et al., 2004; Onishi et al., 2006; Rossini et al., 2007; Hatakenaka et al., 2008; Terumitsu et al., 2009). Compared to fMRI, fNIRS, and PET, MEG and EEG have excellent temporal resolution and have been used to analyze the temporal aspect of cortical sensorimotor information processing (Nagamine et al., 1994; Hari and Fross, 1999; Ball et al., 1999; Kida, et al., 2006; Onishi et al., 2006). The neuromagnetic fields over the hemisphere contralateral to the side of movement change immediately after voluntary movements and termed as movement-evoked magnetic fields (MEFs); these fields are proposed to reflect sensory feedback to the cortex from the periphery (Cheyne and Weinberg, 1989; Cheyne et al., 1991, 1997; Kristeva-Feige et al., 1994, 1995, 1996; Woldag et al., 2003; Onishi et al., 2006). The earliest of these magnetic fields, MEF1, occurs approximately 80–100 ms after the onset of electromyographic activity (Cheyne and Weinberg, 1989; Cheyne et al., 1991, 1997; Kristeva-Feige et al., 1994, 1995, 1996; Woldag et al., 2003). The exact role of peripheral feedback in the generation of MEF1 is not clear, although such feedback may involve both afferent input from muscle spindle receptors monitoring changes in muscle length in the involved agonist or antagonist muscle groups as well as sensory organs in joints and tendons and even skin receptors due to mechanical stretching of the overlying skin (Kristeva-Feige et al., 1994, 1995, 1996; Onishi et al., 2006).

We analyzed the equivalent current dipoles (ECDs) moments and the latency of MEF1 from the onset of joint movement after two types of voluntary finger extension, in order to investigate the contribution of sensory feedback from the periphery to the generation of MEF1 (Onishi et al., 2006). We found that the MEF1 component was not due to the onset of joint movement but due to muscular contraction. In addition, ECD strength and neuromagnetic amplitude did not change even if the strength of the muscle contraction was altered. These findings suggest that MEF1 was elicited only by the activity of the muscle spindle and not by the Golgi tendon organ, cutaneous receptor, or joint receptor. These findings taken together with the evidence provided by Kristeva-Feige et al. (1996) that the MEF1 response was not abolished during an

anesthetic block of cutaneous input suggest that MEF1 may be the result of the activation of muscle receptors sensitive to changes in muscle length or configuration.

The source underlying MEF1 is not fully understood. Many researchers reported that the source of MEF1 should be located in the primary somatosensory cortex, i.e., area 3a, known to receive predominant input from proprioceptive receptors activated during movement (Cheyne and Weinberg, 1989; Cheyne et al., 1991, 1997; Kristeva-Feige et al., 1994, 1995, 1996; Woldag et al., 2003). On the other hand, it has been reported that the ECD of MEF1 located in area 3b, which receives dominant inputs from cutaneous receptors (Oishi et al., 2003), regardless of MEF1 responses is the result of afferent feedback from muscles.

The mechanisms underlying the generation of MEF1 at the cortical level remain difficult to determine. Animal experiments show that muscle afferents initially project into area 3a through group Ia afferent fibers at early latency (Phollips et al., 1971; Schwarz et al., 1973). In humans, the initial proprioceptive response at the thalamus level after motor point stimulation was confirmed at 10–12 ms by direct recording during stereotaxic surgery for patients with Parkinson's disease (Fukuda et al., 2000). Therefore, for a latency of approximately 80 ms after the onset of electromyographic activity, the MEF1 components must not reflect the initial proprioceptive input.

In the present study, we recorded the movement-related cerebral fields (MRCFs) after voluntary finger movement and the somatosensory-evoked magnetic fields (SEFs) elicited by electrical stimulation of a motor point in order to investigate the contribution of muscle afferent feedback to the sensorimotor cortex.

2. Participants and methods

2.1. Participants

Nine healthy, right-handed, male volunteers (age range, 21–46 years; mean ± standard deviation, 30.8 ± 10.0 years) participated in this study. All subjects gave their written informed consent. This study was approved by the ethics committee at the Niigata University of Health and Welfare.

2.2. Motor point stimulation

We used intramuscular, bipolar, Teflon-coated, stainless steel fine-wire electrodes (Unique Medical Ltd., Tokyo, Japan) to stimulate the motor point of the right extensor indicis muscle. The diameter of each electrode was 50 μm, and each electrode tip was

bared for 2 mm. A pair of wire electrodes was inserted into the right indicis muscle by using a 25-gage needle. The guide needle was inserted at a point 8 cm proximal to the ulnar styloid process, toward the Lister's tubercle. The placement of the electrode and its depth in the muscle were adjusted to produce a twitch contraction using electrical simulation (NeuropackΣ; Nihon Kohden, Tokyo, Japan). After we confirmed the muscle contraction during electrical stimulation, the needle was pulled out and only the bipolar wire electrode was retained in the muscle. The surface earth electrode was placed on the forearm, proximal to the wire electrode. To record the SEFs, the motor point of the extensor indicis muscle was stimulated at an intensity 1.2 times that of the motor threshold with a monophasic square-wave impulse of 0.2 ms duration at 1.5 Hz. The mean intensity was 1.5 ± 0.8 mA (range 1.6–2.6 mA). We could confirm insensible muscle contraction by palpation but could not observe the joint movement during electrical simulation at this intensity.

2.3. Movement task

The standard method for recording MRCFs has been described in detail elsewhere (Kristeva-Feige et al., 1997). We modified the method using a specific trigger board. All the subjects performed the tasks with their right hand. Each subject's index finger was placed on a small plate with a light-emitting diode (LED) sensor. When the finger tip was detached from the plate by index finger extension, the LED was cut off, and a trigger signal was input in order to average the MRCF waveforms online. Each subject was instructed to extend the index finger at self-paced intervals of approximately 6 s, with very sharp and small movements after completely relaxing the upper limb muscles. The range of movement was maintained by asking the subject to reach the adjustable line set up approximately 3 cm above the plate.

2.4. Data acquisition

The subjects were comfortably seated inside a magnetically shielded room (Tokin Ltd., Sendai, Japan) with their heads firmly positioned inside a 204-channel whole-head MEG system (Vectorview; Elekta, Helsinki, Finland). This device consists of 204 planar-type, first-order gradiometers arranged as 102 pairs. This configuration of gradiometers specifically detects the signal just above the source current. MEG signals were sampled at 1000 Hz with a band-pass filter ranging between 0.03 and 330 Hz. The data were obtained 1500 ms before and 1000 ms after each trigger for MRCFs and 50 ms before and 300 ms after stimulation for SEFs. The average of 60 epochs for MRCFs and 300 epochs for SEFs were obtained separately.

Before MEG measurement, three anatomical fiducial points (nasion and bilateral preauricular points) and four indicator coils on the scalp were digitized using a three-dimensional (3D) digitizer (Polhemus, Colchester, VT, USA). The fiducial points provide spatial information necessary for the integration of MR images and MEG data, while the indicator coils determine the position of the subject's head in relation to the helmet. T1-weighted MR images were obtained using a 1.5-T system (MAGNEX Epios15; Shimadzu, Kyoto, Japan).

The experiments for each subject consisted of recording MRCFs after voluntary finger extension and the SEF after motor point stimulation and median nerve stimulation. Median nerve stimulation at the wrist was used to obtain a reference location of the ECDs against those locations of MEF1 and SEF elicited by motor point stimulation.

2.5. Data analysis

For analysis of MRCFs, the band-pass filter was set from 0.5 Hz to 50 Hz, with the first 200 ms (-1500 to -1300 ms) used for baseline data. We identified the major component MEF1 just after movement. To analyze SEF, the band-pass filter was set from 0.5 to 100 Hz, and the 20 ms period of data preceding the stimulus was used as the baseline.

The sources of the components of interest in the MRCFs and SEFs were estimated as the ECDs, using a least-squares search with a subset of 16–18 channels over the response area. We used Source Modeling software (Elekta) to model the sources. The ECD locations and moments were calculated using a spherical conductor model of a 3D axis determined using the fiducial points (nasion and bilateral preauricular points). We accepted ECDs with a goodness-of-fit better than 90% for analysis. The accepted ECDs were superimposed onto individual MR images. To obtain the reference ECD location, the right median nerve of the subject was electrically stimulated at the wrist at an intensity that was twice that of the motor threshold, by using a monophasic square-wave impulse of 0.2-ms duration at 1.5 Hz. The mean intensity of SEF was 5.8 mA (range, 4.0–9.2 mA). In addition, the ECD location of the first peak response that occurred approximately 20 ms after median nerve stimulation (N20m) was used as the reference location. Repeated measurement one-way ANOVA and the Bonferroni post-hoc test were used to test for significant differences in the ECD coordinates. The significant level was set at 5%.

3. Results

The typical whole-scalp MRCF and SEF waveforms detected after motor point stimulation in Subject 2 are shown in Fig. 1. We clearly confirmed the MRCF and SEF waveforms at the sensorimotor area contralateral to the movement or stimulated side in all subjects. The MRCF waveforms over the hemisphere contralateral to the movement in Subject 2 were superimposed with a 350-ms period 100 ms before and 250 ms after movement onset for comparison with the SEF waveforms (Fig. 2, left panel). The peak amplitudes indicated MEF1. The right panel of Fig. 2 shows the superimposed SEF waveforms over the hemisphere contralateral to the motor point stimulation in the same subject with a 350-ms period 50 ms before and 300 ms after motor point stimulation. These two waveforms were very similar in form. The most prominent MRCF waveform was MEF1, which was observed at 35.8 ± 9.7 ms after movement onset (Table 1). On the other hand, the most concentrated SEF peak was identified at 78.7 ± 5.6 ms (M70), and the onset latency of M70 was 39.0 ± 5.5 ms after motor point stimulation (Table 1). The time courses of the source strength of MEF1 and M70 for all subjects are shown in Fig. 3.

The ECDs of MEF1, M70, and N20m after median nerve stimulation were superimposed on the schematic illustration (Fig. 4). The mean ECD locations for MEF1 and M70 relative to N20m are shown on the axial, coronal, and sagittal planes in Fig. 4. In the medial–lateral direction, the mean ECD locations of MEF1 and M70 were significantly medial to N20m (MEF1: 7.0 ± 2.9 mm, $p < 0.01$; M70: 5.7 ± 3.0 mm, $p < 0.01$), and these ECD locations were significantly superior to the ECD locations of N20m (MEF1: 4.4 ± 3.4 mm, $p < 0.01$; M70: 3.4 ± 3.0 mm, $p < 0.05$). There were no significant differences between the ECD of N20m and the ECD of MEF1 or M70 in the anterior–posterior direction. Furthermore, there were no significant differences in the ECD locations of MEF1 and M70 in the medial–lateral ($p = 0.78$), superior–inferior ($p = 1$) and anterior–posterior directions ($p = 1$). The direction of the ECD moments of MEF1 and M70 were very similar (Fig. 4).

4. Discussion

We recorded the SEFs elicited by motor point stimulation even though the very low intensity stimulation used in this study caused insensible muscle contraction without joint movements. The most prominent and fastest magnetic field after motor point stimulation was observed at 78.7 ms after the onset of stimulation. This component that

was observed at approximately 78.7 ms (M70) was consistent with the results of previous studies for electrical and magnetic recordings after motor point stimulation of the abductor pollicis brevis muscle (Kimura et al., 1999a, 1999b).

The peak latency of MEF1 was observed at 35.8 ms after movement onset in this study; however, muscle activity occurred before movement onset. In our experimental design for recording the MEF, muscle activity was observed approximately 40 ms before movement onset (Onishi et al., 2006). Therefore, MEF1 occurred approximately 75 ms after the onset of muscle contraction in our experimental system. This peak latency of MEF1 is similar to that of M70. In addition, the ECD location and direction of MEF1 are the same as those of M70. These findings show that MEF1 is the same response as M70, which is elicited by only slight muscle contraction without joint movement. We do not consider that the MEF1 and M70 components are due to the activities of the cutaneous receptor and muscle spindle of antagonist muscle. MEF1 is not generated by proprioceptive input arising from the Golgi tendon organ (Onishi et al., 2006). Therefore, our results show that the MEF1 response is elicited only by the activity of group Ia muscle afferents accompanying changes in agonist muscle configuration.

The peak latency of M70 was observed at approximately 75 ms, but the onset latency was 39 ms after motor point stimulation. It is well established that the peak of the fastest and most prominent SEF response after median nerve stimulation is observed at approximately 20 ms after stimulation (Kawamura et al., 1996; Mauguiere et al., 1997; Nagamine et al., 1998; Hoshiyama and Kakigi, 2001). Using different techniques, many researchers have reported that the motor evoked potential from hand muscles that was elicited by transcranial magnetic brain stimulation was obtained at approximately 20 ms (Barker et al., 1987; Rossini et al, 1987; Rothwell et al., 1987, 1997) and that early sensory activation after mixed median nerve stimulation of the wrist activated the sensorimotor cortices at approximately 20 ms after the stimulus onset in electroencephalographic studies (Allison et al, 1989, 1991; Grimm et al., 1998; Nagamine et al., 1998; Andre-Obadia et al., 1999; Babiloni et al., 2001; Hoshiyama and Kakigi, 2001; Barba et al., 2005). Fukuda et al. (2000) reported that the initial proprioceptive response at the thalamus level after motor point stimulation of the extensor digitorum muscle was confirmed at 10–12 ms by direct recording. Therefore, for an onset latency of approximately 40 ms after the motor point stimulation, the M70 components must not reflect the initial proprioceptive input.

The ECD locations of MEF1 and M70 were estimated to be medial and superior to that of N20m elicited by median nerve stimulation; N20m is accepted as the tangential source in area 3b. The ECD location and direction of MEF1 were very close to those of

M70. Several animal studies have shown that areas 3a and 3b process different sensory information reaching the primary somatosensory cortex; area 3a processes information coming from receptors activated by movement and muscle contraction, while area 3b processes information mainly from cutaneous receptors. MEF1 was postulated to reflect mainly sensory input from the periphery (Cheyne and Weinberg, 1989; Kristeva-Feige et al., 1994). The source underlying MEF1 should be located in the primary somatosensory cortex, area 3a, known to receive predominant input from proprioceptive receptors activated during movement (Wood et al., 1985; Rossini, et al., 1994; Kristeva-Feige et al., 1995). However, the MEG system is inherently biased toward detecting activation in the tangential cortex, and the failure of sources to localize in area 3a may be a limitation. In addition, some MEG studies have indicated the existence of a large amount of activity related to movement in area 3b (Hoshiyama et al., 1997; Tanigushi et al., 2000), and Oishi et al. (2003) reported that the ECD depth of MEF1 was located in area 3b, similar to that of N20m. The ECD depths of MEF1 and M70 in our study indicate that MEF1 and M70 responses do not originate from area 3a, which is located deeper than area 3b.

Muscle spindle afferents that project to area 3a and area 2 do not project to area 3b (Schwarz et al., 1973). Because area 2 is located posterior and superior to area 3b, the MEF1 response is not thought to be elicited from area 2. On the other hand, it has been well established that area 2 is connected to area 4 (Jones and Peters, 1986), and studies based on fMRI have indicated that area 4 is activated by passive movement (Terumitsu et al., 2009). Kawamura et al. (1996) have reported that the ECD of the second peak elicited by median nerve stimulation was localized medial and superior to the ECD of N20m, on the anterior wall of the central sulcus, "area 4." The findings of our study and of the above-mentioned studies suggest that the MEF1 response may originate from area 4. There is still, however, the possibility of area 3a or 3b involvement, as suggested by previous investigators (Cheyne and Weinberg, 1989; Kristeve-Feige et al., 1995). Our results provide further evidence that MEF1 is the same response as M70 and that both responses are elicited by muscle contraction; our results also suggest that ECD of MEF1 may be located in area 4. However, further investigations are required for gaining more insight into the effects of muscle afferent projection to the sensorimotor cortex.

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Legends

Fig. 1

The left panel shows representative whole-scalp movement-related cerebral fields (MRCF) waveforms 1500 ms before and 1000 ms after the onset of movement; the right panel shows representative whole-scalp somatosensory-evoked magnetic fields (SEF) waveforms 50 ms before and 300 ms after motor point stimulation. Superimposed waveforms above both whole-scalp waveforms indicate the waveforms in the square over the sensorimotor area contralateral to the movement or motor point stimulation (Subject 2).

Fig. 2

The left panel shows the representative superimposed MRCF waveforms over the hemisphere contralateral to the movement in Subject 2, with a 350-ms period 100 ms before and 250 ms after the movement onset. The right panel indicates the representative superimposed SEF waveforms over the hemisphere contralateral to the motor point stimulation in the same subject with a 350-ms period 50 ms before and 300 ms after the motor point stimulation.

Fig. 3

Source waveforms of sensorimotor cortices contralateral to the movement or electrical stimulation elicited by the movement or motor point stimulation for all subjects.

Fig. 4

A schematic illustration of the axial, coronal and sagittal views indicating the relative dipole positions of MEF1 and M70. The left, middle, and the right panels show the axial, coronal, and sagittal planes, respectively, on the hemisphere contralateral to the movement or motor-point stimulation. The mean of the equivalent current dipole (ECD) locations for MEF1 and M70 is relative to N20m for all subjects in the axial, coronal, and sagittal planes. The error bars indicate standard deviations. The circle and triangle refer to MEF1 and M70, respectively. The black box shows the ECD location of N20m. The ECDs of MEF1 and M70 were medial and superior to N20m.

Fig. 1

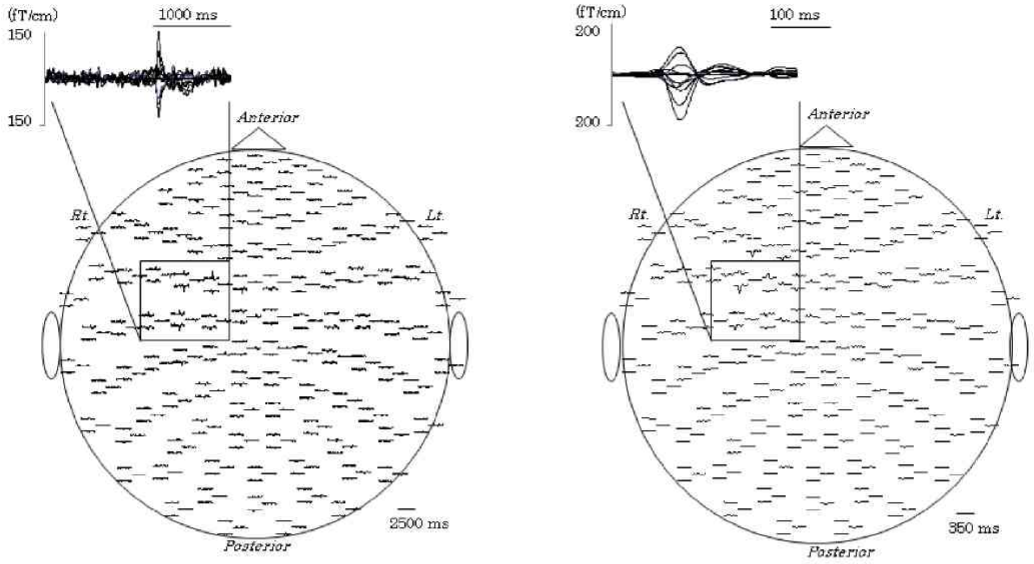
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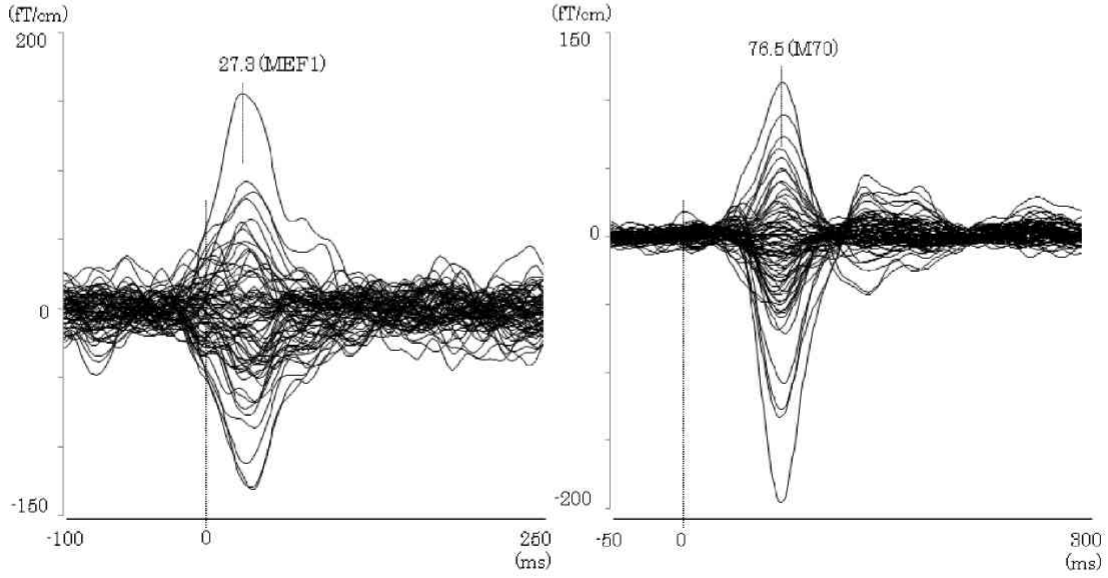
Fig. 2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(fT/cm)
150
76.5 (M70)
0
-200
-50
0
300
(ms)

Fig. 3

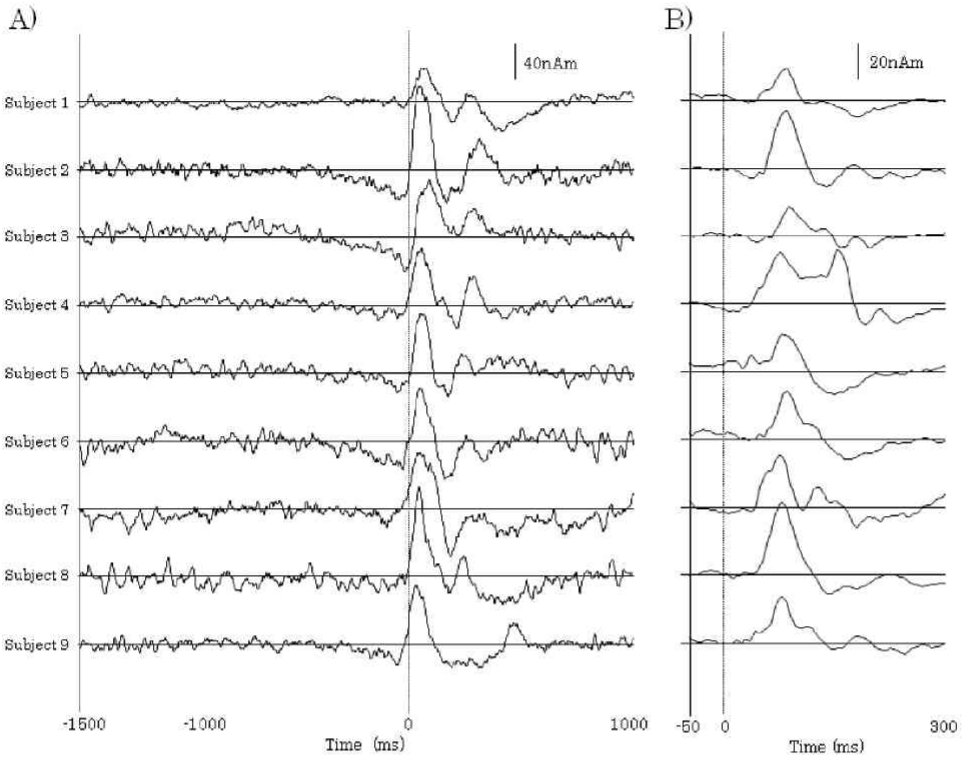
A)
B)
40nAm
20nAm
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
Subject 9
-1500
-1000
0
1000
-50
0
300
Time (ms)
Time (ms)

Fig. 4

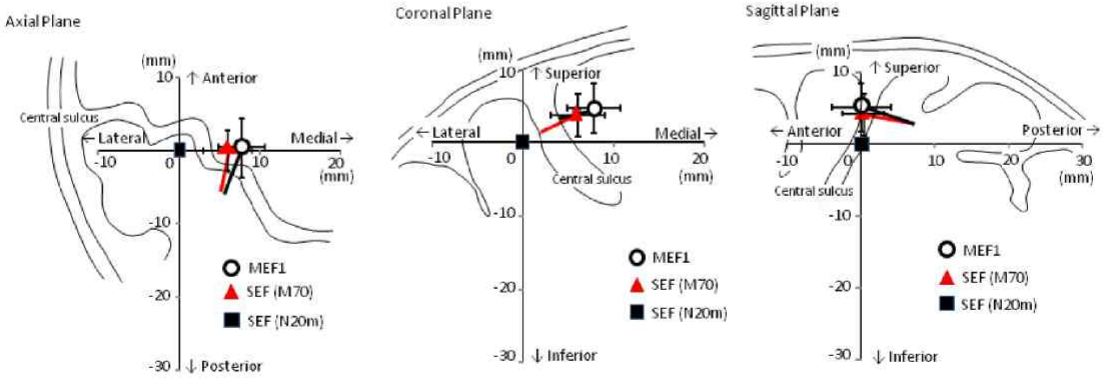
Axial Plane
Coronal Plane
Sagittal Plane
(mm)
↑ Anterior
↑ Superior
↓ Posterior
↓ Inferior
← Lateral
Medial →
← Anterior
Posterior →
Central sulcus
MEF1
SEF (M70)
SEF (N20m)

Table 1

Latency and ECD locations of MEF1 and M70 in all subjects. The ECD locations for MEF1 and M70 relative to N20m are shown on medial-lateral (X), anterior-posterior (Y), and superior-inferior (Z) directions.

	Latency (ms)			ECD location (mm)					
	MEF1 (peak)	M70 (onset)	M70 (peak)	MEF1 (X)	M70 (X)	MEF1 (Y)	M70 (Y)	MEF1 (Z)	M70 (Z)
Subject 1	34.9	35.0	76.5	8.1	4.9	5.8	3.4	3.6	1.4
Subject 2	27.3	44.0	76.5	8.2	4.4	-3.4	-4.5	1.5	0.0
Subject 3	42.5	39.7	82.9	8.7	0.6	-0.9	0.8	3.3	4.2
Subject 4	34.9	30.4	73.4	2.8	6.9	-3.4	-0.6	7.9	6.4
Subject 5	27.3	49.1	81.9	9.0	8.6	-0.9	0.4	1.5	6.3
Subject 6	50.5	41.8	89.3	1.9	2.1	3.3	5.0	9.0	5.7
Subject 7	27.3	35.6	75.5	8.7	6.3	1.9	-1.8	-0.5	-2.0
Subject 8	50.1	37.7	80.8	5.5	7.5	-3.8	-1.5	8.5	5.0
Subject 9	27.3	37.8	71.2	10.2	9.9	6.6	0.6	4.7	3.6
mean	35.8	39.0	78.7	7.0	5.7	0.6	0.2	4.4	3.4
SD	9.72	5.48	5.58	2.9	3.0	4.0	2.8	3.4	3.0