Gating of somatosensory evoked magnetic fields and potentials during the preparatory period of self-initiated voluntary movement

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1. Abbreviations

MEG	Magnetoencephalography
EEG	Electroencephalography
EMG	Electromyogram
EOG	Electrooculogram
PET	Positron emission tomography
fMRI	Functional magnetic resonance imaging
SEP	Somatosensory evoked potential
SEF	Somatosensory evoked magnetic field
MRCP	Movement-related cortical potential
BP	Bereitschaftspotential
NS'	Negative slope
SI	Primary somatosensory area
SII	Secondary somatosensory area
MI	Primary motor area
SMA	Supplementary motor area
SQUID	Superconducting quantum interference device
ECD	Equivalent current dipole
ANOVA	Analysis of variance

2. Abstract

Somatosensory evoked potentials (SEPs) and somatosensory evoked magnetic fields (SEFs) diminished in amplitude during the voluntary movement. This phenomenon is widely accepted as 'gating'. Although it is of interest to point out that a gating effect was presented even before the actual contraction, when this gating effect started in the preparatory period of voluntary movement. Therefore, this study investigated the temporal changes of the SEP/SEF components preceding voluntary movement using a self-initiated movement task.

In the first study, we studied the modulation of SEPs preceding self-initiated plantar flexion. SEPs following electrical stimulation of the right tibial nerve at the popliteal fossa was recorded in nine subjects during a self-initiated plantar flexion of the right ankle once every 5 to 10 s while ignoring electrical stimuli. Plantar flexion was started abruptly with sharp onset from total muscular relaxation. EEGs were recorded from five electrodes on the scalp (Fz, C3, Cz, C4, Pz) according to international the 10-20 system. Based on pre-movement cortical components of movement-related cortical potential (MRCP), Bereitschaftspotential (BP) and Negative slope (NS'), the pre-movement period was divided into six sub-periods (NS'-1, NS'-2, BP-1, BP-2, BP-3 and Pre-BP). In each of the six sub-periods, SEPs were averaged respectively. P30, N40, P53 and N70 were identified at Cz in all subjects. N40 amplitudes were significantly attenuated in the NS'-1, NS'-2, BP-1, BP-2 and BP-3 compared with the stationary

control condition. P53 and N70 amplitudes were not significantly changed.

In the second study, in order to localize the cortical areas which modulated in relation to voluntary movement in detail, the temporal change of SEFs in the preparatory period for self-initiated voluntary movement were investigated. The SEFs following stimulation of the right median nerve was recorded, using a 204-channel whole-head MEG system, in nine healthy subjects during a self-initiated extension of the right index finger every 5 to 7 s. The preparatory period before finger movement was divided into six sub-periods, and the MEG signals following the stimulation in each sub-period were averaged separately. SEFs were also recorded in the resting state. The equivalent current dipole (ECD) strengths for N20m and P60m were not significantly changed in any sub-period before movement compared with those in the resting state. The ECD strength for P30m was significantly smaller 500 ms or less before the movement than during the resting state, and 1500 ms or less before the movement compared to that during the period from 3000 to 4000 ms before movement. The modulation started at least 1500 ms before the movement, and was greater for the P30m than N20m component.

These results indicated that the SEF/SEP components were attenuated even during a period of self-initiated voluntary movement. These findings suggested that the somatosensory inputs from the peripheral receptors ascending to the central nervous system were modulated by motor-related efferent signals at least in the level of the cerebral cortex, centrifugal gating, preceding self-initiated movement.

3. Introduction

There are only two non-invasive techniques to investigate the actual brain function on a millisecond scale in human: Electroencephalography (EEG) and Magnetoencephalography (MEG). EEG, the measurement of electric potential differences on the scalp, is widely applied method of long clinical standing. MEG is closely related to EEG. MEG measures the magnetic fields which were generated from neurons in the cerebral cortex. In both methods, the measured signals are generated by the same synchronized neuronal activity in the brain. The time resolution of EEG and MEG is in the millisecond range, orders of magnitude better than in the other methods. Thus with MEG and EEG, it is possible to follow the rapid changes in the cortical activity that reflect ongoing signal processing in the brain; the electrical events of single neurons typically last from one to several tens of milliseconds.

MEG has the theoretical advantages of localizing brain dipoles due to reduced effects caused by cerebrospinal fluid, skull and skin, and its excellent temporal resolution is much higher than those of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). The strength of the recorded MEG is approximately 10 to 1000 fT. Therefore, it is necessary to use the well sensitive measuring instrument such as superconducting quantum interference device (SQUID). On the other hand, there are two major disadvantages of MEG. The first one is that MEG cannot detect the magnetic signals generated in the deep sites of brain, because the

signals are rapidly reduced with depth of the generator. EEG can measure the signals from deep area of the brain by volume conduction, although spatial resolution is not so well, over a few cm. The second one is that MEG cannot detect the radial component of magnetic signal mainly generated from the cerebral gyri, although it can detect dipole oriented parallel to the cerebral cortex (tangential) generated in the cerebral sulcus very well.

For precise movement, a motor program requires sensory signals from the target body area to be moved, and the appropriate integration of sensory and motor signals is essential. In previous studies which analyzed the effects of voluntary movement on SEPs and SEFs (Giblin, 1964; Abbruzzese et al., 1981; Rushton et al., 1981; Cheron and Borenstein, 1987; Cohen and Starr, 1987; Tapia et al., 1987; Huttunen and Hömberg, 1991; Kristeva-Feige et al., 1996; Kakigi et al., 1997; Morita et al., 1998; Valeriani et al., 1999), effects of voluntary movement on the sensory processing in the central nervous system have been disclosed. One prominent effect of the movement on somatosensory signals was the interaction between given sensory afferents and the signals evoked by the movement. The mechanisms of the interaction between the given sensory afferent signals and other afferent or efferent signals have been explained by a theory named 'gating'. The gating phenomenon was observed as the attenuation of the given sensory response, which could be recorded as SEP and SEF components. It has been reported that active movements (Cheron and Borenstein, 1987; Tapia et al., 1987; Cheron and Borenstein, 1991; Forss and Jousmäki, 1998), passive movements (Abbruzzesse et al.,

1981; Rushton et al., 1981; Huttunen and Hömberg, 1991) and continuous tactile stimulation (Jones, 1981; Kakigi and Jones, 1985; Kakigi et al., 1996) gave rise to gating effects on SEPs/SEFs. During voluntary movement, the gating phenomenon could occur in two possible ways; one was interaction between the given sensory afferents for SEPs/SEFs and the afferent signals evoked by the movement, i.e., afferents signals from the muscles, joint and skin (centripetal gating), and the other was interaction between the given sensory signals and the efferent signals induced by the motor command (centrifugal gating) (Jones et al., 1989). It has been considered that centripetal gating could occur at the peripheral level as well as in the spinal cord and brain, while the centrifugal gating might occur mainly in the cortex and subcortical structures.

With regard to the gating phenomenon produced by voluntary movement, modulation of the SEP components was found not only during movement (Rushton et al., 1981; Cheron and Borenstein, 1987; Kakigi et al., 1995; Forss and Jousmäki, 1998) but also just prior to it (preparatory period) (Starr and Cohen, 1985; Cohen and Starr, 1987; Shimazu et al., 1999; Murase et al., 2000; Asanuma et al., 2003). Although several studies have reported the attenuation of SEP components just before movement (Starr and Cohen, 1985; Cohen and Starr, 1987; Hoshiyama and Sheean, 1998; Shimazu et al., 1999; Murase et al., 2000; Asanuma et al., 2003), the somatosensory activity during the preparatory period remained unknown. It is considered that the gating should occur during the preparatory period of voluntary movement, and that the gating during the preparatory period must be

centrifugal. In previous studies, pre-movement modulation of the somatosensory inputs has been investigated using reaction time tasks (Starr and Cohen, 1985; Cohen and Starr, 1987; Tapia et al., 1987; Böcker et al., 1993; Staines et al., 1997; Hoshiyama and Sheean, 1998; Morita et al., 1998; Shimazu et al., 1999; Murase et al., 2000; Asanuma et al., 2003). However, a reaction time task evokes various cognitive brain activities, such as expectancy, motivation and attention, which may change the sensorimotor activities. Therefore, in the present study, we used a self-initiated movement task to avoid the mixing of neural activities relating to the external cues for the movement.

The present thesis is included two research works. The first is the gating of SEPs during the preparatory period of self-initiated plantar flexion and the second, gating of SEFs during the preparatory period of self-initiated finger extension. In the present studies, the stimulation for SEPs/SEFs was delivered randomly during the experiment, and the voluntary movement was self-paced. I collected the epochs and analyzed them to elucidate when the gating occurred during the preparatory period of the voluntary movement, especially the periods for the BP and NS' (Kornhuber et al., 1965; Shibasaki et al., 1980). This is the first study to investigate the effects of neuronal activities relating to self-initiated movement preparation on somatosensory perception in humans.

4. Subjects and Methods

Study I

Subjects

Nine healthy volunteers participated in the present study (eight males and one female; mean age 24.8 years, S.D. 2.2 years). Informed consent for participation in this experiment was obtained from all subjects. No medication was given to the subjects before the experiment. Each of the subjects sat on a reclining chair with both knees at 150 degrees and both ankles were on forceplates at 120 degrees in a shielded room while SEPs were recorded.

Stimulation procedure

SEPs were measured following the stimulation of the right posterior tibial nerve at the popliteal fossa. Square-wave pulses of 0.2 ms were delivered via surface electrodes with the cathode on the posterior tibial nerve and the anode on the patella. The stimulus intensity was adjusted to be just over the motor threshold which gave 5% of the maximal M wave and monitored to keep a constant stimulus delivered throughout this experiment. The stimulus interval was changed randomly from 250 to 750 ms (mean, 500 ms).

Experimental paradigm

In the present study, SEPs were measured using a self-initiated movement paradigm to investigate the effect of voluntary movement

on SEPs during the preparatory period for the movement. The SEPs were recorded using two sequences. One sequence (Rest sequence) was under stationary condition as a control, in which the subjects kept their legs relaxed and delivered 300 stimuli were delivered. Rest sequence was measured the before and after the Movement sequence. In other sequence (Movement sequence), the subjects were instructed to perform the right plantar flexion as quickly as possible for a short time and then relaxed. They were instructed to repeat the movement every 5 to 7 s, but were allowed to perform the movement at their own pace. In Movement sequence, 500 trials were performed, and the subjects were asked to concentrate on the movement and not to pay attention to the continuous electrical stimulation of the right posterior tibial nerve. They were also asked not to blink during the preparatory period of the movement (approximately 3 s before the movement) and after the movement (1 s after the movement). Each subject practiced the movement for a short time prior to the study.

Data acquisition and analysis

EEGs were recorded from Fz, C3, Cz, C4 and Pz on the scalp according to the international 10-20 system referenced to linked earlobes. Surface electromyograms (EMGs) were recorded from right tibialis anterior and soleus muscle with an interelectrode distance of approximately 2 cm longitudinally. Vertical and horizontal electrooculograms (EOGs) were recorded by placing electrodes above and below the right orbital fossa. The bandpass filter of the amplifier was 5-3000 Hz, 0.03-100Hz and 5-3000Hz for EOGs, EEGs

measuring for MRCPs and SEPs and EMGs, respectively. EEG and EMG data were stored on a personal computer with a sampling rate of 1 kHz.

MRCPs were averaged based on the onset of the rectified right soleus EMG, and onset of MRCPs component, BP and NS', were visually determined. Based on these components, the pre-movement period was divided into six sub-periods (Figure 1): two NS' sub-periods (NS'-1 and NS'-2), three BP sub-periods (BP-1, BP-2 and BP-3) and the preceding BP onset (Pre-BP). Since the electrical stimulation for SEPs was delivered continuously, to determine the SEPs in six pre-movement periods, we selected electrical signals in each sub-period and SEPs in the preparatory periods were separately averaged. The analysis time for SEPs were 200 ms which include a prestimulus period of 50 ms. The SEPs epochs before an inappropriate ankle movement, as evaluated using the EMG and by visual inspection through a monitor, and EOGs signal variation larger then 80 μV were excluded. At least 150 samples were averaged to obtain each SEP trace. The sizes of the SEPs and M wave were measured as the peak-to-peak amplitude.

One-way repeated measures analysis of variance (ANOVA) was used to test the SEPs and M wave amplitude differences. Post-hoc test analysis was conducted using the paired t-test. The level of statistical significance was set at 5% ($p<0.05$).

Study II

Subjects

Nine healthy volunteers participated in the present study (mean age 33.0, range 24-49, S.D. 8.5 years). All subjects were right-handed males. Written informed consent was obtained from each participant prior to the study, which was first approved by the Ethics Committee at the National institute for physiological sciences. No medication was given to the subjects before the experiment.

Experimental paradigm

In the present study, SEFs were measured following stimulation of the right median nerve during a movement paradigm to investigate the effects of voluntary movement on SEFs during the preparatory period for the movement. The subjects sat on a recording chair in the MEG device in a magnetically shielded room. The SEFs were recorded using two sequences. One sequence (Rest sequence) was under the stationary condition as the control, in which the subjects kept their arms relaxed on a table in front of them. In the other sequence (Movement sequence), the subjects performed a voluntary finger extension. In the Movement sequence, the subjects were instructed to extend the right index finger as quickly as possible for a short time and then to relax. They were instructed to repeat the movement every 5 to 7 s, but were allowed to perform the movement at their own pace. This paradigm was fundamentally the same as that for recording MRCPs. The subjects were asked to concentrate on the

movement and not to pay attention to the continuous electrical stimulation of the median nerve. They were also asked not to blink during the preparatory period of the movement (approximately 4 s before the movement) and after the movement (1 s after the movement). Each subject practiced the movement for a short time prior to the study. The subjects repeated the movement at least 300 times (for 30 min) in the Movement sequence.

Median nerve stimulation

The right median nerve was stimulated on the palm side at the wrist with a saddle type electrode. The cathode was placed 3 cm proximal to the anode. The electrode was fixed on the median nerve not to move during the movement of the finger. Constant current square wave pulses (duration, 0.2 ms) were provided, and the intensity was adjusted to produce a slight twitch of the muscle (abductor pollicis brevis). The actual stimulus intensity was 5.5 to 9.3 mA. The interstimulus interval of the stimulation was changed randomly from 600 to 800 ms (mean, 700 ms). Therefore, at least 300 and 2500 stimulations were delivered in the Rest and Movement sequence, respectively.

EMG and EOG recordings

An EMG was recorded to determine each preparatory period of the movement. The EMG was obtained from the right extensor indicis muscle in the forearm using a pair of disk electrodes. One electrode was placed on the belly of the muscle and the other was placed 2 cm

distal to the electrode. The EMG signals were passed through a bandpass filter of 5-200 Hz, and sampled at 995 Hz. Vertical and horizontal EOGs were also recorded with a bandpass filter of 0.1-50Hz and digitized at a rate of 995 Hz. Epochs in which signal variations were larger than 80 μV were excluded from the averaging.

MEG equipment

The SEFs were recorded with a helmet-shaped 306-channel detector array (Vectorview, ELEKTA Neuromag Yod, Helsinki, Finland), which comprised 102 identical triple sensor elements. Each sensor element consists of two orthogonal planar gradiometers and one magnetometer coupled to a multi-SQUID and thus provides three independent measurements of the magnetic fields. In the present study, we analyzed MEG signals recorded from 204-channel planar-type gradiometers. The signals were filtered with a bandpass filter of 0.03-300 Hz, and digitized at 995Hz like the EMG signals.

Prior to the recording, the exact head location with respect to the sensors was found by measuring the magnetic signals produced by currents leading to four head indicator coils placed at known sites on the scalp. Four head position indicator (HPI) coils attached on the subject's head were measured with respect to the three anatomical landmarks using a 3-D digitizer to allow alignment of the MEG and magnetic resonance (MR) image coordinate systems (3.0-T Siemens Allegra). The x-axis was fixed with the preauricular points, the positive direction being to the right. The positive y-axis passed through the nasion and the z-axis thus pointed upward. Current was

then fed to the position indicator coils and the resulting magnetic fields were measured with the magnetometer, which allowed for aligning the individual head coordinate system with the magnetometer coordinate system.

Data acquisition

The preparatory period of voluntary movement was temporally divided into six sub-periods; 0 (EMG onset) to –500 ms, –500 to –1000 ms, –1000 to –1500 ms, –1500 to –2000 ms, –2000 to –3000 ms and –3000 to –4000 ms (Figure 2). Since the electrical stimulation for the SEFs was delivered continuously, we collected the SEF epochs in each sub-period. The analysis time for SEF was 250 ms which included a prestimulus period of 50 ms. The SEF epochs before an inappropriate finger movement, as evaluated using EMG and by visual inspection through a monitor, were excluded. Finally, one hundred and fifty to two hundred stimuli were collected for the Rest sequence and each sub-period of the Movement sequence.

Data analysis

The ECDs of N20m, P30m and P60m were estimated during six sub-periods and Rest sequence. The head was modeled with a sphere best fitting the inner curvature of the skull in the primary somatosensory area (SI) in the individual MR images. The ECDs best explaining the magnetic field distribution over the SI cortex were found by least-squares searches taking account of the signals from at least 20 channels around the signal maxima, so that these covered both

field extremes of the local field distribution over the SI. The goodness of fit (GOF) of the model was calculated and only ECDs explaining more than 90% of the GOF value at selected point of time over a subset of channels were used for further analysis. These calculations resulted in the 3-D locations, orientations, and strength of ECDs (moment) in a spherical conductor model, which was based on the subjects' MR image (Hämäläinen et al., 1993). Peak latency, peak amplitude of ECD strength (moment) and ECD location (x, y and z coordinates) for recognizable consistent components within 100 ms after stimulation of the median nerve, were compared using one-way repeated measured ANOVA, with the sub-period and the Rest sequence as the factor. The F values were obtained after Greenhouse-Geisser correction when appropriate and a correction coefficient epsilon was used. Post-hoc analysis followed by Fisher's PLSD was used for multiple comparisons. The level of statistical significance was set at 5% ($p<0.05$).

5. Results

Study I

All subjects performed the voluntary movement successfully, and clear SEPs and MRCPs were recorded for all of them. BP and NS' were identified in all subjects. The mean onset latency of these components at Cz was 1438.4 ms (S.D. 83.4 ms) and 465.8 ms (S.D. 32.5 ms) before the onset of soleus EMG respectively.

The amplitudes of the M wave which was used as index of constant intensity stimulus were unchanged between the stationary control and six pre-movement sub-periods.

The SEP waveforms evoked by stimulation of the tibial nerve at Cz from one subject are shown in Figure 3. The negative deflection, N40, peaking at around 40 ms after the stimulation (mean, 40.5 ms), was followed by a positive deflection, P53 (mean, 53.4 ms), and a negative deflection, N70, around 70 ms after the stimulation (mean, 69.4 ms). Clear N40, P53 and N70 were identified in the stationary control and the preparatory periods of voluntary movement. Compared to the stationary control condition, N40 amplitude recorded at Cz was significantly attenuated in the preparatory periods of voluntary movement, whereas P53 and N70 were unchanged. The N40 evoked in the NS'-1 ($p<0.01$), NS'-2 ($p<0.01$), BP-1 ($p<0.05$), BP-2 ($p<0.05$) and BP-3 ($p<0.01$) sub-periods were significantly attenuated in amplitude compared to that in the stationary control condition, and the N40 amplitude during NS'-2 ($p<0.01$), BP-1

($p<0.01$), BP-2 ($p<0.01$), BP-3 ($p<0.01$) and Pre-BP sub-periods were smaller than that during NS'-1 sub-period (Figure 4).

Study II

All subjects performed the voluntary movement successfully, and clear SEFs were recorded for all of them. Figure 5 shows the SEF waveforms elicited by stimulation of the right median nerve in one subject. Clear deflections were obtained from the gradiometers on the primary somatosensory cortex in the hemisphere contralateral to the stimulated side. The initial upward deflection, N20m, peaking at around 20 ms after the stimulation (mean, 20.7 ms), was followed by a downward deflection, P30m, around 30 ms (mean, 29.6 ms) and a downward deflection, P60m, around 60 ms after the stimulation (mean, 65.3 ms). These three components were identified in all subjects (Figure 5). One small upward deflection, N45m, was also identified between P30m and P60m, but it did not exceed the baseline in some subjects. Therefore, in the present study, we analyzed only the three components. Responses at a latency longer than 80 ms were recognized in the hemisphere contralateral and ipsilateral to the stimulated side, but the responses were not consistent among the subjects. This long-latency component was considered to be generated in the secondary somatosensory area (SII) in previous studies (Hari and Forss, 1999; Maeda et al., 1999; Kakigi et al., 2000). Since this component was not clearly identified with an interstimulus

interval shorter than 1000 ms (Hari et al., 1993; Wikström et al., 1996; Nagamine et al., 1998), it was not consistent in the present study using a short interstimulus interval (mean, 700 ms). Figure 6 shows the locations of the estimated ECDs on the MR images in one subject. N20m, P30m and P60m were generated in the postcentral wall in the hemisphere contralateral to the stimulated side in all subjects including this one.

Figure 7 shows the grand average SEF waveforms obtained in the Rest sequence and in each sub-period of the Movement sequence. The P30m appeared to show a clear change prior to 1500 ms before the EMG onset, whereas the N20m and N60m components did not change during any of the sub-sequences.

In the statistical analysis, p values calculated by ANOVA for each factor of each response are shown in Table 1, using the sub-period as the measured factor. Since sub-period was not a significant factor for peak latency and ECD location (x, y and z coordinates), values for the Rest and sequence are shown in Table 2.

Sub-period was a significant factor for the ECD strengths (dipole moments) of each component (Table 1, Figure 8). P30m was significantly attenuated in the Movement sequence, whereas N20m and P60m were unchanged. The P30m evoked in the 0 to –500 ms sub-period was significantly attenuated in amplitude compared to that in the Rest sequence ($p<0.01$), and the P30m amplitude during 0 to –500 ms ($p<0.01$), –500 to –1000 ms ($p<0.01$) and –1000 to –1500 ms ($p<0.05$) sub-periods were smaller than that during –3000 to –4000 ms sub-period.

6. Discussion

Evidence of 'gating' between the sensory afferent signals and voluntary movement has been reported (Giblin, 1964; Abbruzzese et al., 1981, Rushton et al., 1981; Cohen and Starr, 1987, Cheron and Borenstein, 1987; Tapia et al., 1987; Huttunen and Hömberg, 1991; Kakigi et al., 1997; Morita et al., 1998; Valeriani et al., 1999; Kakigi et al., 2000), but the responsible site and the mechanisms remained unclear, although the cortex or subcortical structures were speculated to be the major sites. Two major mechanisms for gating effects, centrifugal and centripetal gating, have been discussed in previous studies (Jones et al., 1989; Kristeva-Feige et al., 1996; Kakigi et al., 1997; Valeriani et al., 1999). During voluntary movement, both mechanisms involving centrifugal and centripetal gating might occur. To separate centrifugal from centripetal gating, we designed the present study, in which the SEPS/SEFs were recorded before movement (preparatory period). Since no afferent signals were evoked by voluntary movement, gating that occurred before the movement during the preparatory period was considered due to the interaction between the sensory activity for motor preparation, possibly generated in the cortex, and given sensory afferents following stimulation of the median nerve. Another advantage of the present study was that we recorded the SEPs/SEFs before movement during a self-initiated voluntary movement task. Most previous studies used a reaction time task with a cue signal for voluntary movement, but it was difficult to exclude the effect of the cognitive activity after the

cue signal or the direct effect of the sensory activity following the signal itself.

Study I

Although there have been many studies reporting the gating effect of SEPs/SEFs caused by voluntary movement in the upper limb during and before voluntary movement (Giblin, 1964; Broughton et al., 1965; Coquery et al., 1972; Lee and White, 1974; Papakostopoulos et al., 1975; Jones, 1981; Rushton et al., 1981; Abbruzzese et al., 1981; Cohen and Starr, 1985; Cheron and Borenstein, 1987; Jones et al, 1989; Cheron and Borenstein, 1991, 1992; Hoshiyama and Sheean, 1998; Shimazu et al, 1999; Murase et al., 2000; Asanuma et al., 2003), it is seemed that the modulation of somatosensory inputs caused by active movement from lower limb is not investigated in detail, especially during the preparatory period of voluntary movement. Therefore, in this experiment, I investigated when gating of SEPs occurred in the preparatory periods of self-initiated voluntary movement and whether centrifugal gating effect was related to the motor-related activities recorded on the scalp components, BP and NS'. To my knowledge, this is the first study investigating the temporal modulation of gating effect in lower limb during the preparatory periods of self-initiated voluntary movement.

Unlike somatosensory evoked responses following upper limb stimulation, the number of reports concerning those following lower

limb stimulation is small, and the generating mechanism of each component has not been clarified. The ECD location for around 50 ms component elicited by ankle stimulation was located along to the interhemispheric fissure contralateral to the stimulated nerve, the foot sensory area of the SI (Kakigi et al., 1995; Hari et al., 1996; Shimojo et al., 1996; Kakigi et al., 1997). Although the generator for N40 in the present study is unknown, probably, the tibial nerve 45m component evoked by the ankle stimulation is analogous to the tibial nerve N40 elicited by the stimulation of popliteal fossa.

Whereas gating mechanism has been extensively investigated during a various kinds of movements (Cohen and Starr, 1985; Seyal et al., 1987; Kakigi et al., 1997; Tinazzi et al., 1997, 1998; Valeriani et al., 1998), only a limited number of studies have been performed to evaluate the modulation of SEPs/SEFs during the preparatory period (Staines et al., 1997; Morita et al., 1998; Asanuma et al., 2003). Therefore, the change in the lower limb SEP component during the preparatory period was controversial in previous studies. Asanuma et al. (2003) reported that P40 component, the first somatosensory cortical response, showed significant gating effect using a paradigm in which the signal for triggering movement is the electric stimulus for SEPs. Staines et al. (1997) reported that attenuation of P1-N1 component (N40 in this study) occurred 100 ms prior to EMG onset using the reaction time task. However, since a reaction time task evokes various cognitive brain activities, which may change the sensorimotor activities, this study used a self-initiated movement task to avoid the mixing of neural activities relating to the external cues for

the movement. This study collected the epochs and analyzed them to elucidate when the gating occurred during the preparatory period of the voluntary movement, especially the periods for the BP and NS'. It has been demonstrated that the MRCPs that are seen prior to internally generated movements begin more than 1 s before the onset of voluntary movement. The onset of SEP depression corresponds well to the onset of MRCP component, N40 component started to attenuate in the BP-3 sub-period and abruptly attenuated in the NS-1 sub-period. It thus seems likely that the SEP gating in the preparatory period is closely associated to the motor signals from the movement-related cortical areas. Projection from the primary motor area (MI) to the somatosensory cortex (Jones et al., 1978), to the thalamus (Tsumoto et al., 1975), and to dorsal column cells (Ghez and Pisa, 1972; Coulter, 1974) have been demonstrated and any of these connections could be responsible for the observed gating.

Study II

In this study, wider window (500 to 1000 ms) for each period was used, focusing on the interaction during the period of BP and part of NS', and analyzed SEF change up to 4000 ms before the movement, which has not previously been studied.

The change in the N20 component of the SEPs during the preparatory period was controversial in previous studies. Some authors reported that the amplitude did not change before movement

(Starr and Cohen, 1985; Cohen and Starr, 1987; Shimazu et al., 1999; Murase et al., 2000), while others reported attenuation of the component just before movement (Nishihira et al., 1991; Hoshiyama and Sheean, 1998). In the present study, the N20m dipole moment was unchanged in each period. In the period just before movement, the neural activity in the sensorimotor cortex seemed to change dramatically (Deecke et al., 1969; Gerloff et al., 1998), and gating between the motor potential and the applied stimulation for SEPs/SEFs might occur. However, since the main focus in this study was to know the SEF changes in the pre-movement period, this study did not analyze SEF change just before movement in great detail. Therefore, I used a relatively wider window (500 ms) than that in previous studies so that we did not take into account the SEF change just before movement. In contrast, ECD strength for P30m showed a clear and significant attenuation during the preparatory period. This attenuation was remarkable just before movement (0 to –500 ms sub-period) compared to the resting state. During the 0 to –500 ms sub-period, attenuation of P30m might include major attenuation of the P30 component just before the movement reported in previous papers (Starr and Cohen, 1985; Cohen and Starr, 1987; Nishihira et al., 1991; Hoshiyama and Sheean, 1998). However, it is considered that the P30m attenuation from –500 to –1500 ms before movement did not relate to the motor potential just before movement but to the preparatory brain activity corresponding to BP and part of NS'. To study SEPs/SEFs change before voluntary movement, most of previous studies used reaction time task. The SEP component 25 to

30 ms after the stimulation was attenuated before movement (Starr and Cohen, 1985; Cohen and Starr, 1987; Shimazu et al., 1999, Murase et al., 2000). Starr and Cohen (1985) reported that the attenuation of the P27 component started approximately 100 ms before the EMG onset. During the short period after the cue, interaction between the brain activity following the cue and applied signal for SEFs might occur. However, the modulation of the P30m in the present study seemed to start at least 1500 ms before the EMG onset. In a self-initiated movement task, it was considered that the brain activity following the cue and the anticipatory effect evoked by a cue on the motor preparatory brain activity could be excluded (Kutas and Donchin, 1980; Jahanshani et al., 1995). Therefore, it was possible that the attenuation of P30m in the present study was of selective gating between the self-initiated preparatory brain activity and applied sensory signal for SEFs, although we could not refer to the subject's internal cue.

With regard to the ECD location for N20m, P30m and N60m, the present results were consistent with those of previous studies (Huttunen et al., 1999; Hari and Forss, 1999; Kakigi et al, 2000). The ECDs of these components were identified around the SI in the hemisphere contralateral to the stimulated side. In general, the primary component, N20/N20m, is generated in area 3b of SI (Desmedt et al., 1987; Allison et al., 1991; Huttunen et al., 1999; Hari and Forss, 1999; Kakigi et al., 2000). This area should receive signals during the preparatory period for voluntary movement, but the gating effect on this component is still controversial as described above. The

generator for P30m remains unknown. The generator was suggested to be some areas in the SI (Hari and Forss, 1999; Kakigi et al., 2000), but since the direction of the dipole is opposite to that of N20m, area 4 of the MI may also be involved (Kawamura et al., 1996). The functional difference between N20/N20m and P30/P30m is evident from the results of previous studies of repetitive stimulation (Wikström et al., 1996) and a recovery function (Hoshiyama and Kakigi, 2001; 2002). In addition, the P30/P30m component was more sensitive to the movement gating effect than N20/N20m (Starr and Cohen, 1985; Cohen and Starr, 1987; Kakigi et al., 1995; Forss and Jousmäki, 1998; Shimazu et al., 1999, Murase et al., 2000). We speculated that the effects of voluntary movement or brain activity of motor preparation on P30m might qualitatively differ from those on N20m. Although the qualitative difference could include quantitative difference, we considered that the motor command differently affected N20m and P30m.

General Discussion

This study indicated that the somatosensory input from peripheral body part was modulated in the preparatory period of voluntary movement. The gating of the SEPs/SEFs prior to muscle contraction must be generated by centrifugal mechanism, since the peripheral feedback evoked by the movement cannot have influenced the SEPs/SEFs. However, the specific neural origins for the

centrifugal gating and the site where the gating occurred are not known in this study.

It has been reported that gating during active movement occurred at several level in the central nervous system. Ghez and Pisa (1972) reported that the evoked response in the cuneate nucleus following stimulation of superficial radial nerve was reduced in amplitude in cats. The evoked potential at the somatosensory cortex in monkeys following forearm stimulation was decreased during active movement (Chapman et al., 1988; Jiang et al., 1991). These results suggested that more than one site was responsible for gating. Moreover, intracortical microstimulation of the neurons in the MI in the monkey produced a profound decrease in the magnitude of the short-latency component of the somatosensory response in the SI (Jiang et al., 1990), suggesting that the centrifugal influence from the MI could modulate the SEPs. However, since the N20m following the stimulation of median nerve was not changed and P30m was attenuated in the preparatory period, these results suggested that, in humans, gating of somatosensory input occurs cortical origin, the most likely site occurred the centrifugal gating effect was somatosensory cortex.

In study of monkeys, the supplementary motor area (SMA) was preferentially activated before an internally generated (or self-paced) movement (Mushiake et al., 1991). The SMA activity in this period was also reported in humans recorded from the cortex (Neshige et al., 1988; Ikeda et al., 1992; Hoshiyama et al., 1997; Toma et al., 2002). Therefore, SMA activity might be the main factor for the change in N40 following stimulation of tibial nerve and P30m following

stimulation of median nerve during the preparatory period. Interestingly, the time course of the N40 and P30m modulation, starting from about 1500 ms before the movement and peaking just prior to the movement (NS'-1 sub-period in lower limb and 0 to –500 ms sub-period in upper limb), was similar to that of the MRCP activity. Therefore, though it is a speculation with no definite evidence, the gating effect on N40 and P30m may reflect neuronal activities relating to motor preparation.

Motor-related cortices, such as SMA and MI, have extensive cortico-cortical connections to other cortices such as the SI (Jones et al., 1978) and possibly other sensory associated cortices. In animal studies, efferent signals generated by the motor command inhibited the sensory activity via relay nuclei preceding movements (Ghez and Pisa, 1972), and stimulation of the pyramidal tract inhibited the response in the thalamus following stimulation of the medial lemniscus (Tsumoto et al., 1975). In contrast, the activation of the sensory cortex might be essential to control the motor performance in a feedforward manner, and the interaction taking place in the SI between such an intrinsic activity and the given afferent signals following stimulation of the median nerve might occur at an early stage of the preparatory period for voluntary movement. It should also be taken into consideration that the electrical cortical activity associated with the voluntary movement in the SI and motor-related areas could interfere with the stimulus-evoked potentials. Another, less likely, possibility is that interaction took place in the primary somatosensory cortex between the ascending tactile signals following

median nerve stimulation and the continuously ascending signals relating to proprioception during the preparatory period. However, Hoshiyama and Kakigi (2000) investigated such interaction in detail, and reported that while the afferent proprioceptive signals from the proximal muscles of the limb might cause such an effect, the afferent signals from the distal stimulation were not affected.

In conclusion, this study confirmed the attenuation of the SEPs/SEFs components during a self-paced voluntary movement. The modulation started at least 500 ms before the movement. The possible mechanism was that the motor associated cortices attenuated the SEPs/SEFs components by the centrifugal gating process. Although these finding are important and interesting, the underling mechanisms have yet to be clarified.

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9. Tables

Table 1

ANOVA values for each component when the period (Rest sequence and sub-periods) was the factor.

	P value
Peak latency	
N20m	n.s.
P30m	n.s.
P60m	n.s.
Dipole strength	
N20m	n.s.
P30m	P<0.001
P60m	n.s.
SEF amplitude	
N20m	P=0.011
P30m	P=0.001
P60m	n.s.
N20m coordinate	
x (mm)	n.s.
y (mm)	n.s.
z (mm)	n.s.
P30m coordinate	
x (mm)	n.s.
y (mm)	n.s.
z (mm)	n.s.
P60m coordinate	
x (mm)	n.s.
y (mm)	n.s.
z (mm)	n.s.

Table 2

Peak latency and ECD location (x, y, z coordinate) in Rest sequence

Peak latency (ms)	mean (S.D.)
N20m	20.6 (0.8)
P30m	29.5 (2.7)
P60m	64.6 (12.3)
N20m coordinate	
x (mm)	-44.1 (3.4)
y (mm)	16.0 (10.0)
z (mm)	95.6 (4.8)
P30m coordinate	
x (mm)	-41.5 (4.3)
y (mm)	20.2 (9.7)
z (mm)	95.1 (6.5)
P60m coordinate	
x (mm)	-43.5 (4.3)
y (mm)	18.1 (11.8)
z (mm)	93.4 (10.7)

Peak latency was measured at the time when dipole moment showed the maximum value. The x-axis was fixed by the preauricular points, the positive direction being to the right. The positive y-axis passed through the nasion and z-axis pointed thus upward.

10. Figure Legends

Figure 1

A schematic representation of pre-movement six sub-periods in Study I.

Bereitschaftspotential (BP) and Negative Slope (NS') onsets were identified visually. Judging from the MRCP components (BP and NS'), the pre-movement period was divided into six sub-periods. The six sub-periods were NS'-1, NS'-2 (NS' was divided in two periods equally), BP-1, BP-2, BP-3 (BP was divided in three periods equally) and Pre-BP (preceding the BP onset).

Figure 2

A schema of the sub-periods of the Movement sequence in Study II.

(A) movement-related cortical magnetic fields, (B) a rectified EMG and the onset of the EMG, and (C) time are expressed by minus values before movement. Median nerve stimulation was applied at random (mean, 700ms) and SEFs were averaged separately depending on the sub-period during which the median nerve was stimulated.

Figure 3

SEP waveforms (Cz) during stationary control and pre-movement six periods in one subject.

SEP recordings were evoked by the right posterior tibial nerve stimulation at popliteal fossa. Two control waveforms were pre-SEP control (thick line) and post-SEP-control (thin line). The vertical dotted lines correspond to the peaks of the P30, N40, P53 and N70 components.

Figure 4

Mean and standard deviation of the SEP amplitudes of N40, P53 and N60 components in the Rest sequence and sub-periods of the Movement sequence.

Vertical lines indicate standard deviation. * $p<0.05$, ** $p<0.01$; Statistical significance compared with the values in the Rest sequence. N40 amplitudes were significantly attenuated in the NS'-1, NS'-2, BP-1, BP-2 and BP-3 compared with the stationary control condition. P53 and N70 amplitudes showed no significant change.

Figure 5

Somatosensory evoked magnetic fields following right median nerve stimulation in a subject.

(A) Averaged SEF waveforms following stimulation of right median nerve, recorded with a whole-scalp neuromagnetometer (204-channel). The SEF waveforms viewed from the top of the head. (B) An enlarged waveform obtained from one MEG channel in the primary somatosensory cortex (SI) (framed channel in (A)). Three

main components, N20m, P30m and P60m, were identified. A vertical line indicates the stimulus.

Figure 6

The contour map and the localization of the dipoles for each SEF component on MR images.

The sensor array viewed from the top and left, with an example of field pattern. The red line indicates magnetic flux out of the head and blue line indicated magnetic flux into the head. The ECD locations of N20m, P30m and P60m are superimposed on the subject's MR image. All ECDs (N20m, P30m and P60m) were located in the posterior bank of the central sulcus (SI) in the hemisphere contralateral to the stimulated side.

Figure 7

Change of the grand averaged SEF waveforms (9 subjects) in the Rest and Movement sequences.

The N20m, P30m and P60m components were identified in the waveform in the frame. A solid line indicates the SEF waveform in each sub-period and a dotted line that of the Rest sequence. The P30m in sub-periods 0 to –500ms, –500 to –1000ms, and –1000 and –1500ms, was attenuated, as indicated by the arrows.

Figure 8

Mean and standard deviation of the ECD strengths of N20m, P30m and P60m components in the Rest sequence and sub-periods of the Movement sequence.

Vertical lines indicate standard deviation. * $p<0.05$, ** $p<0.01$; Statistical significance compared with the values in the Rest sequence, # $p<0.05$, ## $p<0.01$; Statistical significance compared with the values for the –4000 to –3000 ms sub-period. Two periods for P30m showed a significant reduction as compared with the Rest sequence and/or the –4000 to –3000 ms sub-period. N20m and P60m showed no significant change.

Figure 1

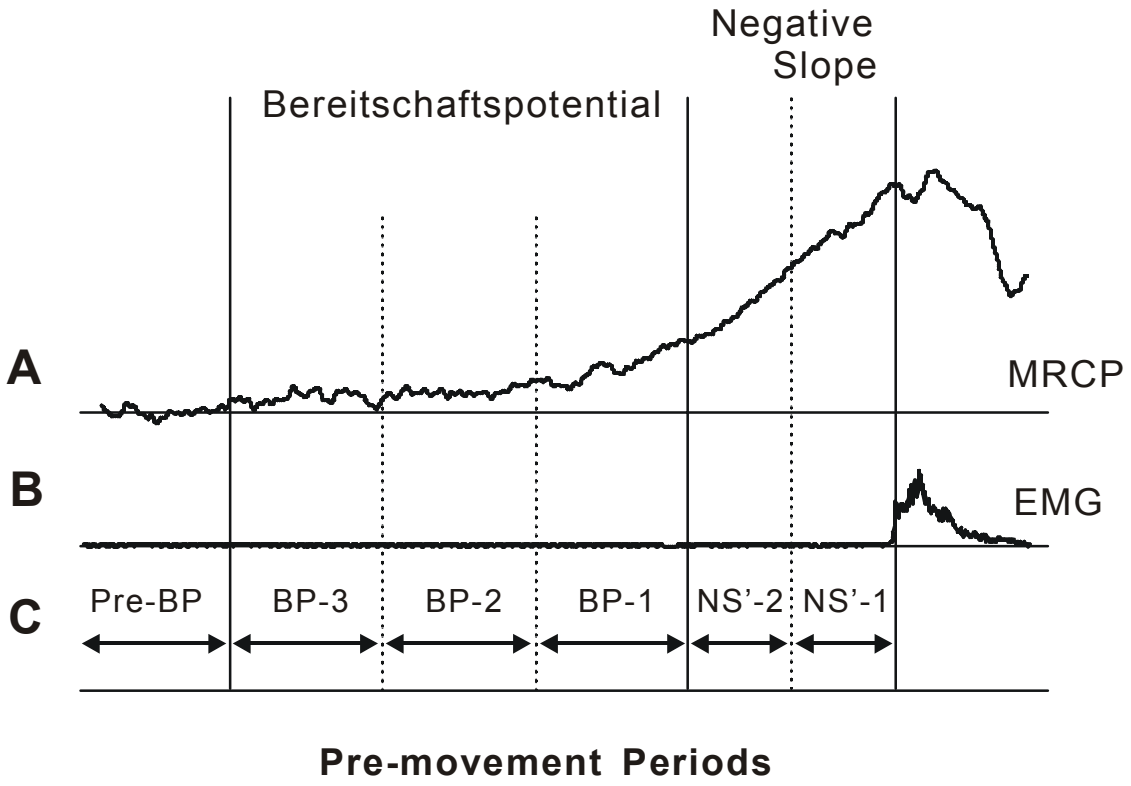

Negative
Slope
Bereitschaftspotential
A
MRCP
B
EMG
C
Pre-BP
BP-3
BP-2
BP-1
NS'-2
NS'-1
Pre-movement Periods

Figure 2

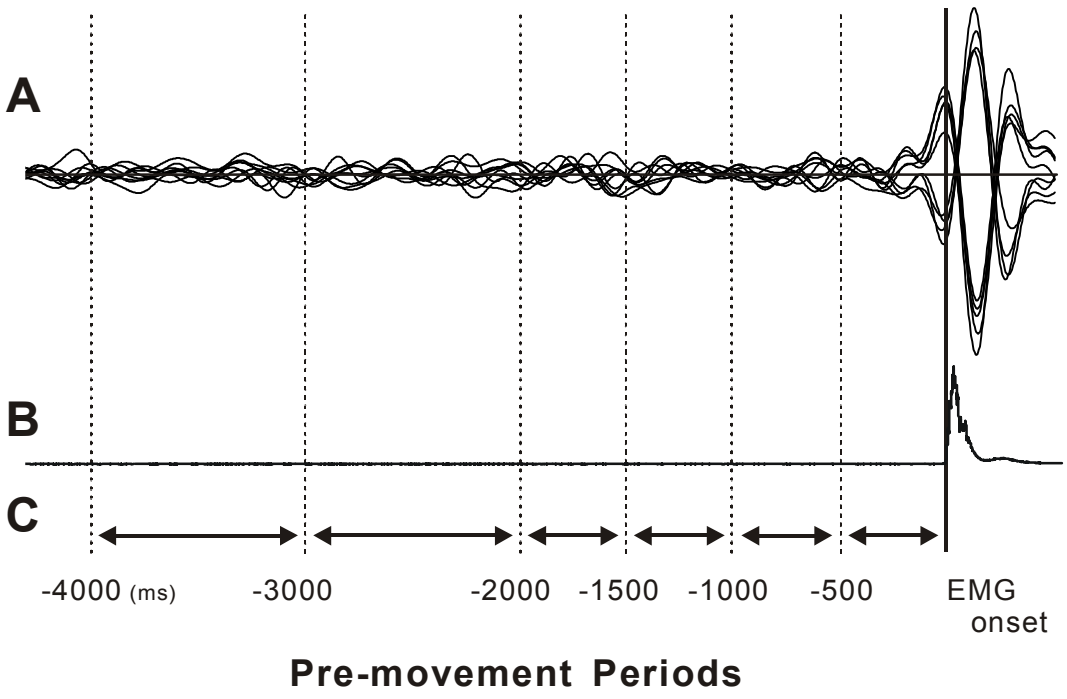

A
B
C
-4000 (ms)
-3000
-2000
-1500
-1000
-500
EMG onset
Pre-movement Periods

Figure 3

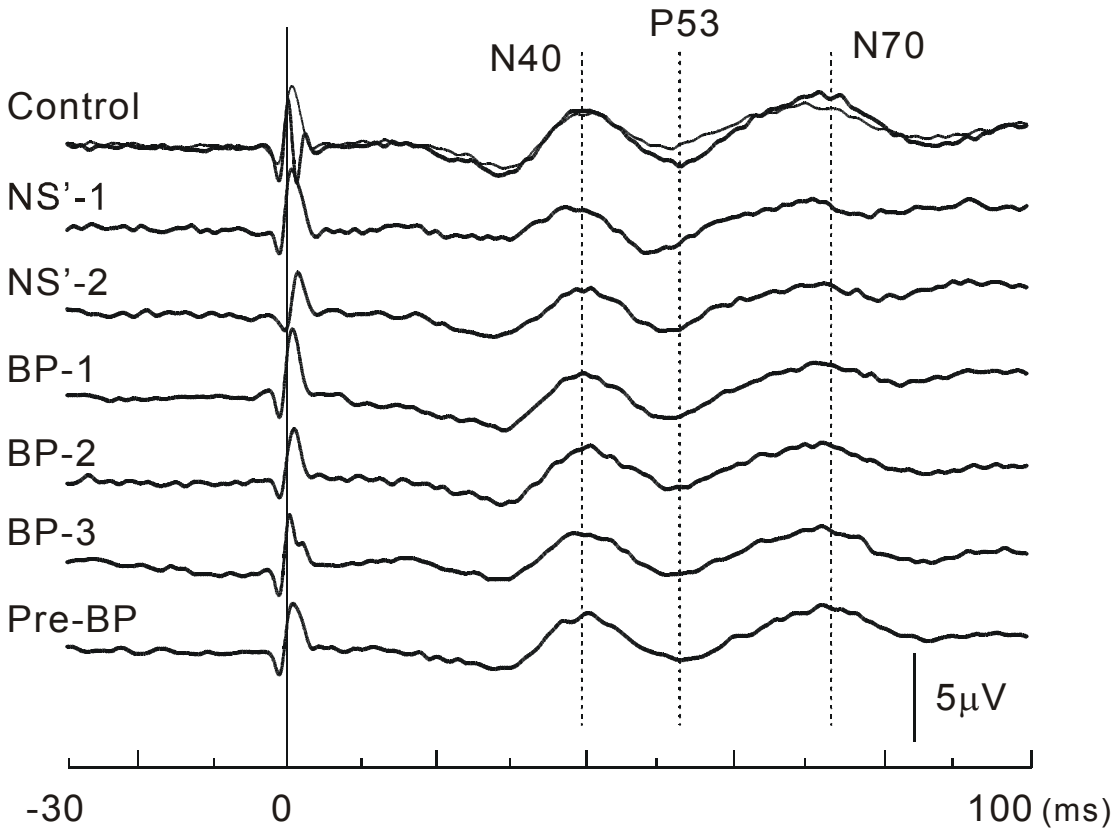


Figure 4

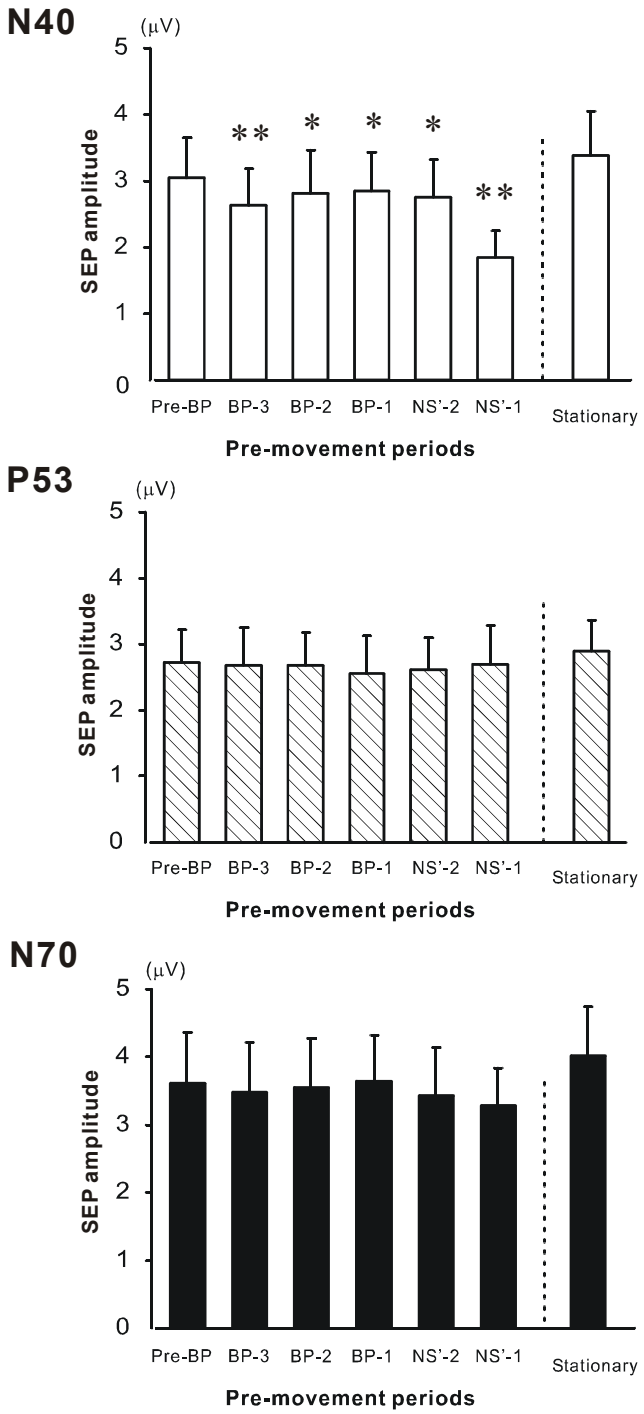

N40
(μV)
5
4
3
2
1
0
SEP amplitude
**
*
*
*
**
Pre-BP
BP-3
BP-2
BP-1
NS'-2
NS'-1
Stationary
Pre-movement periods
P53
(μV)
5
4
3
2
1
0
SEP amplitude
Pre-BP
BP-3
BP-2
BP-1
NS'-2
NS'-1
Stationary
Pre-movement periods
N70
(μV)
5
4
3
2
1
0
SEP amplitude
Pre-BP
BP-3
BP-2
BP-1
NS'-2
NS'-1
Stationary
Pre-movement periods

Figure 5

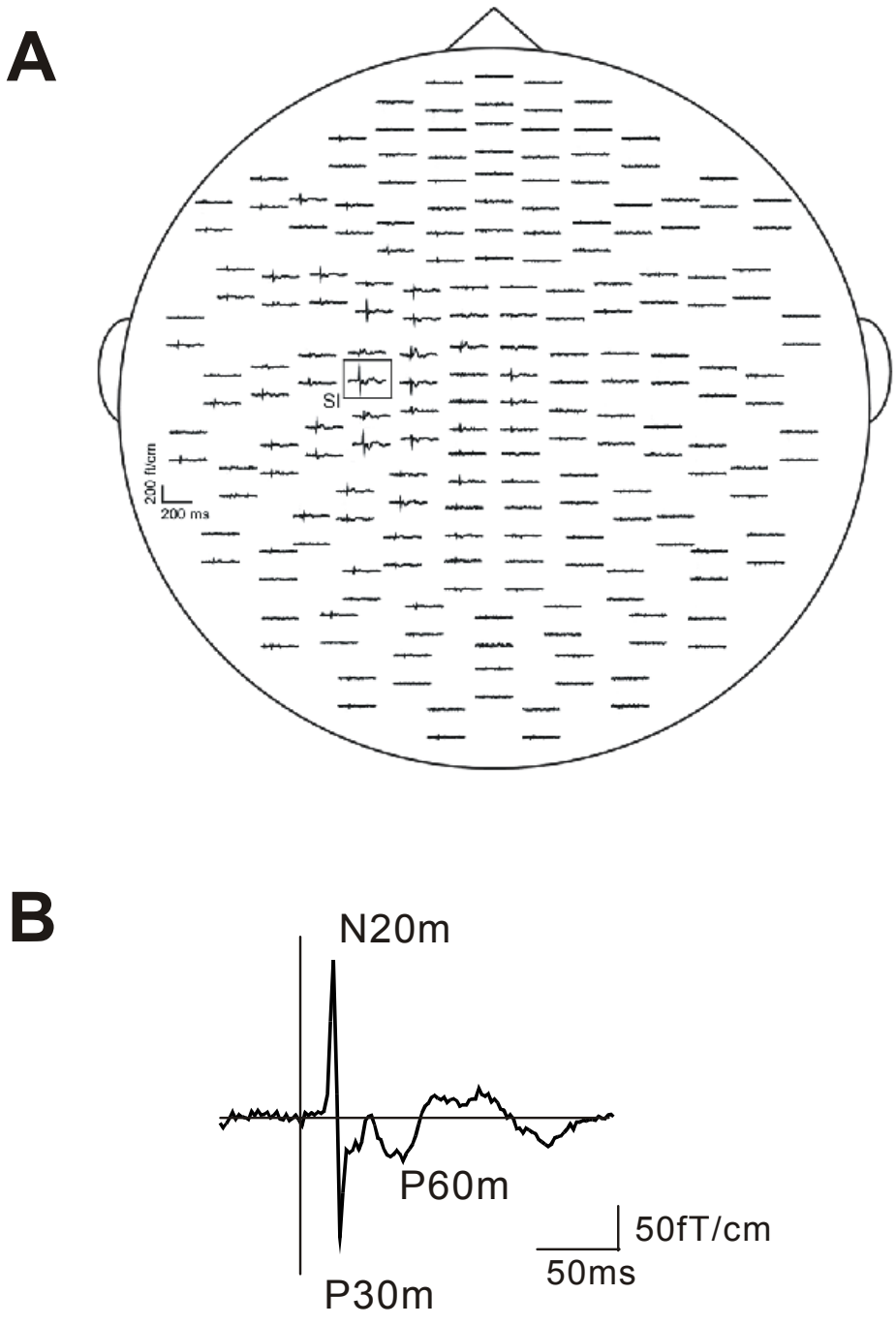


Figure 6

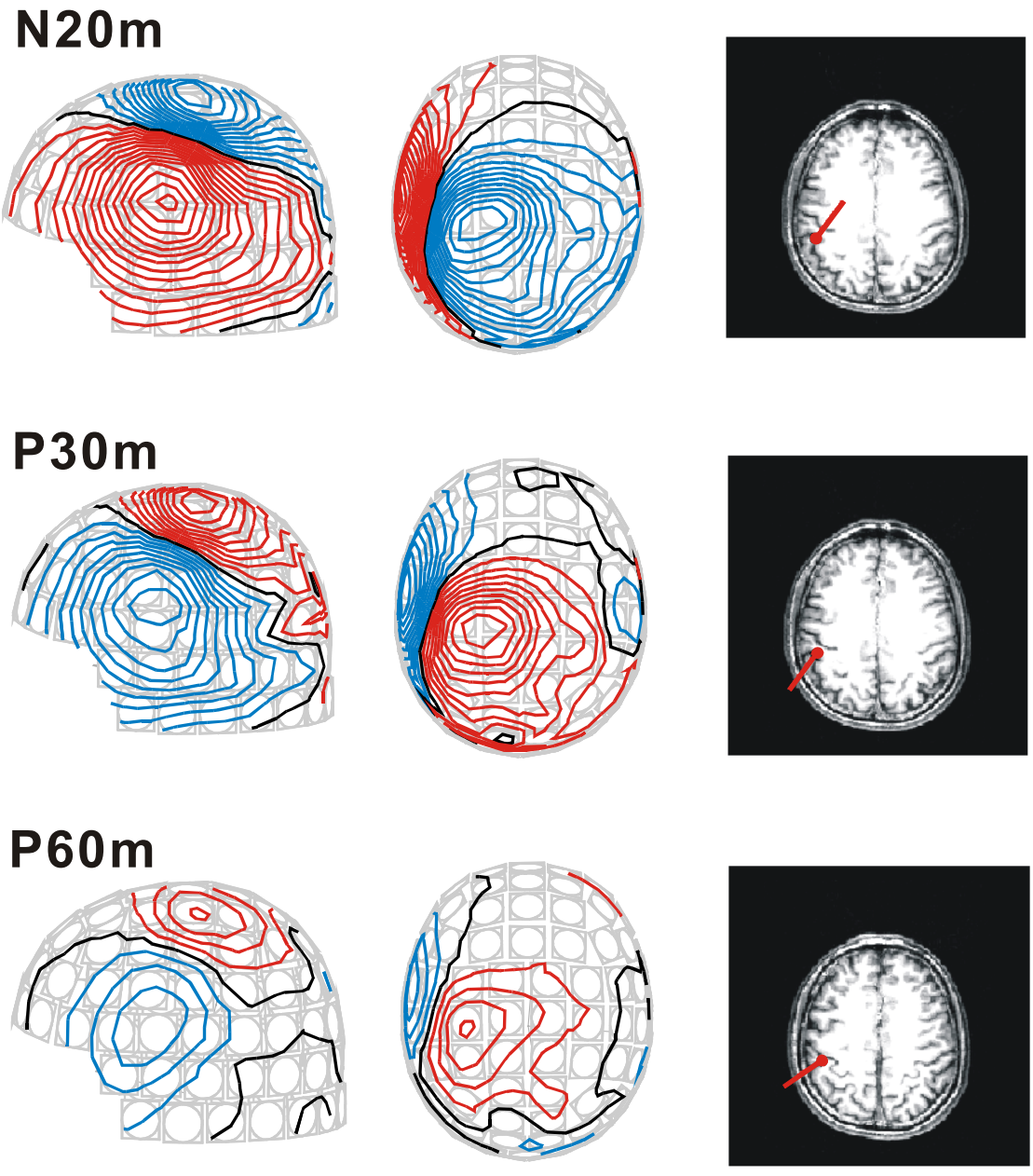


Figure 7

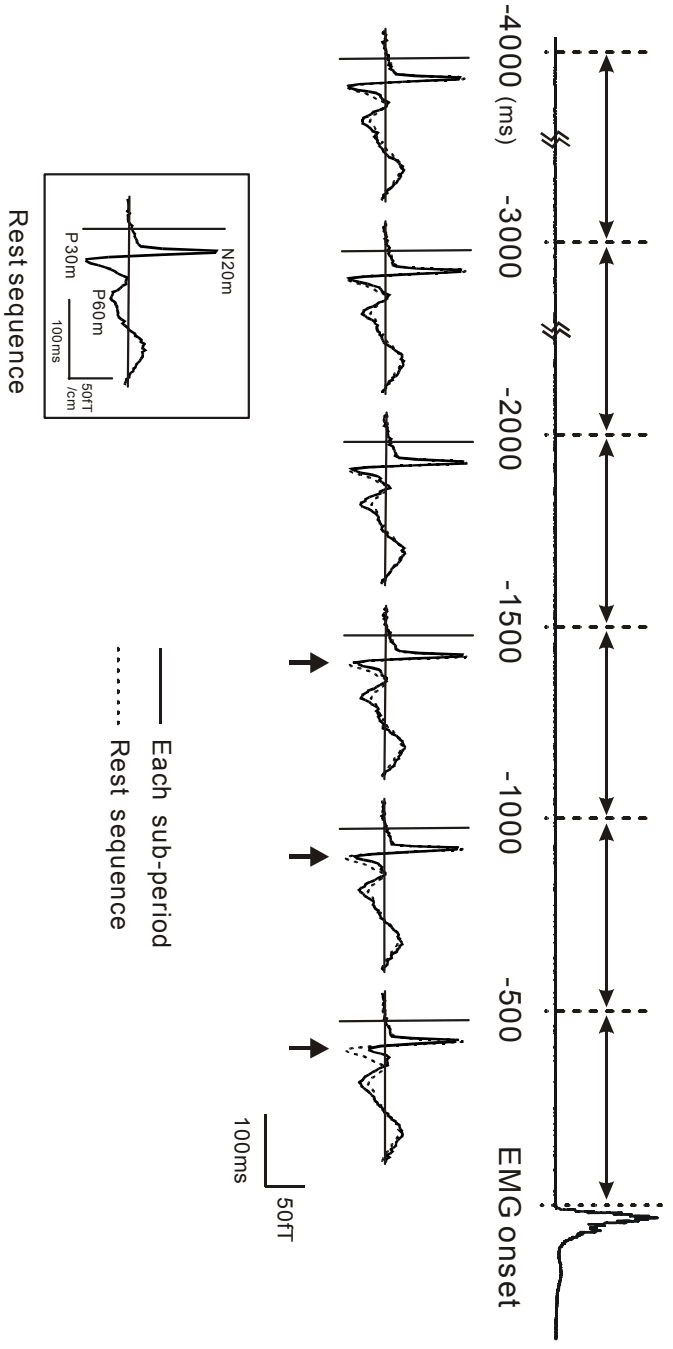
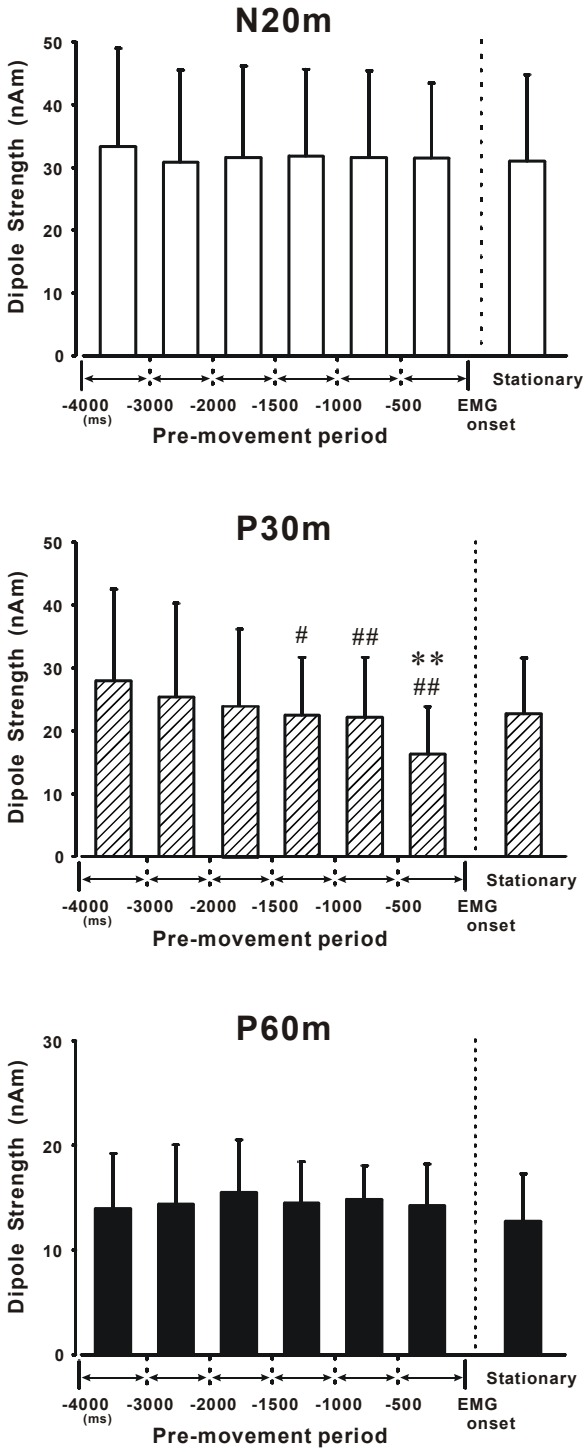

-4000 (ms)
-3000
-2000
-1500
-1000
-500
EMG onset
100ms
50fT
Each sub-period
Rest sequence
N20m
P30m
P60m
100ms
50fT
/cm
Rest sequence

Figure 8


N20m
Dipole Strength (nAm)
50
40
30
20
10
0
Stationary
-4000
(ms)
-3000
-2000
-1500
-1000
-500
EMG
onset
Pre-movement period
P30m
Dipole Strength (nAm)
#
##
**
##
Stationary
Pre-movement period
P60m
Dipole Strength (nAm)
30
20
10
0
Stationary
Pre-movement period