Investigation of somato-motor inhibitory processing in humans using Go/No-go paradigm

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Contents

Abstract

The go/nogo task is a useful paradigm for recording event-related potentials (ERPs) to investigate the neural mechanisms of response inhibition. In nogo trials, a negative deflection at around 140-300 ms, which has been called the 'nogo potentials', is elicited at the frontocentral electrodes, compared with ERPs recorded in go trials. In the first study, we investigated the generators for nogo potentials by recording magnetoencephalography (MEG) during somatosensory go/nogo tasks. MEG data revealed that a long-latency response peaking at approximately 160 ms, termed nogo-M170, recorded in only nogo trials. The equivalent current dipole (ECD) of nogo-M170 was estimated to lie around the posterior part of the inferior frontal sulci in the prefrontal cortex. This finding clarified the spatial and temporal processing related to somato-motor inhibition caused in the posterior part of the inferior frontal sulci in the prefrontal cortex in humans.

In the second study, we investigated the effect of the inhibitory processing with increasing muscle force on motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS). The

subjects performed a warning stimulus (S1) – imperative stimulus (S2) paradigm with go/nogo tasks. S1 was an auditory tone burst, and S2 was an electrical stimulation for the second (go stimuli) or fifth digit (nogo stimuli) of the left hand at an even probability in go/nogo tasks. The recordings were conducted at three force levels; 10 %, 30 % and 50 % maximal voluntary contraction (MVC). After the presentation of S2, the subjects were asked to adjust their force level so as to match the target line with a force trajectory line as quickly and accurately as possible in only the go trials. The amplitude of the MEP, which was recorded from the first dorsal interosseous (FDI) muscle 150 ms after S2, in nogo trials became significantly smaller with increasing muscle force, whereas it became larger in go trials. Our results indicated that stronger inhibitory cerebral activity was needed for a nogo stimulus, in the case where a stronger response was needed for a go stimulus.

General Introduction

When human lives daily life, it is essential for the ability to control inappropriate behaviors and thoughts. This self-inhibition is performed after a sequential process that brain perceives a wide variety of sensory stimuli from environment and judges them precisely. To know the mechanism of inhibitory processing in our brain is just one of the ways to know ourselves.

The go/nogo task is one of the most useful paradigms with which to investigate the neural mechanisms of response execution and inhibition. Response execution has been studied in go trials using an index of behavioral performance like reaction time (RT), but it is difficult to study response inhibition in nogo trials because of the absence of actual behavioral performance. Event-related potentials (ERPs) obtained by time-locked averaging electroencephalography (EEG) have been used to investigate the neural processes in the central nervous system. In nogo trials, two large components, which show a negative deflection at around 140-300 ms (N2) and a positive deflection at around 300-600 ms (P3), are elicited at the frontocentral electrodes, compared with ERPs recorded in go

trials (Simson et al., 1977; Pfefferbaum et al., 1985; Falkenstein et al., 1995, 1999; Kopp et al., 1996; Roche et al., 2005). These components have been called 'nogo potentials' (Kok, 1986; Gemba & Sasaki, 1989; Thorpe et al., 1996), and mainly evoked using visual and auditory stimulation.

We previously reported that nogo-related brain potentials were also found in the somatosensory modality (Nakata et al., 2004, 2005a). The amplitude of nogo-N140 component (N140 evoked by nogo stimuli) was more negative than that of go-N140 (N140 evoked by go stimuli). The enhanced nogo-N140 component seems analogous to the nogo-N2 component during nogo trials of visual and auditory go/nogo tasks, which suggests that these nogo-related brain potentials are not dependent on sensory modalities but reflect common neural activities specific to the inhibitory process. However, the precise cortical regions responsible for somatosensory nogo-N140 and characteristics of inhibitory processing have been unclear.

Therefore, in the first study, we investigated the generator mechanisms of somatosensory nogo-related potentials, using magnetoencephalography (MEG). In the second study, we used transcranial magnetic stimulation

(TMS) to examine the detail characteristics of response inhibitory processing.

Experiment 1: MEG study

Recent neuroimaging studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown nogo-related activity in several regions of the human brain such as the prefrontal cortex, supplementary motor area (SMA), and anterior cingulate cortex (ACC) (Kawashima et al., 1996; Konishi et al., 1999; Durston et al., 2002; Garavan et al., 2002), but their temporal dynamics as a neural network has been unclear because of the limited temporal resolution of hemodynamic imaging methods such as PET and fMRI.

In this experiment, we examined nogo-related neural activity by recording MEG in somatosensory go/nogo tasks. MEG has a high temporal resolution, and is able to localize neural activity directly, compared with EEG (Hari et al., 2000). Therefore, we expected to clarify the temporal dynamics of somato-motor inhibitory processing by analyzing the equivalent current dipole (ECD) estimated by MEG. Our main focus regarding the nogo-related neural activity was the period 140-200 ms after the stimulus onset in the nogo trials to clarify the primary processing for

inhibition, which was recorded in our previous studies (Nakata et al., 2004, 2005a).

Methods

Subjects

Eight normal right-handed subjects (three females and five males; mean age 34.1 years, range 25-42 years) participated in this study. The subjects did not have a previous history of any neurological or psychiatric disorders. Informed consent was obtained from all subjects. The study was approved by the Ethical Committee of the National Institute for Physiological Sciences.

Experimental paradigm

The subjects performed a warning stimulus (S1) – imperative stimulus (S2) paradigm with go/nogo tasks. S1 was an auditory pure tone (60 dB SPL, 50 ms duration), presented binaurally through earphones. For the S2,

we stimulated the second or fifth digit of the left hand with ring electrodes. The electrical stimuli were a current constant square-wave pulse 0.2 ms in duration, and the stimulus intensity was 2.5 times the sensory threshold, which yielded no pain or unpleasant sensation. The anode was placed at the distal interphalangeal joint and the cathode at the proximal interphalangeal joint of the corresponding digit. The probability of the stimulus for the second and fifth digit was even. A pair of S1 and S2 stimuli was given to the subjects with an interval of 1.5 sec. The S1-S1 interval was 5 sec.

The recordings were conducted in three conditions. Condition 1 was the resting control. The subjects were asked to relax and rest quietly with no task. In condition 2, the go stimulus was delivered to the second digit of the left hand, and the nogo stimulus to the fifth digit of the left hand. The subjects had to respond to it by pushing a button with their right thumb (contralateral to the stimulated side) as quickly as possible only after the presentation of a go stimulus. In condition 3, the go and nogo stimuli were reversed in the left hand, that is, the go and nogo stimulus was delivered to the fifth and second digit, respectively. The response task is

the same as condition 2. During the recordings, the subjects were instructed to keep their eyes open and look at a small fixation point positioned in front of them at a distance of approximately 1.5 m. One run comprised 160 epochs of stimulation, which included 80 epochs for the go stimuli and 80 for the nogo stimuli. The order of conditions was randomized in each subject and counterbalanced across all subjects. The practice session consisted of 20 stimuli before the recordings.

MEG recordings and analysis

Brain activities in go/nogo tasks were recorded with a helmet-shaped 306-channel detector array (Vectorview; ELEKTA Neuromag Oy, Helsinki, Finland), which comprises 102 identical triple sensor elements, in a magnetically shielded room. Each sensor element consists of two orthogonal planar gradiometers and one magnetometer coupled to a multi-SQUID (Superconducting Quantum Interference Device) and thus provides three independent measurements of the magnetic fields. The present study analyzed MEG signals from 204-channel planar-type gradiometers, since these planar sensors detect the strongest signal just

above local cerebral sources (Nishitani & Hari, 2002). The signals were recorded with a bandpass of 0.1-100Hz and digitized at 900 Hz, with noise, blinks and eye movements rejected from the analysis automatically. The analysis period of 700 ms included a prestimulus baseline of 100 ms.

Before the recordings, four head position indicator (HPI) coils were attached to specific sites on the subject's head, and then electric current was fed to the HPI coils to determine the exact location of the head with respect to the MEG sensors. The locations of HPI coils with respect to the three anatomical landmarks (nasion and bilateral PA) were also measured using a three-dimensional digitizer to allow alignment of the MEG and magnetic resonance (MR) images obtained with a 3 tesla MRI system (Allegra scanner, Siemens, Erlangen, Germany). The x-axis was fixed with the preauricular points, pointing to the right, the positive y-axis traversing the nasion, and the positive z-axis pointing up. We adopted the head-based coordinate system used in our previous studies (Wasaka et al., 2003; Noguchi et al., 2004).

To identify the sources of the evoked activities, the ECD, which best explains the measured data, was computed by using a least-squares search.

A subset of 14-18 channels including the local signal maxima was used for the estimation of ECDs. These calculations gave the three-dimensional location, orientation, and strength of the ECD in a spherical conductor model, which was based on each subject's MRI to show the source's location. The goodness-of-fit (GOF) value of an ECD was calculated to indicate in percentage terms how much the dipole accounts for the measured field variance. Only ECDs explaining more than 80 % of the field variance during selected periods of time were used for further analysis. The period of analysis was extended to cover the entire period and all channels were taken into account in computing a time-varying multi-dipole model. The strengths of the previously found ECDs were allowed to change while their locations and orientations were kept fixed. The data acquisition and analysis followed Hämäläinen et al. (1993). In addition, the source location for the nogo-related activity was transformed into the Talairach standard brain source (Talairach & Tournoux, 1988), following previous studies (Nishitani et al., 1999; Ploner et al., 2000).

After confirmation of the ECD strengths among the three different conditions, the ECD strengths and peak latencies were submitted to a

two-way repeated measures analysis of variance (ANOVA) with the factor, Digit (second vs. fifth) and Condition (control, go and nogo). F values were obtained after Greenhouse-Geisser correction when appropriate, and then a correction coefficient epsilon was given. The Bonferroni-Dunn test as a post hoc procedure was adjusted for differences in dipole moment strength and peak latency among conditions. Statistical significance was set at $p < 0.05$.

In addition, we analyzed the areal mean signals at each sampling rate in order to compare the amplitude between go and nogo trials. First, we calculated vector sums by squaring MEG signals from two orthogonal planar gradiometers recorded at a subset of channels used for the estimation of ECDs, and then recalculated the square root of this sum. After these calculations (square root of sum of squared signals), we finally had data with a positive value. This method of data analysis followed some previous studies using the same MEG system as the present study (see Tarkiainen et al., 2003; Bonte et al., 2006). A paired *t*-test was used to compare the amplitude between go and nogo trials and a *p* value less than 0.05 was considered significant.

Results

Behavioral data

Table 1 shows the mean RT, false alarm and misses with SD in conditions 2 and 3. Since analyses of each index did not yield significant differences among the conditions ($p > 0.05$, respectively), there seems to be no difference in the difficulty of performing movement tasks.

MEG data

Figure 1A shows the somatosensory evoked magnetic fields for the left second digit in a representative subject. Clear deflections were observed in the centrotemporal regions of both hemispheres in all conditions, suggesting brain activities in several generator areas during 120 ms after the somatosensory stimulation. It should be noted that long-latency responses over the left inferior frontal areas were recorded in only nogo trials and peaked at about 170 ms (Figures 1B and 1C). We termed this component, nogo-M170, corresponding to nogo-M170. Figure 2 shows ECD waveforms of a representative subject for the left

second digit in nogo trials.

The first major MEG signals peaked at about 50 ms in the hemisphere contralateral to the stimulated side (Figure 2), and the generator was estimated by ECD analysis in the postcentral wall, in the primary somatosensory cortex (SI) (Figure 3A). The second signals peaked at 80-120 ms bilaterally (Figure 2), and were generated presumably in the upper bank of the Sylvian fissure, corresponding to the secondary somatosensory cortex (SII), in both hemispheres (Figure 3B). These MEG signals were recorded in all conditions, independent of the sites stimulated, the second and fifth digits. These results were consistent with previous SEF studies following the stimulation of digits (Hari et al. 1990, 1993; Simões et al. 2001). The ECDs for the contralateral SI and ipsilateral SII were analyzed in all the subjects, but one subject was excluded because the contralateral SII had a very small amplitude.

The long-latency signal recorded in only nogo trials, nogo-M170, was estimated around the posterior part of the inferior frontal sulci in the left prefrontal cortex (Figure 4). This activity was recorded in nogo trials of conditions 2 and 3. The mean peak latencies were 161.1 and 162.2 ms in

conditions 2 and 3, respectively. Figure 5 shows the time course of the grand-averaged areal mean signals for the left second digit stimulus. The areal mean signals were significantly larger in nogo trials than in go trials at latency of 171 to 207 ms for the second digit and 168 to 192 ms for the fifth digit (paired *t*-test). The data in peak amplitude of the areal mean signals within this period was also submitted to a two-way repeated measures ANOVA with the factor, Digit (second vs. fifth) and Stimulus (go vs. nogo). The ANOVAs revealed a significant main effect of Stimulus ($F(1, 7) = 19.386$, $p < 0.01$), but there were not significant main effect of Digit ($F(1, 7) = 1.596$, $p > 0.05$) or Digit-Stimulus interaction effect ($F(1, 7) = 0.238$, $p > 0.05$). These results indicated that there was a significant difference of brain responses between go and nogo trials at intervals of about 160-210 ms after the stimulus onset.

The results of ANOVAs for the ECD strength and peak latency in the contralateral SI showed no significant main effect ($F(2, 14) = 0.574$, $p > 0.05$, $F(2, 14) = 3.337$, $p > 0.05$, respectively) (Table 2). This indicated that there were no significant differences in the activities of the contralateral SI among conditions. The same ANOVAs were run for the

contralateral SII and showed a significant main effect of Condition for ECD strength ($F(2, 12) = 15.858$, $p < 0.001$), but not any effect for peak latency. Post hoc analysis indicated that strength in the contralateral SII was significantly greater in the go condition than in the control and nogo conditions ($p < 0.001$ and $p < 0.02$, respectively). For ECD strength in the ipsilateral SII, there was also a strong tendency for a main effect of Condition ($F(2, 14) = 4.424$, $p = 0.069$, $\varepsilon = 0.541$). There were no significant effects for peak latency of SI and bilateral SII (Table 2). We analyzed the ECD strength, latency and source location (x, y and z coordinates) of nogo-M170 for the effects of stimulus sites with paired *t*-tests. However, there were no significant differences for each index ($p > 0.05$, respectively) (Table 3).

Discussion

In the present study, nogo-related neural activity was recorded using MEG in somatosensory go/nogo tasks. Long-latency responses over the left prefrontal cortex were recorded in only nogo trials and peaked at about

160 ms. This activity was also recorded, independent of the sites stimulated, following stimulation of the second and fifth digits.

With respect to the strength of the ECD on MEG, the present study showed that the contralateral SII recorded at 80-120 ms was significantly larger in go trials than control and nogo trials, and that the ipsilateral SII showed a similar tendency, but not so SI activity at about 50 ms (Table 2). These results suggested that spatial selective attention to the target (go) stimulus modulates the neural activity of SII in go trials at 80-120 ms, consistent with previous findings (Hari et al., 1990; Mauguière et al., 1997; Mima et al., 1998; Fujiwara et al., 2002). Fujiwara et al. (2002) speculated that the SII is organized in higher order processing for somatosensory perception, and plays a main role in selective somatosensory attention.

Our previous ERP data based on nogo-N140 could not precisely indicate the regions responsible for the nogo potentials because of the low spatial resolution of EEG. Some previous ERP studies using visual and auditory stimulation suggested that nogo-N2 originates in the frontal lobe based on the topographical distribution (Kok, 1986; Pfefferbaum et al., 1985; Jodo &

Kayama, 1992; Eimer, 1993; Bruin & Wijers, 2002) or dipole modeling with only the ERP waveforms (Kiefer et al., 1998). By contrast, several recent studies showed that nogo-N2 reflects response conflict monitoring by ACC, not response inhibition (Nieuwenhuis et al., 2003; Donkers & van Boxtel, 2004). These findings were consistent with some fMRI studies reporting the role of ACC in response conflict (Braver et al., 2001). Indeed, the precise origin of nogo-N2 has remained a matter of debate. Therefore, we tried to localize the nogo-related neural activities by recording MEG.

Our data showed that the ECD in the prefrontal cortex contralateral to the finger movement peaked at about 160 ms in the somatosensory go/nogo tasks (Figure 2 and Table 3). One previous study using MEG found that visual nogo-related cortical activities peaked at a latency of about 135 ms (Sasaki et al., 1993). It was concluded, based on the magnetic field pattern, that the dorsolateral part of the frontal lobe was activated during the inhibitory processing, which was consistent with the present study. However, the latency of nogo-N2 reported in most previous ERP studies using visual go/nogo tasks was between 200 and 400 ms (Jodo & Kayama,

1992; Eimer, 1993; Fallgatter & Strik, 1999; Bokura et al., 2001; Bruin & Wijers, 2002; Roche et al., 2005). Therefore, it is unknown whether the nogo-related activity reported by Sasaki et al. (1993) reflects the same neural activity as a traditional nogo-N2. In addition, although neuroimaging with PET and fMRI has shown nogo-related neural activity in several regions of the human brain such as the prefrontal cortex, SMA, ACC and parietal cortex (Kawashima et al., 1996; Casey et al., 1997; Konishi et al., 1999; Liddle et al., 2001; Durston et al., 2002; Garavan et al., 2002), it is unclear when each region is activated in nogo trials because of the poor temporal resolution of PET and fMRI. Therefore, our findings seem to be useful for understanding the temporal and spatial dynamics of nogo-related neural activity in the response inhibitory processing in humans. Lavric et al. (2004) using ERP low-resolution electromagnetic tomography (LORETA) also reported higher activation in the N2 time-window in the prefrontal cortex during visual go/nogo tasks, not in ACC. They matched the frequency of the go and nogo trials to minimize differences in response conflict between event types. In the present study, we also matched the frequency for the degree of the response conflict.

Therefore, our nogo-M170 should be related to the neural activity of response inhibition rather than response conflict.

Lesion and monkey studies have shown that the prefrontal cortex plays an important role in response inhibitory processing. Lesions in the prefrontal cortex impair the performance of go/nogo tasks in humans (Drewe, 1975). Moreover, in monkeys, nogo-related field potentials were found in the prefrontal cortex (Sasaki & Gemba, 1986, 1989; Gemba & Sasaki, 1990), and neurons of the prefrontal cortex firing in relation to nogo responses were recorded by single unit studies (Kubota & Komatsu, 1985; Watanabe, 1986; Sakagami & Niki, 1994).

Our data showed the nogo-related activity in the left hemisphere contralateral to the response hand, but not in the right hemisphere, when the subject responded to go stimuli with right thumb. However, some neuroimaging studies showed a right-hemisphere dominance for nogo trials especially in the inferior prefrontal cortex, independent of the response hand of the subject in go trials (Kawashima et al., 1996; Konishi et al., 1999; Garavan et al., 1999), while others showed bilateral prefrontal activity (Casey et al., 1997; Liddle et al., 2001; Watanabe et al., 2002).

There appears to be two possible hypotheses to explain the discrepancy of the nogo-related activities between our findings and these previous studies. The first hypothesis is that nogo-related activity has modality differences. Some ERP studies reported that the amplitude of N2 was much smaller following auditory than visual stimuli (Falkenstein et al., 1995, 1999; Kiefer et al., 1998). Falkenstein et al. (1999) suggested that the inhibitory processing as reflected in N2 is modality specific. In a monkey study, Gemba and Sasaki (1990) also reported that nogo potentials after an auditory stimulus were observed in the rostral part of the dorsal bank of the principal sulcus, as opposed to the caudal part of the same bank after a visual stimulus. In addition, since most neuroimaging studies have used visual go/nogo tasks, the characteristics of nogo-related neural activity in response to auditory and somatosensory stimulation have not been clarified. Therefore, it is likely that our nogo-related activity showed the hemisphere dominance contralateral to the response hand, relating to the modality specificity of the somatosensory stimulation. The second hypothesis is that the neural activity of the somatosensory inputs caused by the stimulation of the left hand influenced the nogo-related activity in the right

hemisphere contralateral to the stimulated hand. That is, even if the nogo-related activity was elicited in both hemispheres, the nogo-related magnetic field might not be detected due to the influence of the somatosensory-related magnetic field in the right hemisphere contralateral to the stimulated hand.

In conclusion, the present experiment clarified the spatial and temporal processing related to somato-motor inhibition caused in the posterior part of the inferior frontal sulci in the prefrontal cortex in humans.

Experiment 2: TMS study

It is known that nogo potentials are influenced by the status of motor preparation. A larger N2 in nogo trials is evoked by increasing the time pressure for response speed (Jodo & Kayama, 1992; Band et al., 2003), by the presence of a preceding cue signal (Kopp et al., 1996), and by a low error rate (Falkenstein et al., 1999). These results indicate that the motor preparation for a faster and more accurate response results in larger nogo potentials, and that a stronger inhibitory processing is required to suppress the motor execution in these conditions than under the opposite conditions. Another possible factor modulating the inhibitory process would be the strength of motor execution for go trials, since the control of the response force is important for precise motor execution. Therefore, given that a stronger motor execution is needed, a stronger inhibitory process is expected to be required to suppress the motor execution with a stronger response force. However, this hypothesis has not been examined on neurophysiological studies previously.

Transcranial magnetic stimulation (TMS) has been used to investigate

both excitatory and inhibitory effects on the cerebral cortical excitability during the subjects performed go/nogo tasks (Hoshiyama et al., 1996, 1997; Leocani et al., 2000; Waldvogel et al., 2000; Sohn et al., 2002; Yamanaka et al., 2002). Motor evoked potentials (MEPs), which are recorded from the target muscle after applying TMS, have been used as an index of excitability on primary motor cortex (MI). Common findings of these studies were a decrease in the amplitudes of MEP at 100-200 ms after nogo stimuli, and an increase after go stimuli. Although these also showed the inhibition of both agonist and antagonist muscles (Hoshiyama et al., 1997) and the contralateral homologus muscle (Leocani et al., 2000), there has been no TMS-based study examining the relation between muscle force in go trials and the strength of the inhibitory processing in nogo trials.

In this experiment, therefore, we investigated the effect of the inhibitory processing with increasing muscle force on MEPs, using somatosensory go/nogo choice reaction tasks. A single TMS pulse was applied after 150 ms of a S2 signal in go and nogo trials.

Methods

Subjects

Nine normal right-handed subjects (nine males and one female; mean age 31.4 years, range 24-42) participated. None of the subjects had a history of neurological or psychiatric disorder. Informed consent was obtained from all subjects. The study was approved by the Ethical Committee of the National Institute for Physiological Sciences, Okazaki, Japan.

Experimental procedure

The subjects performed a warning stimulus (S1) – imperative stimulus (S2) paradigm with go/nogo tasks. The S1 was an auditory pure tone (60 dB SPL, 50 ms duration), presented binaurally through earphones. For S2, we stimulated the second or fifth digit of the left hand with ring electrodes. The electrical stimulus was a current constant square-wave pulse 0.2 ms in duration, and the stimulus intensity was 2.5 times the sensory threshold, which yielded no pain or unpleasant sensation. The anode was placed at

the distal interphalangeal joint and the cathode at the proximal interphalangeal joint of the corresponding digit. The second digit was used for the go stimulus at a probability of 0.5, and the fifth digit for the nogo stimulus at a probability of 0.5. A pair of S1 and S2 stimuli was given to the subjects with an interval of 1.5 sec. The inter trial interval was 5 sec.

The recordings were conducted at three force levels: 10 %, 30 % and 50 % maximal voluntary contraction (MVC) of each subject. The subjects sat in a reclining armchair in a quiet and electrically shielded room. They were asked to squeeze a handgrip for about 1 s to measure the maximum voluntary force with their right hand. Before this MVC measurement, the subjects were instructed to practice squeezing three to five times. After this determination, 10 %, 30 % and 50 % MVC were calculated. The target and force trajectory lines were displayed on an oscilloscope in front of the subjects at a distance of approximately 1 m, and the force data were recorded on a computer. The target line was indicated by a horizontal cursor on an oscilloscope during each condition. After the S2, the subjects were asked to adjust their force level so as to match the

target line with the force trajectory line as quickly and accurately as possible, only when the go stimuli were presented. All subjects, who were verbally instructed by the experimenter, had training session to perform fast and accurate contractions before the experiment. The training was performed 20-30 trials for each condition so that subjects could match the target line with the force trajectory line. Then they had a rest for 5-10 min before the recordings.

Experiment session

We applied stimuli with a 7-cm figure-of-eight coil connected to a Magstim Super Rapid (The Magstim Company, Dyfed, UK). TMS was delivered over the hand motor cortex of the left hemisphere, and we determined the optimal position and direction of the coil where the largest MEP was obtained from the right first dorsal interosseous (FDI) muscle. The stimulating coil was orientated to generate induced current in a posterior to anterior current direction. The optimal position for eliciting MEPs in the contralateral FDI was established and marked directly on the scalp. Resting motor threshold was defined as the minimum intensity

evoking MEPs of more than 50 μV in at least five out of 10 trials in FDI. The intensity of TMS thorough the experiment was set at 110 % of the resting motor threshold.

The TMS was triggered 150 ms after the S2 signal both in go and nogo trials. This timing followed the methods of some previous studies, which showed inhibitory cerebral activity in nogo trials (Sasaki et al., 1993; Hoshiyama et al., 1996, 1997; Nakata et al., 2004, 2005a, 2005b). One condition comprised 60 epochs of stimulation, which included 30 epochs for the go stimuli and 30 for the nogo stimuli. In addition to the above-mentioned conditions, a resting control condition with no specific task was recorded to compare the amplitudes. One run lasted about 5 min. The order of conditions was randomized for each subject and counterbalanced across all subjects. The EMG of FDI was recorded with a bandpass of 10-1000 Hz, and the sampling rate was 2000 Hz.

Data analysis

For the amplitudes of MEPs, peak-to-peak measurements were conducted. The EMG was also monitored to eliminate slow responses

exceeding 500 ms and incorrect responses from the averaging. Additionally, we eliminated force error trials exceeding 2 times the standard deviation of the muscle force average for each condition. A trial, which had the MEP including the error EMG clearly, was eliminated from the averaging.

The amplitudes of MEPs for go and nogo trials were submitted to separate ANOVAs with a factor of Condition. For the behavioral, the false alarm, misses and force error rates were analyzed with repeated measures ANOVAs for a factor of Condition. For all repeated measures factors with more than two levels, it was tested whether the sphericity assumption was violated. In all cases, the sphericity was maintained. Thus, the Greenhouse-Geisser correction was not used in the present study. When significant effects were identified, the Bonferroni-Dunn post hoc multiple-comparison was adjusted to identify the specific differences among conditions. Statistical significance was set at $p < 0.05$.

Results

Behavioral data

Table 4 shows the false alarm, misses and force error rate. For each index, there were no significant differences among the conditions.

MEPs

The mean amplitude of resting MEP was 1.33 ± 0.69 mV for the resting-go trials (the second digit) and 1.27 ± 0.65 mV for the resting-nogo trials (the fifth digit), respectively. The amplitudes of MEPs decreased gradually with increasing muscle force in nogo trials, but increased in go trials. This was supported by repeated measures ANOVAs. That is, significant main effects of Condition were present for nogo trials ($F(2, 16) = 10.532$, $p < 0.01$) and go trials ($F(2, 16) = 6.383$, $p < 0.01$). In addition, the post hoc test indicated that the amplitude of MEP for nogo trials was significantly smaller in the 50 % MVC condition than 10 % ($p < 0.01$) and 30 % ($p < 0.05$) MVC conditions, respectively, and that the amplitude of MEP for go trials was significantly larger in the 50 % MVC condition than

10 % MVC condition ($p < 0.01$) (Figure 6).

Discussion

In the present study, we investigated the effect of the inhibitory processing with the change in output of muscle strength on MEPs in somatosensory go/nogo tasks. The MEPs on nogo trials became significantly smaller with increasing muscle force, whereas these became larger in go trials.

The inhibitory processing would be influenced by the difficulty in performing the tasks (Falkenstein et al., 1999). However, the behavioral data of the present study revealed no significant differences among the conditions in the false alarm, misses and force error rate (Table 4). Thus, it is unlikely that the difficulty in performing the tasks was related to the results of the present study.

Previous studies reported a positive relationship between response speed and the inhibitory process on ERPs. Jodo and Kayama (1992) found that the amplitudes of nogo-N2 were significantly larger in subjects

showing a shorter RT. Band and colleagues (2003) also reported that the amplitude of nogo-N2 varied with speed instruction in same subjects. However, to our knowledge, this is the first study to focus on the relationship between muscle force and the inhibitory process.

It is recognized that the increasing force level in muscle output relates to a larger number of pyramidal tract neurons and/or a higher discharge rate of the recruited neurons during voluntary movement in monkeys (Evarts, 1968; Smith et al., 1975). Recent neuroimaging studies using fMRI in humans reported a stronger fMRI signal in motor-related cortical fields with an increase in the output of muscle force (Thickbroom et al., 1998; Dai et al., 2001). Therefore, it is probable that the increase of MEPs in the go trials indicated an increase in motor-related activities with muscle force during the preparatory period.

For these enhanced motor-related activities, stronger inhibitory cerebral activity is needed for voluntary movements with increasing muscle force. The amplitudes of MEPs in nogo trials became significantly smaller with increasing muscle force. At 100-200 ms after the stimulus presentation, some studies have reported strong inhibitory brain activities following

TMS. Hoshiyama et al. (1996, 1997) and Leocani et al. (2000) found the inhibition of the corticospinal pathway after the nogo signal. They suggested that suppression of corticospinal excitability could have resulted from nogo-related brain activities. Our results support this suggestion, and furthermore suggest that the strength of the inhibitory processing is modulated by the output change of muscle strength.

Although the present study could not show the cortical region responsible for the nogo effects, our previous study indicated that the neural activity was arisen from the posterior part of inferior frontal sulci in the prefrontal cortex (Nakata et al. 2005b). Sasaki and colleagues (1993) also demonstrated in a MEG study using a visual go/nogo task that cortical activities peaking at 135 ms are predominant following nogo trials. In monkeys, nogo-task-related activities have also been found in the prefrontal cortex at intervals of 100-150 ms (Sasaki and Gemba, 1986; Gemba and Sasaki, 1990). Recent neuroimaging studies in humans with PET and fMRI have also demonstrated the involvement of prefrontal regions related to inhibitory processes (Kawashima et al., 1996; Garavan et al., 1999; Konishi et al., 1999; Rubia et al., 2001). These previous studies

suggested that prefrontal cortex plays an important role in response inhibitory processing. However, Bates and Goldman-Rakic (1993) and Fuster (2001) reported that there are no direct connections between the prefrontal cortex and the motor cortex in monkeys. Therefore, we may be able to speculate that the increased nogo activities in the prefrontal cortex influenced strongly the primary motor cortex with increasing muscle force via the premotor cortex and/or supplementary motor area (SMA). Indeed, some neuroimaging studies showed the neural activities of these regions in nogo trials (Kawashima et al., 1996; Watanabe et al., 2002).

In conclusion, we confirmed a positive relationship between muscle force and the inhibitory processing. Our results showed that the amplitudes of MEP in nogo trials became smaller with increasing muscle force. Stronger inhibitory cerebral activity was needed for a nogo stimulus, in the case where a stronger response was needed for a go stimulus.

General Conclusion

In the present two neurophysiological studies, we used MEG and TMS and investigated the neural mechanisms of somato-motor inhibitory processing. MEG data revealed that the processing was related to the neural activity of the prefrontal cortex, and that the period was at 160-170 ms after the stimulus onset in the nogo trials. In addition, we confirmed a positive relationship between muscle force and the inhibitory processing. When considering the inhibitory pathway, our TMS findings showed that the activity of primary motor cortex was modulated by the inhibitory signals from prefrontal cortex.

However, the detail mechanisms of inhibitory processing have remained a matter of debate. For illuminating this issue, further studies are needed.

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Tables

Table 1: The mean RT and error rates in the two movement conditions with S.D.

	Cond. 2	Cond. 3
RT (ms)	259.1 (48.7)	266.3 (39.6)
False alarm (%)	1.3 (1.0)	1.7 (1.2)
Miss (%)	0.8 (0.8)	1.3 (1.4)

There were no significant differences for each index among conditions.

Cond.: Condition

Table 2: The mean peak amplitude and latency of the sources with S.D. for each condition.

	Dipole Strength (nAm)			Peak Latency (ms)		
	cSI	cSII	iSII	cSI	cSII	iSII
Control	14.9 (6.0)	26.3 (9.1)	22.2 (8.8)	53.6 (8.8)	92.3 (12.8)	96.0 (11.5)
Go	14.6 (7.0)	44.9 (14.5)	30.9 (13.2)	53.8 (8.3)	90.1 (9.9)	95.7 (11.0)
Nogo	12.3 (4.7)	33.5 (9.7)	31.7 (13.5)	48.9 (5.3)	90.8 (12.7)	96.9 (12.3)

The results of ANOVAs for the dipole strength of the contralateral SII showed a significant main effect of Condition ($F(2, 12) = 15.858$, $p < 0.001$). Post hoc analysis indicated that strength was significantly greater in go than control and nogo ($p < 0.001$ and $p < 0.02$, respectively). The dipole strength in the ipsilateral SII also showed a strong tendency toward a main effect of Condition ($F(2, 14) = 4.424$, $p = 0.069$, $\varepsilon = 0.541$).

cSI = contralateral SI, cSII = contralateral SII, iSII = ipsilateral SII

Table 3: Talairach coordinates, dipole strength and peak latency of nogo-M170 with S.D.

	x (mm)	y (mm)	z (mm)	Dipole Strength (nAm)	Peak Latency (ms)
Con. 2	-48.8 (7.6)	15.6 (3.9)	24.1 (5.0)	16.8 (8.6)	161.1 (20.8)
Con. 3	-46.6 (6.3)	16.4 (5.2)	23.3 (3.6)	18.8 (8.4)	162.2 (25.9)

Coordinates x; left-to-right, y; posterior-to-anterior, z; inferior-to-superior

There were no significant differences for each index among conditions with the paired *t* test ($p > 0.05$, respectively).

Table 4: The error rates in the three conditions with S.D.

	10%	30%	50%
False alarm (%)	1.5 (2.1)	1.2 (1.5)	1.3 (1.5)
Miss (%)	0.3 (0.8)	0.3 (0.6)	0.2 (0.5)
Force error (%)	2.6 (1.2)	2.2 (1.6)	2.2 (1.7)

There were no significant differences for each index among conditions.

Figures

Figure 1

MEG signals for the left second digit in a representative subject. (A) The somatosensory evoked magnetic field (SEF) waveforms over 204 planar coils from the top of the head in three conditions. (B) An enlarged waveform recorded in left inferior frontal areas. (C) Magnetic field patterns for each condition at 170.5 ms. All data in A-C were digitally filtered (0.1-40Hz bandpass) for display purposes.

Figure 2

The time-course of ECD strength of cSI, cSII, iSII and prefrontal activities in nogo trials for the left second digit of a representative subject.

Figure 3

Location and orientation of the main response estimated in a representative subject superimposed on MRI scans. (A) Axial slice at the level of SI (B) Coronal slice at the level of SII. cSI = contralateral SI,

cSII = contralateral SII, iSII = ipsilateral SII, L = left, R = right.

Figure 4

Nogo dominant activity in a 3D image of all eight subjects. The activity was estimated around the posterior part of the inferior frontal sulci in the left prefrontal cortex. Blue and red points indicate the activities for the left second and fifth digits, respectively.

Figure 5

The grand-averaged areal mean signals for the left second digit and the paired *t*-test value at each sampling point between go and nogo trials. The scale for the paired *t*-test is a common logarithm. $P < 0.05$ was considered to be significant.

Figure 6

The amplitude ratio of mean MEP to mean control MEP with S.D.. The amplitude of MEP for go trials was significantly larger in the 50 % MVC condition than 10 % MVC condition, and the amplitude for nogo trials was

significantly smaller in the 50 % MVC condition than 10 % and 30 % MVC conditions. * $p < 0.01$, ** $P < 0.05$.

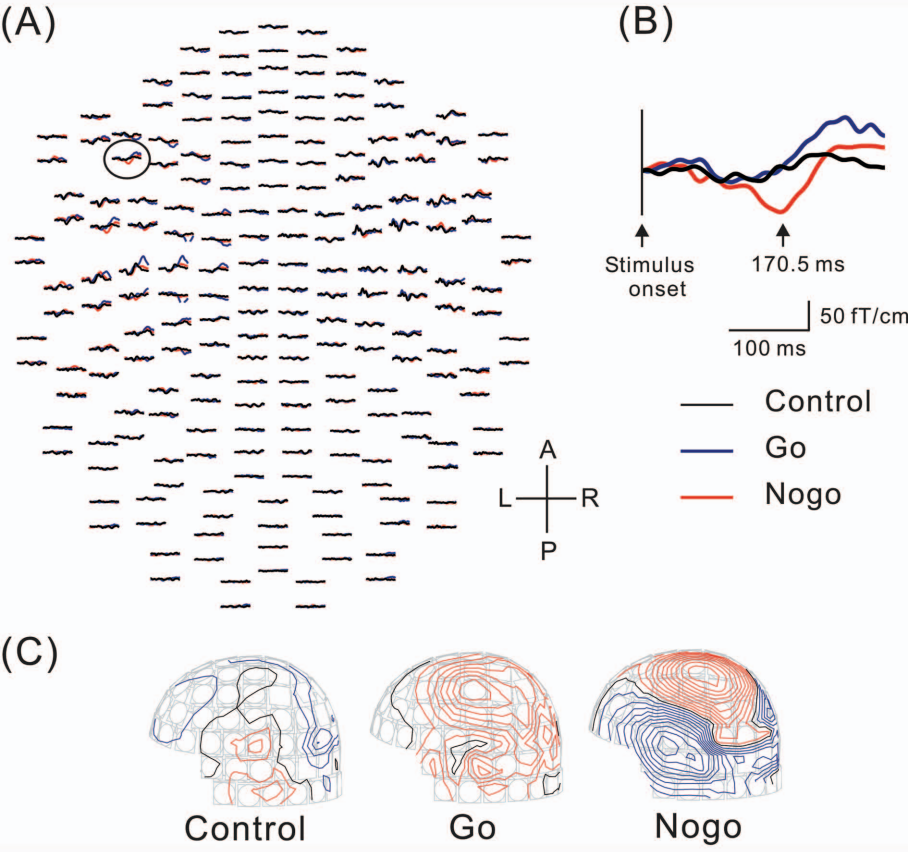
(A)
(B)
Stimulus onset
170.5 ms
50 fT/cm
100 ms
Control
Go
Nogo
A
L
R
P
(C)
Control
Go
Nogo

Figure 1

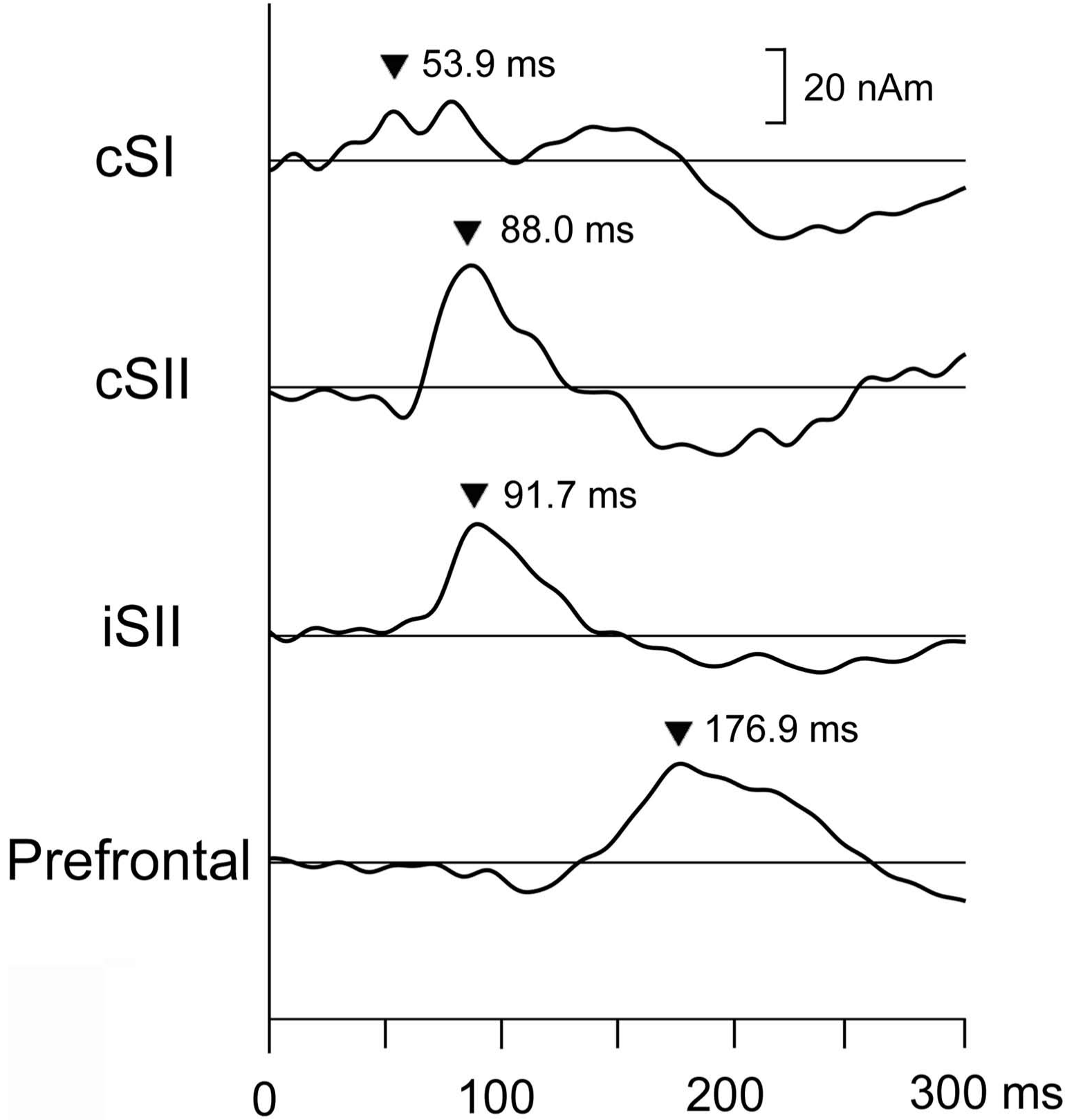
53.9 ms
20 nAm
cSI
88.0 ms
cSII
91.7 ms
iSII
176.9 ms
Prefrontal
0
100
200
300 ms

Figure 2

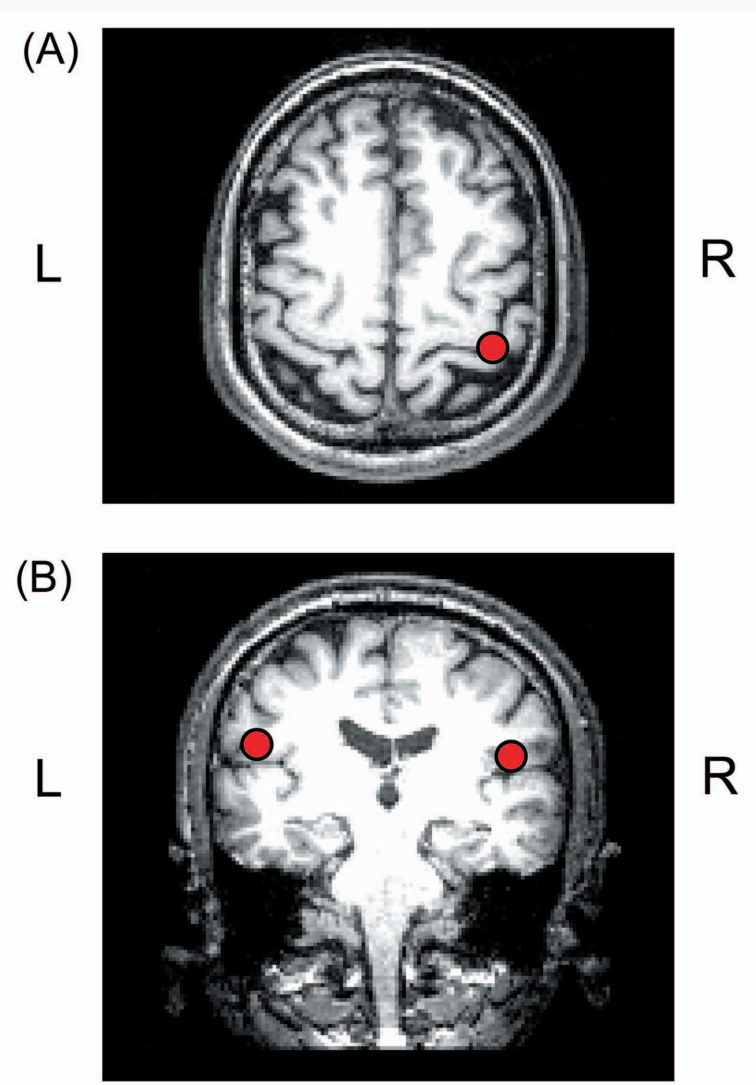

Figure 3

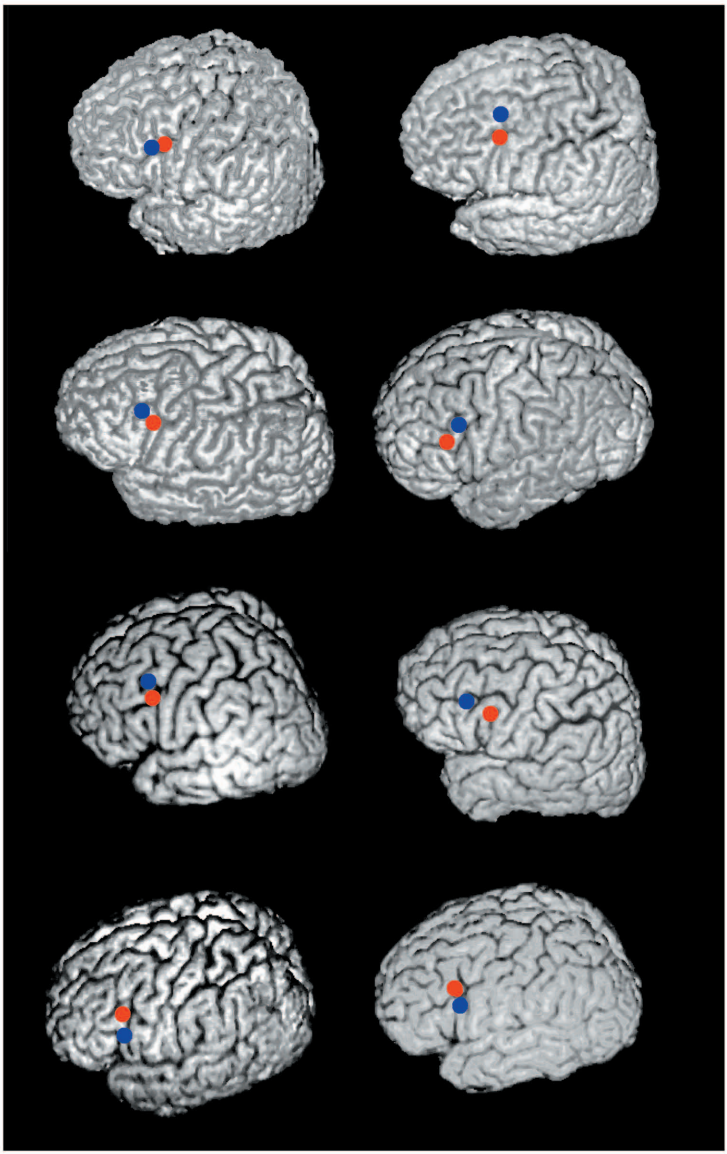

Figure 4

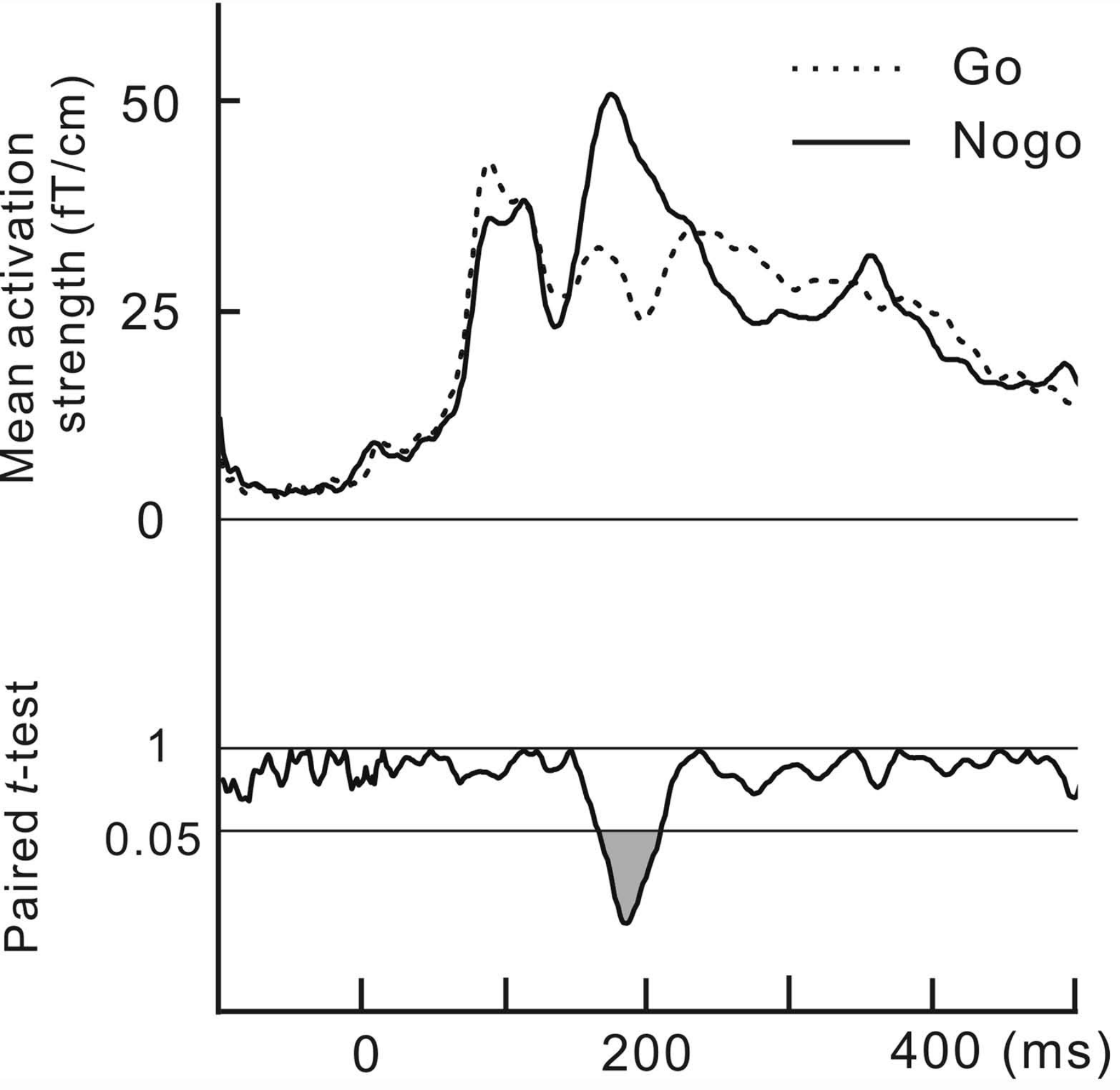
Go
Nogo
Mean activation strength (fT/cm)
50
25
0
Paired t-test
1
0.05
0
200
400 (ms)

Figure 5

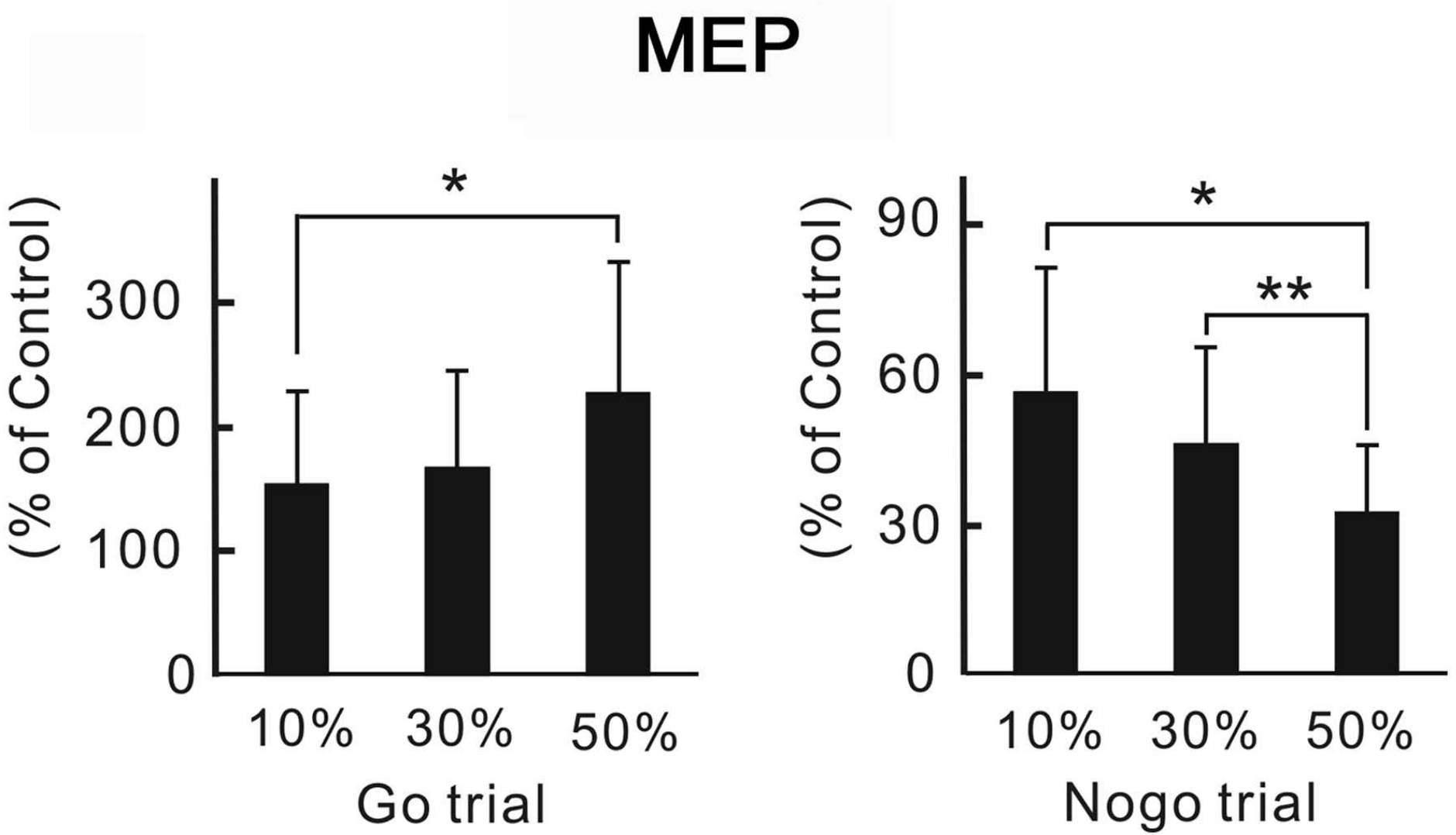
MEP
(% of Control)
300
200
100
0
*
10%
30%
50%
Go trial
(% of Control)
90
60
30
0
*
**
10%
30%
50%
Nogo trial

Figure 6