Title:

Neuromagnetic Activation of Primary and Secondary Somatosensory Cortex Following Tactile-on and Tactile-off Stimulation

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Abstract

OBJECTIVE: Magnetoencephalography (MEG) recordings were performed to investigate the cortical activation following tactile-on and tactile-off stimulation.

METHODS: We used a 306-ch whole-head MEG system and a tactile stimulator driven by a piezoelectric actuator. Tactile stimuli were applied to the tip of right index finger. The interstimulus interval was set at 2000 ms, which included a constant stimulus of 1000 ms duration.

RESULTS: Prominent somatosensory evoked magnetic fields were recorded from the contralateral hemisphere at 57.5 ms and 133.0 ms after the onset of tactile-on stimulation and at 58.2 ms and 138.5 ms after the onset of tactile-off stimulation. All corresponding equivalent current dipoles (ECDs) were located in the primary somatosensory cortex (SI). Moreover, long-latency responses (168.7 ms after tactile-on stimulation, 169.8 ms after tactile-off stimulation) were detected from the ipsilateral hemisphere. The ECDs of these signals were identified in the secondary somatosensory cortex (SII).

CONCLUSIONS: The somatosensory evoked magnetic fields waveforms elicited by the 2 tactile stimuli (tactile-on and tactile-off stimuli) with a mechanical stimulator were strikingly similar. These mechanical stimuli elicited both contralateral SI and ipsilateral SII activities.

SIGNIFICANCE: Tactile stimulation with a mechanical stimulator provides new possibilities for experimental designs in studies of the human mechanoreceptor system.

1. Introduction

Tactile input from the periphery activates several cortical areas. The primary somatosensory cortex (SI), in the postcentral gyrus, carries out the first stage in cortical processing of the somatosensory stimuli. The second somatosensory cortex (SII) is in the upper wall of the sylvian fissure. Several cortical imaging tools, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG), have provided unequivocal evidence of the activity in sensory processing areas such as SI and SII (Hari and Forss, 1999; Dresel et al., 2008; Ledberg at al., 1995). Compared to fMRI and PET, MEG has an excellent temporal resolution and has been used successfully to analyze the temporal aspect of cortical sensory information processing (Hari and Forss, 1999; Karhu and Tesche, 1999; Inui et al., 2004). In some MEG studies, intra-epidermal and transcutaneous electrical stimulation (Inui et al., 2003), YAG laser stimulation (Nakata et al., 2004; Nakata et al., 2008), and mechanical stimulation using pneumatics or finger clips (Karageorgiou, et al., 2008; Hoechstetter et al., 2000; Hoechstetter et al., 2001) etc. have been used to analyze the cortical activity following nociceptive or non-nociceptive stimulation. Since laser and intra-epidermal stimulation can activate nociceptors of thin myelinated A-delta fibers without stimulating tactile afferent fibers, these stimulators are ideal for investigations of the nociceptive system.

It is extremely difficult to produce accurate and real-life-like tactile stimuli. Consequently, many of the non-nociceptive somatosensory research performed using MEG system have depended on unnatural stimuli such as electric pulses. Although pneumatics and finger clips have sometimes been used to investigate the human non-nociceptive sensory system (Karageorgiou, et al., 2008; Hoechstetter et al., 2000; Hoechstetter et al., 2001), such stimulation activates multiple tactile receptors. Because the rise time of the mechanical stimulation was not clearly defined in these studies, the temporal aspect of cortical activity following the non-nociceptive mechanical stimulation was not identified as clearly as those following electrical or nociceptive stimulation.

In addition, pneumatics and finger clips stimuli have limited points of application at various parts of the body. Although only Jousmaki et al. (2007) have presented a novel solution to produce tactile stimuli on various parts of the body for MEG study, the stimulus intensity of their device is not clear. In the present study, we used a precise and consistent tactile stimulator driven by piezoelectric actuators to investigate the neural activity in the somatosensory cortex following tactile stimulation.

Recently, Yamashiro et al. (2009) have reported that electrical-off stimuli elicited activity in both the contralateral and ipsilateral SII areas, but not in the contralateral SI area. On the other hand, it is not clear whether mechanical-off stimuli elicit contralateral SI activity as much as electrical-off stimuli because the skin displacement that occurs as a result of mechanical-off stimulus is slower than that following mechanical-on stimulus. Hence, we also investigated the effects of tactile-off stimulation generated by removal of a constant mechanical pressure to activate SI and SII cortices.

2. Subjects and Methods

2.1. Subjects

Nine healthy, right-handed male volunteers (age range, 21–46 years; mean ± standard deviation, 30.4 ± 10.1 years) participated in this study. All subjects gave their written informed consent. This study was approved by the ethics committee at Niigata University of Health and Welfare.

2.2. Stimuli

An array of 4 tiny plastic pins (2.4 × 2.4 mm; similar to Braille) driven by piezoelectric actuators (KGS, Saitama, Japan) was used to obtain the somatosensory evoked magnetic fields (SEF; Fig. 1-a). Specifications of each pin were as follows: 1.3 mm diameter; height of the protrusion 0.7 mm with a variable pushing force of 0.031–0.12 N/pin. The distance between pins was set at 2.4 mm. Our subjects detected tactile-on stimuli more easily than tactile-off stimuli. The mechanical delay from the onset of the trigger signal to the time when the pins reached at their highest position was 0.64 ms.

In this study, tactile stimuli were applied to the tip of the right index finger. The interstimulus interval was set at 2000 ms, which included a constant stimulus of 1000 ms duration (Fig. 1-b).

2.3. Data Acquisition

Subjects were seated comfortably inside a magnetically shielded room (Tokin Ltd., Sendai, Japan) with their heads firmly positioned inside a 306-ch whole-head MEG system (Vectorview, Elekta, Helsinki, Finland). This device consists of 204 planar-type, first-order gradiometers arranged as 102 pairs and 102 magnetometers. This configuration of gradiometers specifically detects the signal just above the source current. MEG signals were sampled at 1000 Hz with a band-pass filter ranging between 0.03 and 330 Hz.

Before MEG measurement, 3 anatomical fiducial points (nasion and bilateral preauricular points) and 4 indicator coils on the scalp were digitized using a 3D digitizer (Polhemus, Colchester, VT, USA). The fiducial points provide spatial information necessary for integration of magnetic resonance (MR) images and MEG data, while the indicator coils determine the subject’s head position in relation to the helmet. T1-weighted MR images were collected using a 1.5-T system (MAGNEX Epios15, Shimadzu, Kyoto, Japan).

2.4. Data Analysis

To analyze SEF, the band-pass filter was set between 0.5 and 100 Hz, and the 20-ms period of data preceding the stimulus was used as the baseline. SEF signals were obtained 20 ms before and 2000 ms after the onset of the tactile-on stimulus, and a total of 300 epochs for SEFs was averaged. The sources of the components of interest in the SEFs were estimated as the equivalent current dipoles (ECDs) using a least-squares search using a subset of 16–18 channels over the response area. We used "Source Modeling" software (Elekta, Helsinki, Finland) to model the sources. The ECD locations and moments were calculated using a spherical conductor model of a 3D axis determined using the fiducial points (the nasion and bilateral preauricular points). We accepted ECDs with a goodness-of-fit better than 90% for analysis. Accepted ECDs were superimposed onto individual MR images.

The paired *t*-test was used to test for significant differences in the latency of SEF component and the locations of ECDs. The significant level was set at 5%.

3. Results

We confirmed some of the peaks of SEF waveforms around the somatosensory cortex in the bilateral hemispheres (Fig. 2). In all subjects, tactile-on stimuli (on-stimuli) elicited five-peak SEFs as P1, P2, P3, P4, and P5 from the bilateral hemispheres. Tactile-off stimuli (off-stimuli) generated by removal of a constant pressure also elicited five-peak SEFs as R1, R2, R3, R4, and R5 (Fig. 3). Time courses of the source strength of contralateral SI and ipsilateral SII cortices for all subjects are shown in Fig. 4. In these SEFs, peak latencies of P1 and R1 occurred at 57.3 ± 11.2 ms and at 58.2 ± 12.3 ms, respectively, in the contralateral hemisphere. Table 1 shows the peak latencies of SEF signals in bilateral hemispheres. In the contralateral hemisphere, the most concentrated SEF peaks of P2 and R2 were identified at 133.0 ± 10.6 ms after on-stimuli and at 138.5 ± 14.5 ms after off-stimuli. There were no significant differences in peak latency between P1 and R1 or between P2 and R2. All ECDs corresponding to these peaks were located in area 3b (Fig. 5). Early responses were observed at about 30 ms from the contralateral hemisphere after both stimuli in 2 of the 9 subjects, but ECDs were not calculated precisely.

On the other hand, the more-delayed SEF peaks of P3 and R3 were observed at 168.7 ± 18.3 ms and 169.8 ± 18.9 ms, respectively, and corresponding ECDs were identified in SII of the ipsilateral hemisphere in all subjects (Fig. 5). There were no significant differences in latency of the observed peaks and in location of the corresponding ECDs between P3 and R3.

The most-delayed peaks of P4 and R4 were recorded in the contralateral hemisphere in 6 of 9 subjects, and the other SEF peaks of P5 and R5 were in the ipsilateral hemisphere in 7 out of 9 subjects (Table 1). The ECDs corresponding to these peaks could not be calculated precisely, with the goodness-of-fit being lower than 80% in all subjects.

4. Discussion

In this study, tactile stimuli with low intensity were used, and clear SEF signals were recorded from bilateral hemispheres after both on- and off-stimuli. The present study provided 2 important findings.

First, SEF waveforms elicited by the 2 mechanically different stimuli (both on- and off-stimuli) were strikingly similar. This result showed that prominent SEF signals were evoked not only by the onset of tactile-on stimuli but also by tactile-off stimuli generated by the removal of a constant mechanical pressure. Therefore, we assumed that the observed peaks of SEF were caused by the rapid-adapting mechanoreceptors, such as Meissner's corpuscles and/or the Pacinian corpuscles, which tend to fire only during the initial application and removal of constant mechanical stimuli, and are important in the detection of changes in the displacement of the skin (Johansson RS and Flanagan JR, 2009; McGlone F and Reilly D, 2009). Slow-adapting mechanoreceptors (Merkel cell complex and Ruffini corpuscles) might be constantly being activated during the on-stimulus (Johansson RS and Flanagan JR, 2009; McGlone F and Reilly D, 2009); however, this activity was asynchronous. Therefore, we assumed that the averaged SEF could not reflect the activity.

This study demonstrates that the peak latency of the earliest prominent signal (P1 and R1) was elicited approximately 57 ms in the contralateral SI after both on- and off-stimuli. This latency was different from those elicited using different methods. Previous reports have indicated values of 20 ms after electrical stimulation of the median nerve (Shimojo M, et al., 1996; Forss et al., 2001) and finger clip stimulation (Hoechstetter et al., 2001), 30–50 ms after transcutaneous electrical stimulation (Inui et al., 2003; Iguchi et al., 2005), 40–50 ms after pneumatic stimulation (Karageorgiou et al., 2008), 94–162 ms after intraepidermal stimulation (Nakata et al., 2004; Inui et al., 2002), and about 170 ms after YAG laser stimulation of nociceptors (Nakata et al., 2004; Nakata et al., 2008). However, the latency of the most prominent response in Jousmaki's study using brush tactile stimulation (Jousmaki et al., 2007) was 54 ms in the contralateral hemisphere, which is in close agreement with the results of our study. Since both Jousmaki's and our studies utilized very low-intensity stimulation, it is possible that the earliest prominent signal in contralateral SI might be elicited specifically from non-nociceptive receptors via A-beta tactile afferent fibers. However, it is well known that the conduction velocity of the human sensory nerve is 50–70 m/s. Mechanical stimulation of the skin activates the responses with a delayed rise time in mechanoreceptors compared with electrical stimulation. Therefore, we assumed that the long latency in this study might be caused by a relatively longer period for mechanoreceptors activation.

In this study, contralateral SI activity was elicited by tactile-off and tactile-on stimuli. Recently, Yamashiro et al. (2009) reported that electrical-off stimuli did not elicit contralateral SI activity. Mechanical-off stimuli cause changes of the skin surface and activate mechanoreceptors. Therefore, we considered that mechanical-off responses were different from electrical-off responses, and that contralateral SI activity was elicited by mechanical-off stimuli.

Second, SII activity in the ipsilateral hemisphere observed in this study was elicited by light tactile stimulation. Based on our observations, input from non-nociceptive receptors, such as Meissner's corpuscles and/or the Pacinian corpuscles, seems to cause the ipsilateral SII activity. This is contrary to previous studies in terms of the nature of the stimulus used for the elicitation. Several studies used nociceptive stimuli (Nakata et al., 2004; Nakata et al., 2008) and non-nociceptive electrical stimuli (Inui et al., 2003; Yamashiro et al., 2009) to record SII activity. It has also been reported that SII activity was enhanced by cognitive tasks involving the recognition of texture (Ledberg et al., 1995), integration of information from 2 body halves (Hari et al., 1998; Simoes et al., 1999), sensorimotor integration (Forss and Jousmaki, 1998; Kida et al., 2006; Wasaka et al., 2005), attention (Iguchi et al., 2005; Mima et al.,1998), and learning and memory (Ridley and Ettlinger, 1976; Ridley and Ettlinger, 1978).

Moreover, we could not observe SII activity clearly in the contralateral hemisphere. Previous studies have shown that MEG responses from SII are bilateral, but the activity observed in the contralateral hemisphere is typically much earlier in timing and greater in amplitude that those in the ipsilateral hemisphere (Hari and Forss, 1999). In our study, prominent responses were recorded approximately 130 ms after both stimuli, but only in

SI and not in SII (3b) of the contralateral hemisphere. Karageorgiou et al. (2008) hypothesized that the inconsistent SII response could be attributable to a masking of dipoles in SII by overlying SI activity. We assumed that one of the possibilities for the lack of observation of SII activity in the contralateral hemisphere may be due to the masking effect by SI activity. For example, it is conceivable that the time course of SI activity is similar to that of SII, and the amplitude of SI activity is far greater than that of SII activity. However, this possibility could not be clarified in this study having single-dipole analysis. Therefore, we intend to perform further investigations to separate SII activity from SI activity.

SII receives input from the contralateral SI and SII thorough the corpus callosum (Jones and Peter, 1986) and directly from thalamus (Rose et al., 1996; Zhang et al., 1996). A direct input from thalamus to SII has also been described (Forss et al., 1999). Forss et al. (1999) showed that ipsilateral SII was activated in stroke patients even if both the contralateral SI and SII areas are lesioned. Our results provide further evidence that low-intensity tactile-on and tactile-off stimuli elicit ipsilateral SII activity. However, the functional role of SII cortex is less clear than that of SI. Therefore, further investigations are required for gaining more insight into the mechanism of activation in the SII area.

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Table 1
Peak latencies of somatosensory evoked magnetic fields

	After on-stimulus (ms)		After off-stimulus (ms)		Number of subjects
Contralateral	P1	57.3 ± 11.2	R1	58.2 ± 12.3	9
Hemisphere	P2	133.0 ± 10.6	R2	138.5 ± 14.5	9
	P4	279.0 ± 31.2	R4	277.7 ± 31.2	6
Ipsilateral	P3	168.7 ± 18.3	R3	169.8 ± 18.9	9
Hemisphere	P5	308.9 ± 42.0	R5	312.9 ± 41.9	7

Legends

Figure 1

Tactile Stimulator and Stimulation Parameter

(a) An array of 4 tiny plastic pins (2.4 × 2.4 mm) of tactile stimulator was driven by piezoelectric actuators. Specifications of each pin are 1.3 mm diameter, 0.7 mm height of the protrusion. The distance between pins was set at 2.4 mm.

(b) The interstimulus interval was set at 2000 ms including 1000 ms of a constant stimulus.

Figure 2

Representative whole-scalp SEF waveforms with period between 20 ms before and 2000 ms after the onset of tactile-on stimulation obtained from Subject 2 are shown. The recording period includes 1000 ms of a constant stimulus and 1000 ms after the removal of a constant stimulus.

Figure 3

Superimposed SEF signals following tactile-on stimulation were obtained from the contralateral (a) and the ipsilateral (b) hemispheres (Subject 2). Tactile-on stimulation elicited five-peak SEFs as P1, P2, P3, P4, and P5 from the bilateral hemisphere. Tactile-off stimulation also elicited five-peak SEFs as R1, R2, R3, R4, and R5.

Figure 4

Source waveforms of contralateral SI and ipsilateral SII cortices elicited by the tactile stimulation for all subjects.

Figure 5

Results of ECD analysis in Subject 2. The locations of ECDs are superimposed on the same subject's MR images. Upper panel shows the contralateral hemisphere to the right finger stimulation. ECDs corresponding to the P1 and P2 (on-stimulation) as well as R1 and R2 (off-stimulation) were all located in SI. Lower panel shows the ipsilateral hemisphere to the stimulation. ECDs corresponding to the P3 and R3 were observed in SII. Yellow circle and white box refer to on-stimulus and off-stimulus, respectively.

Figure 1

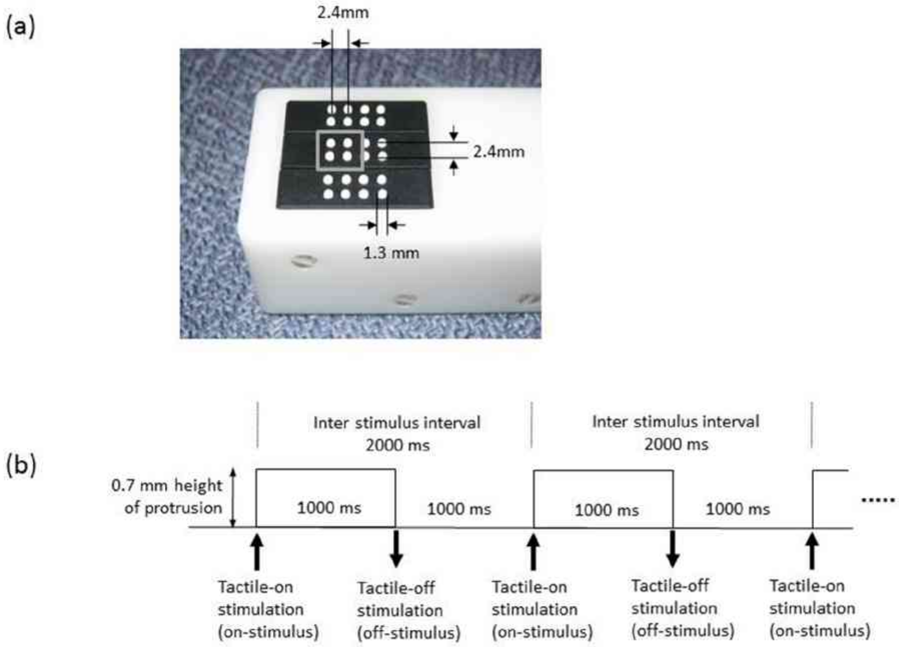


Figure 2

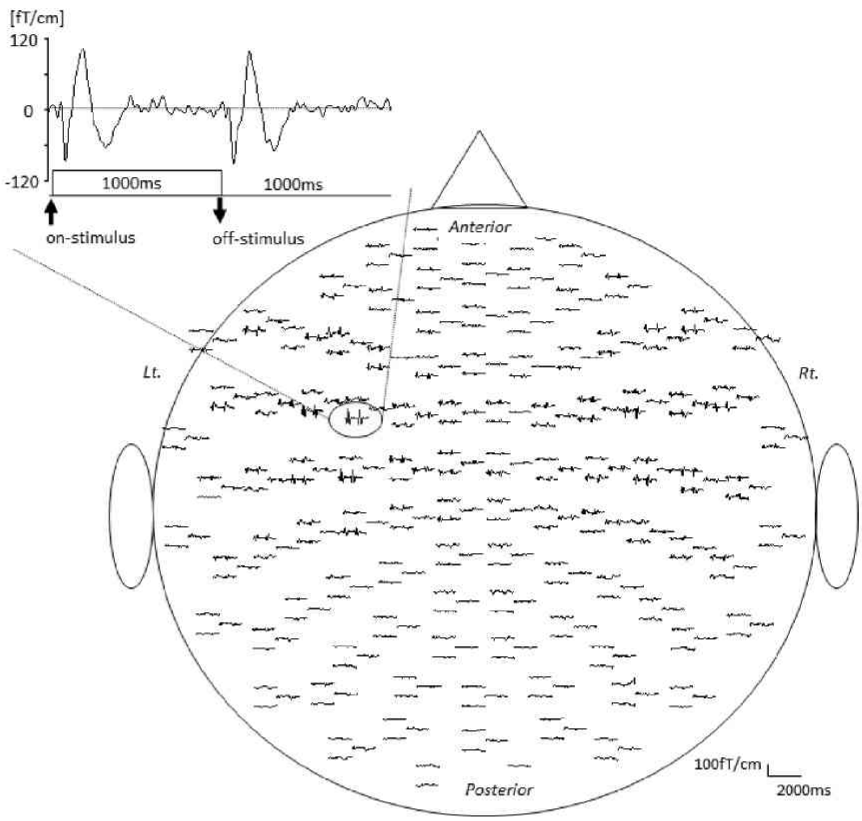


Figure 3

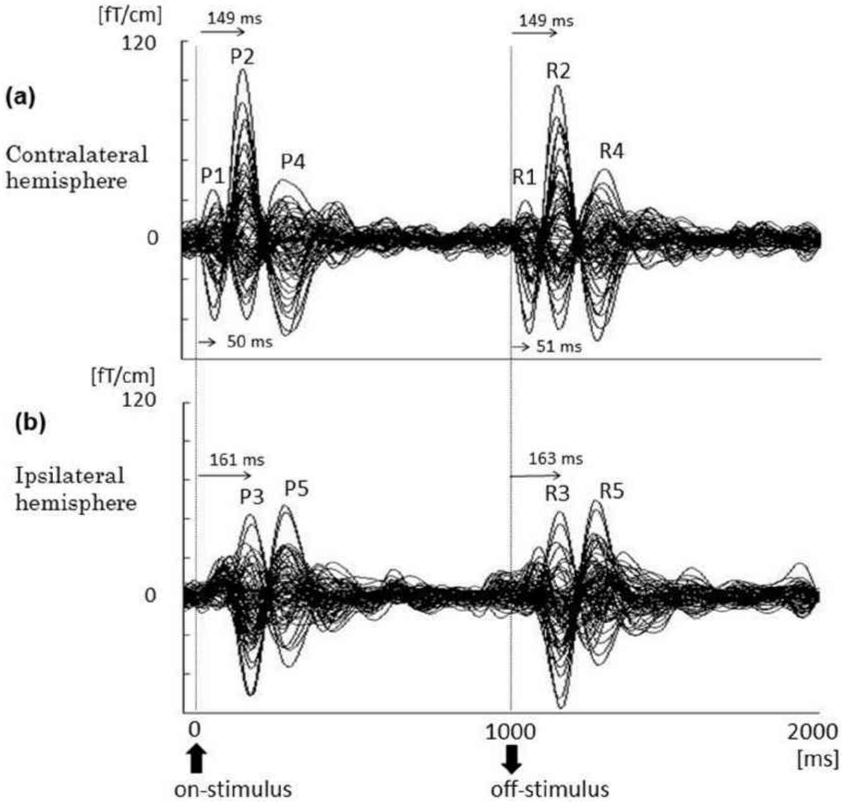


Figure 4

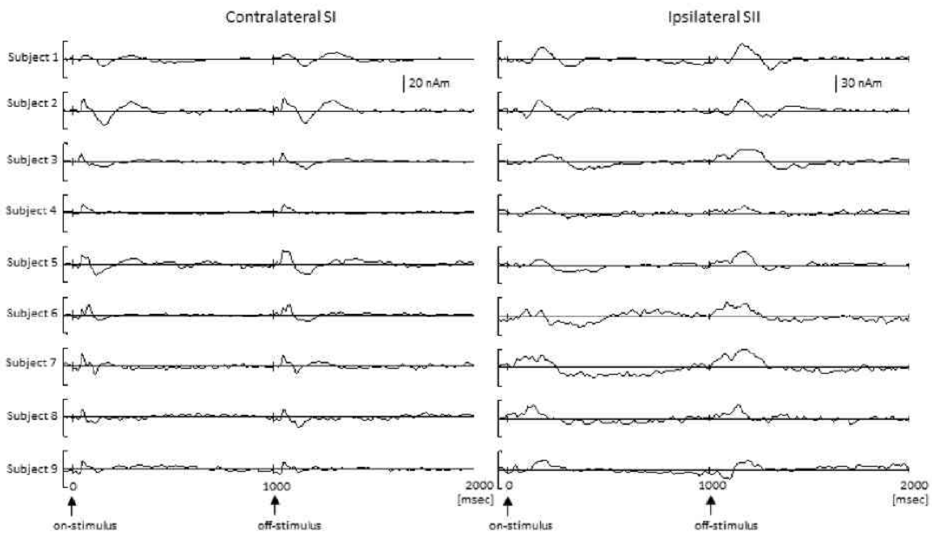
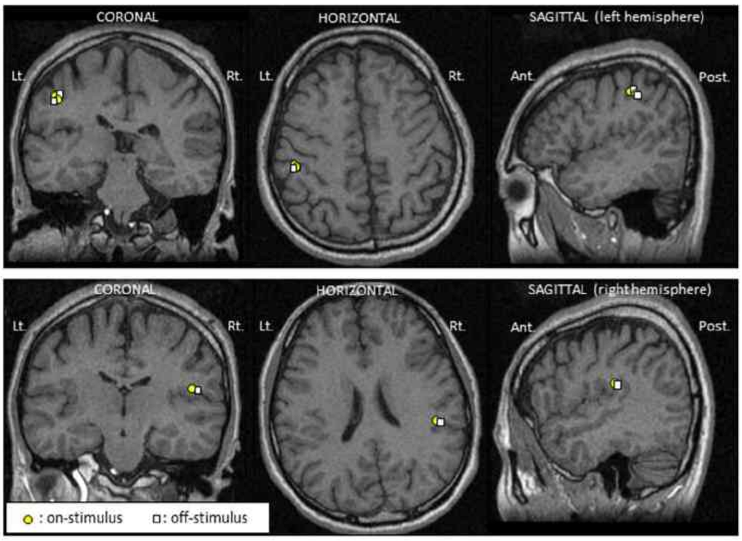


Figure 5


CORONAL
HORIZONTAL
SAGITTAL (left hemisphere)
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