Time-varying cortical activations related to visual-tactile cross-modal links in spatial selective attention

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Abstract

The neural mechanisms underlying unimodal spatial attention have long been studied, but the cortical processes underlying cross-modal links remain a matter of debate. To reveal the cortical processes underlying the cross-modal links between vision and touch in spatial attention, we recorded magnetoencephalographic (MEG) responses to electrocutaneous stimuli when subjects directed attention to an electrocutaneous or visual stimulus presented randomly in the left or right space. Neural responses recorded around the bilateral sylvian fissures at 85 ms and 100 ms after the electrocutaneous stimulus were significantly enhanced by spatial attention in both the touch-irrelevant and relevant modalities. Source analysis revealed that the sylvian responses were generated in the secondary somatosensory cortex (SII). An early response, M50c, generated in the contralateral primary somatosensory cortex (SI), was not modulated by attention. There were no significant attentional changes in the source location or magnetic field distribution, suggesting attentional facilitation of the neural activity in SII itself, rather than a tonic bias effect or overlapping of separate neuronal populations. The results show that spatial attention enhances responses to tactile inputs in SII, independent of sensory modality attended. The underlying mechanism remains to be determined, but may be an increase in gain.

Key words
Spatial attention, Cross-modal links, Magnetoencephalography, Somatosensory, Visual
Introduction

Spatial selective attention enables the quick and accurate processing of sensory signals from attended locations, and helps to extract relevant target signals from a great number of sensory signals. The neural systems underlying spatial selective attention are now well understood, but most previous studies have focused on purely unimodal situations. These studies have indicated that neural responses to stimuli presented at attended locations increased in comparison with those at unattended locations using the techniques of electroencephalography (EEG) (Hillyard et al., 1973; Desmedt and Robertson et al., 1977; García-Larrea et al., 1995; Valeriani et al., 2003; Kida et al., 2004a), magnetoencephalography (MEG) (Mima et al., 1998; Lam et al., 2001), positron emission tomography (PET) (Corbetta et al., 1990; 1993), and functional magnetic resonance imaging (fMRI) in humans (O’Craven et al., 1997; Beauchamp et al., 1997; Corbetta et al., 2000), and single-neuron recordings in monkeys (Luck et al., 1997; Meftah et al., 2002). With regard to the mechanisms and functions of attention, one remaining problem is the cross-modal links among different sensory modalities in spatial attention, which have been extensively studied in behavioral psychophysics (Spence and Driver, 1996; Spence et al., 2000; Lloyd et al., 2003; Spence et al., 2006), and using EEG (Eimer and Driver, 2000; Eimer et al., 2001; 2002; Eimer et al., 2004), fMRI (Macaluso et al., 2000), and transcranial magnetic stimulation (TMS, Chambers et al., 2004) for about a decade. For instance, directing attention to visual stimuli presented at specific locations not only improves up/down elevation discrimination of the stimuli, but also improves the discrimination of and enhances the responses to tactile stimuli presented near the visually-attended locations. Exogenous characteristics of the
cross-modal links were also investigated (Kennett et al., 2001). These impressive findings have raised the question of whether the mechanisms of selective attention are separate modality-specific, or purely supramodal attentional, separable-but-linked systems (Spence and Driver, 1996; Driver and Spence, 1998; 2000; Eimer, 2004; Macaluso and Driver, 2004; Chamber et al., 2004). However, the spatiotemporal dynamics of the cortical processes on which this attentional system acts are insufficiently understood.

There are three potential mechanisms of within-modal spatial attention. One is a gain regulation mechanism (Hillyard and Mangun, 1987; Posner and Dehaene, 1994; Hillyard et al., 1999; Kanwisher and Wojciulik, 2000), which is derived from animal studies indicating attentional influences on evoked electrical responses in the sensory pathway (Hermandez-Peon et al., 1956; 1966; Oatman and Anderson, 1977). These early studies revealed an enhancement of the response when the animal’s attention was directed to a stimulus, but a reduction when attention was directed elsewhere (Hermandez-Peon et al., 1956; 1966; Oatman and Anderson, 1977). There is abundant evidence supporting the gain regulation mechanism (Moran and Desimone, 1985; Hillyard and Mangun, 1987; Corbetta et al., 1991; Luck et al., 1997; Reynolds et al., 2000).

A second mechanism is an attention-induced activation of a separate neuronal population which is not activated by unattended stimuli (Näätänen et al., 1978; Näätänen, 1992). This has been well investigated in EEG studies as the so-called endogenous component of event-related brain potentials (ERP), while the classical gain regulation mechanism corresponds to the enhancement of an exogenous component (Hillyard et al., 1999). If a response is enhanced by attention together with changes in
the scalp distribution and waveform of the response, the attentional enhancement is interpreted as a result of the overlapped activation of a separate neuronal population. In their EEG studies, by contrast, Hillyard et al. have regarded the attentional enhancement without changes in the spatial distribution or waveform as evidence of the enhanced activation of the same neuronal population as that for unattended stimuli, i.e., the gain regulation mechanism.

The third mechanism is a tonic bias effect, indexed by a sustained baseline increase in activity in single-neuron recordings (Luck et al., 1997) or PET (Rees et al., 1997). Such a sustained baseline increase will produce sustained attentional modulation like slow deflections in the EEG/MEG recordings. However, because of baseline corrections commonly used in the EEG/MEG recordings, they cannot investigate the possibility that sustained baseline changes may contribute to modulate neuronal responses to attended vs. unattended stimuli. Therefore, if the attentional modulation is observed as not a sustained but a phasic effect in the EEG/MEG studies, the gain regulation mechanism better explains the modulation than does the tonic bias effect. Accordingly, the attentional enhancement of an evoked response without changes in waveform and spatial distribution predicts a gain regulation mechanism (Hillyard et al., 1999). However, the mechanisms underlying cross-modal links in spatial attention are still unknown. EEG/MEG measures which record a neural response with high temporal resolution are a good way to examine these possible mechanisms which can act dynamically within the order of several milliseconds. In addition, MEG, which records a neural response with a higher spatial distribution than EEG, may provide important information, although, of course, it should be considered that there is neural activity which can not be detected by MEG.
Here, we used whole-head MEG to reveal time-varying cortical processes underlying the cross-modal links in visual-tactile spatial selective attention. To this end, we analyzed neural responses to electrocutaneous stimuli in a selective attention task where a visual or electrocutaneous stimulus was presented in a random order on the right or left side (hand or hemifield) when vision or touch was task-relevant. Unimodal attention studies in the somatosensory modality have found little or no effect on the neural response in the primary somatosensory cortex (SI) to a somatosensory stimulus, but the enhancement of responses with a latency of 80 ms~ in the secondary somatosensory cortex (SII) in humans (Mima et al., 1998; Fujiwara et al., 2000; Hamada et al., 2004). Higher attentional sensitivity in SII is also reported in monkeys (Meftah et al., 2002; Chapman and Meftah, 2005). Previous EEG studies failed to find links from vision to touch in spatial attention when touch was completely task-irrelevant (Eimer and Driver, 2000), but demonstrated clear evidence of links when vision was primary and touch was of secondary relevance to the task or using a cueing task (Eimer and Driver, 2000; Eimer et al., 2001; 2002). MEG has the advantage of recording magnetic fields induced by tangential currents such as the activity in the upper wall of the sylvian fissure (SII), and therefore can reveal the cortical locus of cross-modal links, which are blind to EEG. Therefore, we hypothesized that directing attention to visual stimuli enhances the response in the somatosensory cortex, especially in SII, to tactile stimuli which are presented near the visually-attended locations, as well as directing attention to the tactile stimuli.
Materials and methods

Subjects

Recordings were obtained from eleven healthy right-handed subjects (two women and nine men), aged 23 to 40 years old. All subjects gave written informed consent prior to the study, which was first approved by the Ethics Committee at the National Institute for Physiological Sciences.

Stimulation

The subjects were seated in a magnetically-shielded and semi-darkened room, and put their hands and forearms comfortably on an obliquely oriented board in front of them. An electrocutaneous or a visual stimulus was presented in a random order on the left or right side to elicit neural responses (Figure 1). A double-pulse visual stimulus was infrequently embedded in a sequence of single-pulse visual stimuli, thus providing four types of visual stimuli differing in spatial location and number of pulses. The duration of the single-pulse stimulus was 300 ms, whereas the double-pulse stimulus was illuminated for 120 ms, turned off for 60 ms, and illuminated again for 120 ms. The visual stimuli were presented through two plastic optical fibers (diameter 1 cm, length 3 m, Multi-core POF LUMINOUS, Asahi Kasei, JAPAN), one each on the left and right side. A red light emitting diode (LED, luminance 35 cd/m², measured at the subject’s nasion) was attached to one end of each fiber outside of the shielded room. The other end was located in the shielded room (Figure 1). The fiber was covered with black resin so that subjects could see the light only at one section. The apparatus induced no magnetic artifacts and enables one to present a visual stimulus at preferred locations,
e.g., near the subject’s hands as in this study.

A single-pulse (frequent) or double-pulse (infrequent) electrotactile stimulus was presented in a random order to the second digit of the left or right hand, thus providing four types of tactile stimuli differing in spatial location and number of pulses. The duration of the single-pulse stimulus was 0.2 ms, and in the case of the double-pulse stimulus, two stimuli were successively presented at an interval of 180 ms. The electrical stimulus was delivered to the second digit through a ring electrode (the cathode was attached to the proximal part of the finger, and the anode to the distal part). The stimulus intensity was adjusted to 2.5 times the sensory threshold which was determined by the method of limits.

Task

In the present study, we used a classic selective attention task to test attentional modulation (Hillyard et al., 1973; Eimer and Driver, 2000; Kida et al., 2004a). This is one of the general experimental paradigms used to test sustained attention. Subjects executed the stimulus discrimination task under four conditions in which the direction of attention varied (left/tactile, right/tactile, left/visual, and right/visual attention conditions). In each condition, a total of eight kinds of stimuli differing in spatial location (left and right), sensory modality (vision and touch), and number of pulses (single and double) were presented in a random order at a random interstimulus interval (ISI, 800–1200 ms). Double-pulse stimuli were presented also for the irrelevant modality. The subjects were instructed to fixate on a point at a viewing distance of 40 cm, and to put the second digit of each hand near the visual stimuli. In the touch-relevant/attend-right condition, subjects were instructed to attend covertly to
electrocutionary stimuli presented to the right second digit, and to count silently the
number of electrocutionary double-pulse stimuli presented to the digit. Therefore, in
this condition, the visual single-pulse stimulus presented in the right hemifield was
regarded as an external input from the task-irrelevant modality but was spatially
attended (cross-modal spatial attention). By contrast, the electrocutionary single-pulse
stimulus presented to the right second digit was regarded as a spatially attended input
from the relevant modality (within-modal spatial attention). The electrocutionary and
visual single-pulse stimuli on the left side were regarded as spatially unattended inputs
from the task-relevant and irrelevant modalities, respectively. In each of the other three
conditions, subjects were asked to attend to the designated side, and to count only the
number of double-pulse stimuli presented on the designated side in the relevant
modality. They reported the number after the termination of each block. Each of the four
attentional conditions was run in a randomised order. Each condition contained about
600 trials (about 250 single-pulse electrocutionary, 250 single-pulse visual, 50
double-pulse electrocutionary, and 50 double-pulse visual, presented approximately
equally on the left and right sides), divided into two blocks. Each block lasted about 5
minutes. The number of double-pulse targets varied between blocks (11~14 per block,
24~26 per condition) to ensure subjects counted the target stimuli. Two blocks were run
for each condition. The experiment lasted about 50~60 minutes. The inter-stimulus
interval (ISI) between stimuli in each sensory modality (including single- and
double-pulse stimuli) was 1600~2400 ms, between double-pulse stimuli (including
visual and tactile stimuli) was ~6 s, and between double-pulse target stimuli was ~24 s.
Before each condition, subjects were given verbal instructions about the direction of
attention to be directed and the type of stimuli to be counted.
Recordings and analysis

The data started to be acquired a few seconds after verbal instructions were issued by an experimenter at the beginning of each condition, and then, after a few more seconds, stimulation started. The second block was also started with verbal instructions, a few minutes after the termination of the first block. The MEG was recorded with a helmet-shaped 306-channel detector array (Vectorview, ELEKTA Neuromag Yo, Helsinki, Finland), which comprised 102 identical triple sensor elements. Each sensor element consisted of two orthogonal planar gradiometers and one magnetometer coupled to a multi-SQUID (superconducting quantum interference device) and thus provided three independent measurements of the magnetic fields. We analyzed the MEG recorded from 204-channel planar-type gradiometers. They were filtered with a bandpass filter of 0.03-150 Hz and digitized at a sampling rate of 1,024 Hz. The analysis period was from 100 ms before to 250 ms after the stimulus. Only neural responses to the electrocutaneous single-pulse stimulus (frequently-presented standard stimulus) were analyzed, for the following reasons. (1) We aimed to examine pure selective attention effects, not ‘target’ effects involved in the modulation of the target-evoked response (García-Larrea et al., 1995; Kida et al., 2004a). (2) We could not analyze the MEG waveform in response to the target double-pulse stimuli because of the low signal-to-noise ratio due to the small number of values averaged. (3) The MEG waveform evoked by the target double-pulse stimuli was difficult to obtain because of the momentary electrical artifact caused by the second pulse of the double-pulse stimulus. The MEG data were filtered offline with a lowpass filter of 50 Hz. The four head position indicator coils attached on the subject’s head were measured with respect
to the three anatomical landmarks (nasion and bilateral preauricular points) using a 3-D digitizer prior to the main experiment outside the shielded room to allow alignment of the MEG and magnetic resonance image (MRI) coordinate systems (3.0-T Siemens Allegra). Prior to the MEG recording after the fixation of the subject’s head to the helmet-shaped sensor, a current was fed to four HPI coils placed at known sites and the resulting magnetic fields were measured with the magnetometer, to obtain the exact location of the head with respect to the sensors. 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.

Eye movements were monitored by an eye movement monitor camera (ISCAN, ISCAN Inc., Massachusetts, U.S.A.). Trials with eye movements exceeding 0.5 degrees from the fixation point and with eye blinks were also excluded from the analysis. Trials with horizontal and vertical eye movements of over 1 degree or with MEG signals exceeding 3,000 fT/cm were rejected from the averaging of MEG data.

We first calculated vector sums from the longitudinal and latitudinal derivatives of the response recorded on the planar-type gradiometers at each of the 102 sensors’ location. This was obtained by squaring MEG signals for each of two planar-type gradiometers at a sensor’s location, summing the squared signals together, and then calculating the root of the sum \( \sqrt{(\delta B/\delta x)^2 + (\delta B/\delta y)^2} \); we here call this the “root sum square, RSS”), (Kida et al., 2006a). The calculation was carried out for all 102 sensors’ locations. Next, we used the obtained RSS waveforms and iso-contour map of the RSS amplitude to look for a peak channel showing the greatest amplitude for each prominent response, because those waveforms had several responses with a different spatial distribution of amplitude. Then, the peak amplitude and latency of prominent responses
in the RSS waveform were measured at the peak channel.

Since we did not deal with MEG responses to all kinds of double-pulse stimuli and of visual stimuli, we obtained 8 kinds of waveform in response to the tactile single-pulse stimulus in a total of 4 conditions, and then arranged them into a 2 by 2 by 2 array according to spatial attention (attended or unattended), relevant modality (touch or vision), and stimulus side (left-hand or right-hand).

To examine whether the spatial distribution of magnetic responses was different or similar between attended and unattended conditions, we calculated Pearson’s correlation coefficient $r$ for conditions of SSR amplitude at the peak latency. The higher the correlation coefficient is, the more similar the spatial distributions of the two MEG responses are (if the correlation coefficient is 1.0, the two MEG responses tested have an identical spatial distribution). The coefficient was calculated for all possible pairs of two conditions.

To identify the source of the equivalent current dipoles (ECDs), sources of measured responses to somatosensory stimulation were modeled with time-varying current dipoles (Sarvas, 1987; Hämäläinen et al., 1993). The MEG signals were evaluated at successive time points, best describing the most dominant source of the response, by a least-squares search in a spherical volume conductor model for the head by using 18-24 sensors around a sensor that had been used to measure the peak amplitude of RSS waveforms. This analysis resulted in the 3-D location, moment, and direction of each ECD in a spherical conductor model. 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. ECDs which account for more than 90% of the GOF value in the sensor subset were accepted for further analysis. Finally, all sensors were...
used to compute the time-varying multi-dipole model allowing the strength of the previously found ECDs to change over the entire period of the analysis while the source locations and orientations were kept fixed.

For the peak amplitude and latency of the RSS waveform, and the peak moment and 3-D location of ECDs, a three-way analysis of variance (ANOVA) with repeated measures was performed with spatial attention (attended and unattended), relevant modality (touch and vision), and stimulus side (left and right) as factors. As we describe in the Results, five responses were analyzed in this study. Because these responses were obtained from different numbers of subjects, the three-way ANOVAs were performed separately for each of five responses. Furthermore, to examine different modulation of the responses, a four-way ANOVA with a factor of response were performed. If the sphericity assumption was violated in Mauchly’s sphericity test, the Greenhouse-Geisser (G-G) correction coefficient epsilon was used to correct the degree of freedom, and then F- and p-values were recalculated. When the G-G correction was applied, the epsilon and corrected results were reported. A two-tailed paired t-test was used for the post-hoc analysis. Statistical significance was set at P<0.05.

Count accuracy was assessed by calculating the absolute deviation of the subject’s target count from the correct target count in each of two blocks (absolute error), and then converting the total number of absolute errors to a percentage of the total correct count (a higher error rate represents more frequent failures to count the stimulus. 0% means that the subject’s count equals the correct count, and 100% means no counting).
Results

Behavioral performance

The rate of count error was very low (0.96% [S.E., 0.64] in the touch-relevant/attend-right condition, 1.41% [0.73] in the touch-relevant/attend-left condition, 0.96% [0.64] in the vision-relevant/attend-right condition, and 1.41% [0.73] in the touch-relevant/attend-left condition), indicating that participants almost perfectly executed the counting task in all conditions. A two-factor ANOVA (direction of attention [left vs. right] * relevant sensory modality [vision vs. touch]) also showed that the error rates were not significantly affected by direction of attention (F (1,10) = 0.94, P = 0.36, n.s.) and relevant sensory modality (F (1,10) = 0.002, P = 0.96, n.s.), and there was no interaction (F (1,10) = 0.002, P = 0.96, n.s.).

Somatosensory evoked magnetic responses

Figure 2 shows the procedure used in this study (waveforms of magnetic fields recorded from gradiometers, the RSS waveform, iso-contour maps of magnetic fields, and iso-contour maps of RSS signals; data obtained for the electrocutaneous single-pulse stimulus to the left second digit in the touch-relevant/attend-left condition from a representative subject). The absence or presence of the response was carefully determined by visual inspection using superimposed waveforms in several conditions and the iso-contour map. These data include peaks around SI in the hemisphere contralateral to the stimulus side (latency of about 50 ms, M50c), two peaks around the sylvian fissure of the contralateral hemisphere (about 85 ms and 150 ms, M85c and M150c), and two peaks around the sylvian fissure in the ipsilateral hemisphere (about
100 ms and 150 ms, M100i and M150i). The M50c iso-contour map had a strongly-focused activation around SI contralateral to the stimulation. The M85c and M100i maps had bilateral activations over the sylvian fissures in both hemispheres. The 150-ms map also had bilateral activations around the sylvian fissures in both hemispheres. Earlier components, the so-called N20m and P35m generated in SI, were clearly found in some subjects, but not in others due to a low signal-to-noise ratio. Therefore, they were not analyzed in this study. M50c, M85c, and M100i were found for all 11 subjects, M150c for 10 subjects, and M150i for 9 subjects.

Figure 3 indicates the waveform of RSS at the sensor which showed the greatest amplitude for each response to the electrocutaneous stimulus. Figure 4 (left panel) shows the peak amplitude of RSS for each response. A three-way ANOVA showed a significant main effect of attention for the amplitude of M85c (F (1,10) = 18.8, P < 0.001), M100i (F (1,10) = 23.8, P < 0.001) and M150c (F (1,9) = 9.2, P < 0.001), with amplitude enhanced by spatial attention. This spatial attention effect was significant both when touch was task-relevant (M85c, F (1,10) = 21.9, P < 0.005; M100i, F (1,10) = 30.6, P < 0.001; M150c, F (1,9) = 8.7, P < 0.05) and when vision was task-relevant (M85c, F (1,10) = 13.2, P < 0.01; M100i, F (1,10) = 9.3, P < 0.05; M150c, F (1,9) = 6.9, P < 0.05), as also revealed by the two-way ANOVA. It seems that the amplitude of M85c showed a gradual increase from the vision-relevant/unattended condition to vision-relevant/attended and touch-relevant unattended, and then to touch-relevant/attended in Figure 3. This tendency was also evident in Figure 4 and predictive of a main effect of spatial attention and of relevant modality. However, a three-way ANOVA showed an effect of spatial attention (as mentioned above), but not a significant main effect of relevant modality (F (1,10) = 2.2, P = 0.17, n.s.), interaction
between spatial attention and relevant modality ($F_{(1,10)} = 0.73, P = 0.41, \text{n.s.}$), or interaction among the three factors ($F_{(1,10)} = 0.28, P = 0.61, \text{n.s.}$). The reasons why it appeared as if there was a main effect of relevant modality were (1) the slightly larger number of subjects showing an increase in amplitude with touch relevance compared to the others showing a decrease and (2) the variability of the effect of relevant modality.

For M50c, a three-way ANOVA showed no significant main effect of spatial attention ($F_{(1,10)} = 0.6, P = 0.45, \text{n.s.}$). A significant main effect of relevant sensory modality was found for M100i ($F_{(1,10)} = 9.8, P < 0.05$), with amplitude enhanced when touch was task-relevant compared to when vision was task-relevant. A stimulus side-relevant modality interaction was also found for M100i ($F_{(1,10)} = 5.6, P < 0.05$). A subsequent two-way ANOVA showed that for the left-hand stimulus, the amplitude was enhanced when touch was task-relevant compared to vision ($F_{(1,10)} = 15.9, P < 0.01$) but for the right-hand stimulus, it was not changed by the relevant modality ($F_{(1,10)} = 0.7, P = 0.43, \text{n.s.}$). For M150c, a three-way ANOVA showed that a stimulus side-spatial attention interaction did not reach the significant level ($F_{(1,9)} = 4.9, P = 0.053$).

The peak latency of the responses in the RSS waveform was not significantly changed by attention or relevant modality. A four-way ANOVA with response (2 levels: M85c and M100i) showed a main effect of response ($F_{(1,10)} = 44.1, P < 0.001$), with it being earlier for M85c than M100i. Another four-way ANOVA (2 levels: M150c and M100i) showed a main effect of response ($F_{(1,8)} = 22.9, P < 0.001$) and an interaction between stimulus side and response ($F_{(1,8)} = 6.0, P < 0.05$). A subsequent three-way ANOVA showed that the latency of M150c was earlier than M150i for the left hand stimulus ($F_{(1,8)} = 60.2, P < 0.001$), but not for the right-hand stimulus ($F_{(1,8)} = 1.4, P = 0.26$).
The magnetic field distribution seemed to be very similar among conditions (Figure 4, right panel). To examine the similarity, we compared magnetic field distributions for each pair of spatial attention (attended and unattended) and relevant sensory modality (touch and vision) for each stimulus side (left- and right-hand stimulus) by calculating Pearson’s correlation coefficient $r$ with the peak amplitudes of RSS at all 102 sensors for each pair (six pairs were analyzed for each response for each stimulus side). The data from the subject displayed in the left panel showed a highly positive correlation in most conditions, as plotted below the iso-contour map. The mean value of correlation coefficients across subjects was also calculated for each response for each stimulus side. Correlations for all pairs showed a highly positive correlation ($R>0.7$, $P<0.001$), indicating that the magnetic field distribution was similar among all conditions.

**ECD analysis**

Figure 5 shows the location of ECDs superimposed on two-dimensional and three-dimensional MRI scans for somatosensory responses. The ECD of M50c was located around the posterior bank of the central sulcus, corresponding to area 3b in SI. The ECDs of M85c and M100i were located in the upper wall of the sylvian fissure in both hemispheres, corresponding to SII. The ECDs of bilateral M150 were also located around the upper wall of the sylvian fissure in both hemispheres. ANOVA indicated that the 3-D coordinates of the ECD location for each response were not significantly different among conditions. Figure 5 (center panel) shows the time course of ECD moment revealed by the multidipole analysis. Table 1 shows the peak moment of ECD. As a result of the three-way ANOVA for each response, a significant main effect of
attention was found for the peak moment of SII M85c (F (1,10) = 26.9, P < 0.001), SII M100i (F (1,10) = 45.9, P < 0.001), SII M150c (F (1,9) = 11.8, P < 0.001) and SII M150i (F (1,8) = 11.8, P < 0.001), with the peak moment increased by spatial attention. A main effect of relevant sensory modality for the peak moment of SII M100i did not reach the significant level (F (1,9) = 4.2, P = 0.073). A stimulus side-spatial attention interaction was found for SII M150c (F (1,9) = 8.9, P < 0.05), such that spatial attention increased the peak moment of this response for the left-hand but not right-hand stimulus. The peak latency of the ECD moments did not significantly change with spatial attention or relevant modality. The inter-hemispheric difference of the peak latency showed the same results as the analysis of RSS. These results in the ECD analysis were consistent with the analysis of RSS with regard to spatial attention effects.
Discussion

The present study used MEG to examine modulation of the neural activity in SI and SII by within-modal and cross-modal spatial attention. We observed significant modulation of the response in SII by within-modal and cross-modal spatial attention, with amplitude enhanced with spatial attention, but no modulation of the response in SI. This enhancement was observed without changes in peak latency, the spatial distribution of responses, and ECD location. The most important finding of the present study is that MEG responses to tactile stimuli were enhanced by spatial attention irrespective of whether touch or vision was task-relevant.

Methodological considerations

In this study, we applied a classical selective attention task to examine cross-modal attentional modulation. This task has long been used to examine selective attention effects on the so-called EEG N1 response in a unimodal situation (Hillyard et al., 1973; Näätänen et al., 1978; see also review Hillyard et al., 1999; Näätänen, 1992). There are a number of advantages to this design. For example, (1) the difference in non-specific arousal level between to-be-attended and to-be-unattended stimuli can be removed by randomizing the interstimulus interval and the order of stimulus presentation, (2) the target effect or detection-related neural responses can be removed by presenting both target and non-target (standard) stimuli and then analyzing neural responses to non-target stimuli, and (3) the response can be recorded with a better signal-to-noise ratio because a relatively-short ISI is possible and then a larger number of stimuli can be presented in one experiment. This also helps to minimize fatigue and
head and body movements which are undesirable in an MEG recording. A recent EEG study applied this kind of experimental design to the examination of cross-modal links in spatial selective attention from vision to touch (Eimer and Driver, 2000), but failed to find such links. Using this task, we first demonstrated cross-modal links from vision to touch in spatial selective attention, indexed by neural responses in SII at a latency of 80 ms~.

Some previous studies investigating tactile-visual attention used a vibrotactile or tactile-pressure stimulus (Eimer and Driver, 2000; Eimer et al., 2000; 2001), while we used an electrical stimulus as in other studies (Desmedt and Robertson, 1977; García-Larrea et al., 1995; Mima et al., 1998; Kida et al., 2004a; b; c; 2006b), for the following reasons. (1) Responses can be more easily and reliably recorded for an electrical stimulation than for a natural tactile stimulation possibly because of a high signal-to-noise ratio for the former. (2) There are numerous long-accumulated findings about cortical responses to electrical stimulation in EEG and MEG studies.

The reason why single- and double-pulse stimuli were used was to better demonstrate spatial attention effects. Spatial attention experiments generally require the discrimination of a target stimulus embedded in a sequence of non-target (standard) stimuli. We considered that non-target and target stimuli must be presented at the same location to keep directing attention to that location. Thus, a single- and double-pulse stimulus was used as a target stimulus and non-target stimulus, respectively, because in this case, subjects must direct spatial attention to the first pulse of the double-pulse stimuli to detect it and inevitably direct attention to the single-pulse stimulus. Then, only MEG responses to tactile stimuli were analyzed to avoid the contamination of the target effect or detection-related activity which is not a pure selective attention effect.
We also used the equivalent stimulus onset asynchrony (SOA) from the first to the second pulse of the double-pulse stimulus between sensory modalities. The duration of electrocutaneous stimulation is commonly 0.1~0.5 ms, and a long duration is unusual (e.g. 100 ms). Therefore, we used different durations for visual and tactile stimuli. Since the performance of the counting task was almost the same between the detection of visual and tactile target stimuli, we do not consider that the use of different durations undermines the reliability of the present findings. A similar experimental design using single-pulse and double-pulse stimuli was also used by Eimer and Driver (2000).

In this study, since all the participants performed all the tasks (a within-subject experiment), one may imagine subjects forgetting which modality was task relevant during one block or being otherwise influenced by the previous block of trials. The good performance indicated by lower error rates in counting in all the conditions shows that subjects did not forget which modality was task relevant. In addition, we randomized the order of conditions and therefore can avoid the contribution of order effects.

*Within-modal spatial attention effect*

The M85c and M100i responses were enhanced in magnitude by spatial attention when touch was task-relevant, indicating a within-modal spatial attention effect. These responses were located in the upper wall of the sylvian fissure in bilateral hemispheres, respectively, corresponding to SII. This localization is consistent with previous MEG studies (Hari et al., 1993; Kakigi et al., 2000; Inui et al., 2003a; b; Wasaka et al., 2005; Nakata et al., 2005; Kida et al., 2006a; Akatsuka et al., 2006) and intracranial recordings in humans (Frot and Mauguière 2000). An enhancement of the
response by spatial attention was observed in both the RSS amplitude and ECD moment. The within-modal attentional enhancement in SII has been consistently observed in somatosensory attention studies using MEG (Mima et al., 1998; Hoechstetter et al., 1998; Fujiwara et al., 2000; Hamada et al., 2004), although these neglected the spatial aspect of attention. For instance, Mima et al. (1998), Hoechstetter et al. (1998), and Hamada et al. (2004) compared MEG responses to stimulation of the left median or digital nerve between active and passive attention tasks. Fujiwara et al. (2000) compared responses to median nerve stimulation between somatosensory attention (attend somatosensory) and auditory attention (ignore somatosensory) tasks. Thus, we first demonstrated that within-modal spatial attention enhances neural responses at a latency of 80 ms in human SII. The absence of attentional modulation in SI is consistent with the above-mentioned attention studies that did not manipulate the spatial aspect of attention (Mima et al., 1998; Hoechstetter et al., 1998; Fujiwara et al., 2000; Hamada et al., 2004). Animal studies also reported a higher sensitivity of neurons in SII than SI to attentional manipulation (Meftah et al., 2002; Chapman and Meftah, 2005).

Some EEG studies reported that the N120 (García-Larrea et al., 1995) or N140 response (Kida et al., 2004a) recorded over the temporal area, which was assumed to originate from SII (García-Larrea et al., 1995), was not modulated by spatial attention, inconsistent with the present study showing the enhancement of the SII response. MEG has the advantage of picking up synchronized neural activities in the wall of the sulcus or fissure such as SII, because theoretically it records magnetic fields produced by currents oriented tangentially to the surface of a spherical symmetric conductor (e.g., brain surface). In contrast, EEG records summated electric fields resulting from tangentially- and radially-oriented currents. This may explain the difference between
results obtained with MEG and EEG studies.

On the other hand, previous studies including ours have reported that the N140 recorded from fronto-central electrodes was enhanced in amplitude by spatial attention (Desmedt and Robertson, 1977; Michie et al., 1987; García-Larrea et al., 1995; Kida et al., 2004a), as opposed to the absence of attentional enhancement of temporal N120 or N140. Therefore, some of these studies assumed that the fronto-central N140 (a negative peak of the so-called vertex response) has a different function from the temporal N120 or N140 (García-Larrea et al., 1995; Kida et al., 2004a). We also found an attentional enhancement of the responses around this latency (M150c) especially for the left-hand stimulation, which were located around SII in most subjects. The activity of the estimated source was also enhanced by spatial attention. However, MEG studies reported that the activity in the anterior cingulate cortex or supplementary motor area (SMA) largely contributes to the fronto-central N140 (Allison et al., 1992; Waberski et al., 2002), and MEG studies also found activity in the SMA (Forss et al., 1996) and posterior parietal cortex (Forss et al., 1994; Hoshiyama et al., 1997) at this latency. Therefore, we can not conclude whether the enhancement of responses around the sylvian fissure at a latency of 150 ms~ corresponds to that of the fronto-central N140. The present MEG analysis focused on the activity in SI and SII, but the relationship between spatial attention and the temporal dynamics of activity in other areas should be investigated in future studies.

Cross-modal spatial attention effect

A similar enhancement by spatial attention was found even when vision was task-relevant, with an enhanced amplitude of the M85c and M100i responses in SII to
tactile stimuli presented near where attention was directed to visual stimuli, thereby demonstrating a cross-modal link from vision to touch. The M50c response was not significantly modulated by spatial attention. Thus, the cross-modal link in selective spatial attention from vision to touch is associated with somatosensory cortical processing at a latency of about 85 ms~ in SII. Eimer and colleagues have extensively studied cross-modal links in spatial attention using EEG (Eimer and Driver, 2000; Eimer et al., 2001; 2002). In their early study, Eimer and Driver (2000) used a similar selective attention task to that employed in the present study, and reported that there was no evidence of cross-modal links from vision to touch when touch was completely task-irrelevant (i.e., when vision was completely task-relevant), while cross-modal links were found when vision was primary and touch was of secondary relevance to the task. These results led them to conclude that their findings were consistent with a behavioral study by Spence et al. (2000), who applied Posner’s expectancy attention paradigm to the examination of cross-modal links (Spence et al., 1996). The behavioral study of visual-tactile cross-modal links by Spence et al. (2000) reported speeded and more accurate responses to both vibrotactile and visual target stimuli, when the target modality was not cued but the likely target side was cued prior to the target stimulus, compared to when the unlikely target side was cued or a neutral cue was presented. In their later studies using a cueing task different from the earlier one, Eimer et al. (2001; 2002) reported the existence of cross-modal links from vision to touch. We used MEG to find new cross-modal spatial attention effects even when touch was completely task-irrelevant in a selective attention task similar to the early study by Eimer and Driver (2000). In addition, the cross-modal spatial attention effect was observed at an earlier latency than reported in the EEG studies using a cueing task. As mentioned
above, MEG has an advantage over EEG in being able to record the activity in SII, which explains the difference between our results and Eimer’s results. The present study thus provides neurophysiological evidence of the involvement of neural activity at 80 ms~ in cross-modal links from vision to touch even when touch is completely task-irrelevant. In addition, we indicated the contribution of not SI but SII to the cross-modal links. The EEG studies mentioned above have excellently demonstrated temporal loci of cross-modal links, but the spatial loci were obscured due to inherent weaknesses such as the volume conduction of the electric field and the problem caused by the reference electrode.

The theoretical attentional system for the organization of endogenous spatial attention can be explained in three ways. First, there may be quite separate modality-specific systems that operate independently of their respective representations of visual and tactile (and auditory) space. Second, there may be a single supramodal attentional system that allocates attention to locations in space regardless of the modality of the target being attended, modulating perception, and neural activity as a function of location across sensory modalities. Third, there is indeed a separable modality-specific attentional system, but with links such that visual spatial attention tends to result in tactile attention to the corresponding location in tactile space, and vice versa (Spence and Driver, 1996; Driver and Spence, 2004). Since we found cross-modal attentional modulation, the quite separate modality-specific system is not suitable to the cross-modal attentional modulation. If there is a supramodal attentional system, the size of the spatial attention effect should be the same between tactile-evoked and visual-evoked responses (or between tactile and visual judgements). The present study did not analyze neural responses to visual stimuli, and therefore can not directly
approach this mechanism. Previous studies have suggested behavioral or neurophysiological evidence of a separable-but-linked system (Spence and Driver, 1996; Chambers et al., 2004) and a supramodal system (Eimer and van Velzen, 2002).

One more general important point regarding cross-modal links is whether the observed effects of attention regardless of whether vision or touch was relevant truly demonstrate the existence of meaningful cross-modal links in the behavioral context. Since we recorded neural responses in either situation where touch was completely relevant or irrelevant, it is unclear whether the observed cross-modal modulation is truly essential for human behavior or is an inevitable by-product of the within-modal attention effects. However, the possible behavioral interpretations for the present study are (1) that attention in the secondary modality always and inevitably shifts to the same direction as in the primary modality (i.e., the cross-modal effect is an inevitable and non-meaningful phenomenon), (2) that attention shifts in the same fashion as (1), but it might just be that the subject can’t be bothered in some sense to shift one but not the other (i.e., this can be said to be an effective behavioral strategy), (3) that attention in the secondary modality shifts in the same direction as in the primary modality when attention is not needed in the secondary modality, but can also shift in a different direction from the primary modality when attention is needed for the secondary modality at a different location from the primary modality (i.e., the cross-modal effect can be flexibly changed depending on the behavioral significance). Spence and Driver (2000, Experiment 4) reported that when participants had a very strong spatial expectancy regarding the likely target location in just one modality (the most common primary modality), then their covert spatial attention tended to shift there not only in that modality, but also in the other (secondary) modality. Thus, Spence and colleagues
argued that the only way to show the obligatory nature of such links was to make it disadvantageous for attention in the secondary modality to shift in the same direction as attention in the primary modality (Spence and Driver, 1996; Spence et al., 1996; Lloyd et al., 2003). Therefore, the next step for unveiling the neural system underlying cross-modal links is to examine changes in cross-modal attentional modulation as a function of the priority of modality and the degree of directional expectancy in a cueing task (e.g., in certain kinds of dual-task situations or with the manipulation of the likely target side in just one modality). On the other hand, the ability to record neural responses to sensory stimuli in the completely task-irrelevant modality is a feature specific to neuroimaging studies which can not be achieved by behavioral studies requiring a subject’s behavioral response or report, and thereby the novelty of the present study is evident.

Possible mechanisms for attentional modulation

In early EEG studies, the enhancement of a response by attention without changes in its spatial distribution and waveform had been considered the enhancement of an exogenous component of ERPs (Hillyard et al., 1973; Hillyard and Mangun, 1987). Later, this was called a gain regulation mechanism (Hillyard et al., 1999). Several previous studies also have suggested that attention can modulate the gain of neural responses to visual stimuli (Moran and Desimone, 1985; Reynolds et al., 2000, Corbetta et al., 1990; 1991; Martinez et al., 1999; Hawkins et al., 1990; Luck et al., 1997). This concept seems to be based on the idea that the same neuronal population as that synchronously activated by unattended stimuli is facilitated by a top-down attentional signal. The present study revealed an attentional enhancement of evoked magnetic
responses in SII without changes in the magnetic field distribution, waveform, and ECD location of the responses. In addition, the response for attended stimuli was likely to have the same phasic waveform as that for unattended stimuli. The combination of these results favors the classical gain regulation mechanism that the neuronal population activated by unattended stimuli was more strongly activated by attended stimuli, rather than either a tonic bias effect as indexed by a sustained baseline increase in activity during directing attention (Luck et al., 1997; Kastner et al., 1999) or the attention-induced activation of a separate neuronal population (Näätänen et al., 1978). Therefore, the present findings extend this gain regulation mechanism to cross-modal spatial selective attention. Such a gain regulation mechanism would presumably give an improved signal-to-noise ratio to inputs from attended locations, so that more information can be extracted from relevant portions of the extra- or intra-personal space (Hawkins et al., 1990; Hillyard et al., 1999).

However, considering the original meaning of ‘gain’ which represents an input-output relationship, the present findings are not enough to demonstrate a gain regulation mechanism. According to simple mathematical expressions, gain regulation and baseline shifts are defined as multiplicative and additive attentional effects, respectively (Kanwisher and Wojciulik, 2000). In the case of multiplicative gain regulation, the magnitude of a response to a given stimulus when attended “A” should equal the product of an attentional gain multiplier “g” and the magnitude of the response to the same stimulus when unattended “U” (U*g=A). In the case of additive baseline shifts, the magnitude of the response to a given stimulus when attended “A” should be higher by a constant “K” than the magnitude of the response to the same stimulus when unattended (U) (U+K=A). According to this hypothesis, the gain regulation mechanism
produces a stronger attentional enhancement when the strength of a given stimulus is higher. On this point, the classical definition of the gain regulation mechanism seems to be vague. To better demonstrate the gain regulation hypothesis, it is useful to examine how MEG responses vary as a function of stimulus strength and the direction of attention.

EEG can record activity deep in the brain, whereas MEG is less sensitive to deep activity. Accordingly, the attentional modulation we observed may be regarded as a cortical phenomenon. Of course, the present study did not completely exclude the possibility that the neural systems underlying cross-modal spatial attention activate a separate neuronal population related to other processes which may be blind to MEG (e.g., area 1 or 2, or deep brain tissue) and the possibility of tonic bias effects. In fact, some EEG studies have demonstrated the co-existence of the gain regulation mechanism and the attention-induced activation of a separate neuronal population (Teder et al., 1993; Johannes et al., 1995). Somatosensory EEG studies have also found both the former (Josiassen et al., 1982) and latter effects (Michie et al., 1987; Garcia-Larrea et al., 1995; Valeriani et al., 2003; Kida et al., 2004a). PET (Rees et al., 1997) and single-neuron (Luck et al., 1997) studies have also reported both a baseline increase in activity and gain regulation. Possibly, there are multiple mechanisms underlying attentional modulation of neural and behavioral responses, although this was not directly tested in the present study.

A recent study using a cross-modal temporal order judgment task indicated that the peak latency of the visual evoked potentials (P1 and N1) was earlier when attention was directed to vision than when it was directed to touch, providing electrophysiological support for the existence of prior entry (Vibell et al., 2007). We
could not find differences in the latency of the tactile-evoked responses in terms of attention and modality relevance.

With regard to the somatosensory cortical hierarchy, SII forms a ventral stream (Pons et al., 1992; Krubitzer et al., 1995), which projects to the premotor (Cavada and Goldman-Rakic, 1989; Rizzolatti and Luppino, 2001) and prefrontal cortices (Carmichael and Price, 1995), and may be associated with the fine discrimination of somatosensory inputs (Romo et al., 2002; Binkofski et al., 1999). This functional notion about SII seems to be well consistent with the above-mentioned function of the gain regulation mechanism. Top-down attentional signals to enhance sensory-evoked neuronal responses may come from frontal and parietal areas (Kanwisher and Wojciulik, 2000; Corbetta and Shulman, 2002; Fuggetta et al., 2006), especially from multimodal areas activated during the performance of attention tasks (Macaluso et al., 2001; Macaluso et al., 2003). Considering the attentional hierarchy, a similar but different possible physiological idea is a feedback mechanism from higher- to lower-order areas, which is accompanied by reducing stimulus-evoked refractoriness or inhibition in cortical ensembles, as recently suggested based on monkey studies in the visual system (Mehta et al., 2000a; 2000b; Schroeder et al., 2001). This hypothesis seems interesting and plausible, in that it may integrate findings of human and monkey studies at several levels of physiology, and it is therefore essential to experimentally examine in detail whether this hypothesis can be applied to the response modulation by within-modal or cross-modal spatial attention in humans.
Conclusions

The present study used MEG to reveal the time course of neural responses related to visual-tactile cross-modal links in spatial selective attention, focusing on somatosensory cortical activities. The high temporal and spatial resolution analysis for the attentional modulation revealed that the cross-modal link is represented by cortical processes around SII at the latency of 80 ms~. The mechanism underlying this cross-modal attentional modulation remains to be determined, but it is speculated that there may be an increase in gain and/or other mechanisms.
Acknowledgements

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Table 1. Peak moment (nAm) of ECD and the results of a three-factor ANOVA. Values in parentheses show standard error.

<table>
<thead>
<tr>
<th>Stimulus side</th>
<th>Left hand</th>
<th></th>
<th>Right hand</th>
<th></th>
<th>ANOVA</th>
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<td></td>
<td>Touch</td>
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<td>Touch</td>
<td>Vision</td>
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<td>Relevant modality</td>
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<td>ATT</td>
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<td>SI M50c</td>
<td>14.6 (1.9)</td>
<td>15.1 (1.8)</td>
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<td>16.2 (2.0)</td>
<td>14.8 (1.9)</td>
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<td>SII M85c</td>
<td>55.2 (10.0)</td>
<td>28.4 (4.4)</td>
<td>41.4 (10.2)</td>
<td>27.0 (6.2)</td>
<td>57.9 (12.0)</td>
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<td>SII M100i</td>
<td>48.3 (6.1)</td>
<td>22.0 (3.5)</td>
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<td>18.0 (3.8)</td>
<td>37.2 (8.6)</td>
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<td>SII M150c</td>
<td>-44.5 (6.7)</td>
<td>-19.5 (2.7)</td>
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<td>-20.5 (5.5)</td>
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<td>SII M150i</td>
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<td>-33.7 (6.2)</td>
<td>-21.0 (2.7)</td>
<td>-31.5 (6.2)</td>
</tr>
</tbody>
</table>

Results of the three-factor ANOVA

ATT: Attended; UATT: Unattended

A: Main effect of spatial attention (attended vs. unattended); AS: Interaction between spatial attention and stimulus side; n.s.: not significant; *: P<0.05; **: P<0.01.
Figure Legends

Figure 1. Schematic illustration of the stimuli used in this study. (A) Stimulus alignment. (B) Section of the optic fiber used to present the visual stimulus. (C) Stimulus sequence. A vertical line shows a single-pulse stimulus, and a pair of vertical lines, a double-pulse stimulus. Electrocutaneous and visual stimuli were presented with equal probability and in a random order on the left or right side (hand or visual field). The double-pulse stimulus was infrequently presented in a sequence of single-pulse stimuli. The interstimulus interval varied randomly between 800 and 1,200 ms.

Figure 2. Analysis used in this study. Data were obtained from a representative subject. (A) Waveforms of magnetic fields recorded from orthogonal planar-type gradiometers in response to the electrocutaneous single-pulse stimulus (frequent standard stimulus) presented to the second digit of the left hand. (B) Three-dimensional iso-contour maps of magnetic fields recorded from the gradiometers. Areas surrounded with red and blue contour lines show the outflux and influx of magnetic fields, respectively. (C) Waveforms of RSS (root sum square). This was obtained by squaring each of the magnetic signals recorded from two gradiometers at a sensor’s location, summing the squared signal together, and then calculating the square root of the sum. (D) Two-dimensional iso-contour maps of RSS signals at several time points. Dotted circles represent target activation at the latency. We used the RSS waveform and iso-contour map to look for the peak sensor which showed the greatest amplitude for each response, and then measured the peak amplitude and latency at this peak sensor. Small white circles represent peak channels for SI and bilateral SII. The ECD for each response was
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**Figure 3.** Waveforms of RSS signals at the peak sensor showing the greatest amplitude
for each response. Vertical lines (zero) indicate the onset of the electrocutaneous
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**Figure 4.** The left panel shows the peak amplitude of RSS signals (error bars show
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**Figure 5.** Results of the ECD analysis. The left panel indicates the analysis of the response to the left hand stimulus (LHS), and the right panel, that to the right hand stimulus (RHS). (A) Location of ECDs superimposed on a three-dimensional MRI scan in one subject. (B) Location of ECDs superimposed on a two-dimensional MRI scan in another subject. ECDs were estimated to be located in the posterior bank of the central sulcus, corresponding to SI, and bilaterally in the upper bank of the sylvian fissure in the left and right hemisphere, corresponding to bilateral SII. (C) Time course of the
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