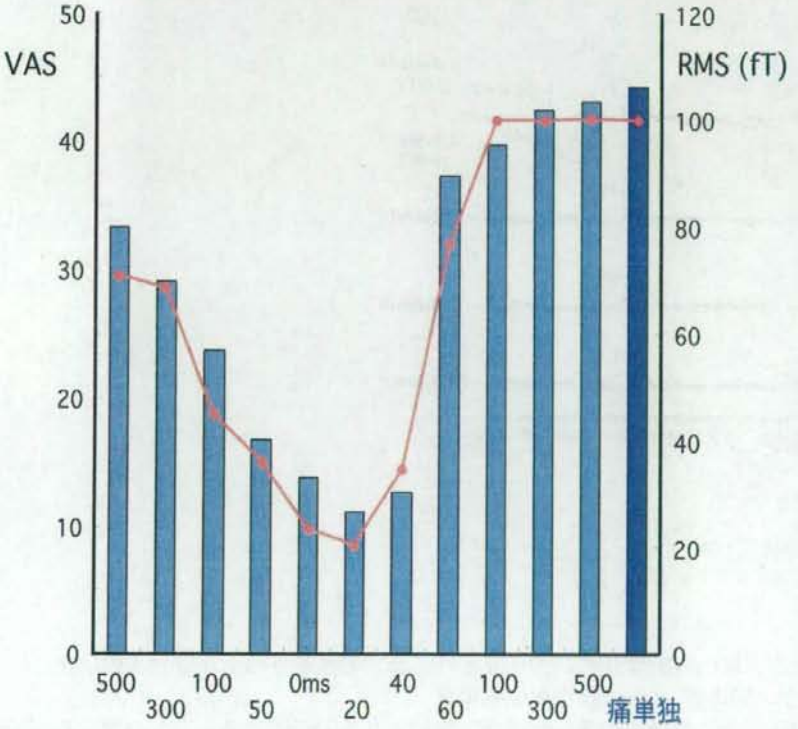
触覚刺激による痛覚抑制は皮質レベルで生じる

Inui K, Tsuji T, Kakigi R: Temporal analysis of cortical mechanisms for pain relief by tactile stimuli in humans. Cerebral Cortex. 16(3): 355-365, 2006.

痛む部位に触覚刺激を加えると疼痛が軽減することはよく知られており、実験的にも確認されている。しかしながらその機序は明らかにされていない。MelzackとWall（1965）による関門制御説の提唱以来、多くの研究がこの抑制の責任部位を脊髄と考えそのメカニズムを検討してきたが、抑制が皮質レベルで生じる可能性についてはほとんど検討されてこなかった。

９名の健康成人男性の背中（第９胸椎の高さ）に、痛覚刺激（ES、表皮内電気刺激法）と触覚刺激（TS、皮膚表面電気刺激）を種々のタイミングで与え、大脳皮質の応答を脳磁図を用いて記録した。TSからESまでのconditioning-test interval（CTI）は11条件で、それぞれ-500、-300、-100、-60、-40、-20、0、50、100、300、500ミリ秒である。これにES及びTS単独呈示のコントロール条件を加え、計13条件の記録を行った。

痛みの程度（VASスコア）は、CTI - 20msの条件で最も低かった。脳磁図では、ESにより刺激後150ミリ秒付近を頂点とする明瞭な磁場成分が全例で記録され、信号源解析の結果は第一次体性感覚野と第二次体性感覚野が主な活動源であることを示した。ペア刺激の際のESに対する皮質応答は、先行するTSにより顕著に抑制されたが、遅れて皮質に到達する触覚信号（CTI -40, -60, -100 ms）によっても明瞭に中断された。この結果は、この抑制が皮質レベルで生じたことを示す。抑制の程度は、TSの信号がESの信号よりも脊髄に先に到達するか遅れて到達するかに影響を受けず、脊髄の関与は小さいか、なかったものと考えられる。



各条件における脳磁場反応の大きさ（棒グラフ、値はRMSで示す）と自覚的痛覚強度（折れ線グラフ、値はVASで示す）いずれも、痛覚が触覚よりも20ミリ秒ないしは40ミリ秒早く刺激される条件で最も小さい。この条件では、脊髄には痛覚が大脳皮質には触覚が先に到達する。

別紙４

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Centrifugal modulation of human LEP components to a task-relevant noxious stimulation triggering voluntary movement

Hiroki Nakata [a,b,c,*], Kiwako Sakamoto [a,d], Yukiko Honda [a], Hideki Mochizuki [a], Minoru Hoshiyama [a,b], Ryusuke Kakigi [a,d]

[a] Department of Integrative Physiology, National Institute for Physiological Sciences, Myodaiji, Okazaki, 444-8585, Japan
[b] School of Health Sciences, Nagoya University, Nagoya, Japan
[c] Japan Society for the Promotion of Science, Tokyo, Japan
[d] Department of Physiological Sciences, School of Life Sciences, The Graduate University for Advanced Studies, Hayama, Kanagawa, Japan

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ABSTRACT

In the present study, we investigate the top-down centrifugal modulation of neural responses to a task-relevant noxious stimulation triggering voluntary movement by recording magnetoencephalography (MEG) and electroencephalography (EEG) simultaneously. An auditory warning signal was followed 2–3 s later by a noxious YAG laser stimulation as an imperative signal delivered to the left hand dorsum. Ten normal subjects performed three different conditions, Control, Movement, and Count. In Control, the subjects were asked to relax and rest quietly with no task. In Movement, the subjects extended the left index finger after imperative stimuli. In Count, the subjects counted the number of imperative stimuli silently. The amplitude of the N2 component recorded by EEG, which peaked about 220 ms after noxious stimulation, was significantly attenuated in Movement, but not in Count, compared to Control. The root-mean-square (RMS) from both hemispheres, and areal mean signal (AMS) amplitudes and the equivalent current dipole (ECD) strengths from SI/PPC and bilateral SII recorded at around 170 ms by MEG were not significantly different among the three conditions. In contrast, ECD strengths and AMS amplitudes from the anterior cingulate cortex (ACC), which showed a similar peak to the N2 component, were smaller in Movement than Control and Count. We therefore suspect that neural activities related to generator mechanisms of N2, especially including ACC, are inhibited by movement-related neural activities during the preparatory period. The present findings indicate a characteristic of pain–motor integration in a movement preparatory period.

Introduction

Many studies have investigated somatosensory–motor integration by recording somatosensory evoked potentials (SEPs) during voluntary movement. Characteristically, the amplitudes of short-latency components are attenuated, while those of long-latency are enhanced (Giblin, 1964; Kakigi, 1986; Hoshiyama and Sheean, 1998; Rossini et al., 1999; Valeriani et al., 2001; Nakata et al., 2003), and this phenomenon is termed 'gating'. The modulation of neural responses during movement is mainly the result of two major mechanisms (Jones et al., 1989; Wasaka et al., 2005a; Kida et al., 2006a). The first mechanism is centrifugal, whereby signals from neurons involved in producing movement modulate ascending somatosensory signals at cortical or subcortical levels. The second mechanism is centripetal, whereby ascending somatosensory signals generated by voluntary movement modulate ascending signals eliciting the SEPs. In addition, since such modulation also has been found in the preparatory period of voluntary movement (Starr and Cohen, 1985; Staines et al., 1997; Shimazu et al., 1999; Murase et al., 2000; Asanuma et al., 2003; Kida et al., 2004, 2006a,b; Wasaka et al., 2005a,b, 2006), the centrifugal mechanism is closely related to the gating effects (Nakata et al., 2003).

This gating effect has been also researched by recording somatosensory evoked magnetic fields (SEFs) using magnetoencephalography (MEG), and similar results were found regarding the cortical responses. That is, the early responses generated from primary somatosensory cortex (SI) were attenuated during voluntary movement, whereas the late responses in the secondary somatosensory cortex (SII) were strengthened (Rossini et al., 1989; Kakigi et al., 1995a, 1997; Huttunen et al., 1996; Forss and Jousmäki, 1998; Lin et al., 2000). Such modulation also occurred before voluntary movement (Wasaka et al., 2003, 2005c; Kida et al., 2006c).

Studies using SEPs and SEFs have focused on the somatosensory–motor integration following the tactile stimulation of ascending Aβ fibers during voluntary movement. However, there are some studies investigating the pain–motor integration following the noxious

* Corresponding author. Fax: +81 564 52 7913.
E-mail address: nakata@nips.ac.jp (H. Nakata).

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stimulation of ascending Aδ fibers. Kakigi and colleagues reported that the amplitudes of laser-evoked potentials (LEPs) elicited by noxious CO_2 laser stimulation were attenuated during voluntary movement at vertex electrodes, indicating the opposite results to the modulation of late-components of SEPs (Kakigi and Shibasaki, 1992; Kakigi et al., 1993). In addition, our previous study using laser-evoked magnetic fields (LEFs) showed that voluntary movement attenuated neural activities of SI and SII evoked by noxious stimulation (Nakata et al., 2004), which was also the opposite to the above-mentioned studies. These results indicate that the characteristic of pain–motor integration ascending Aδ fibers is different from that of somatosensory–motor integration ascending Aβ fibers. However, the mechanisms for pain–motor integration are still unknown because of the small number of studies, compared to those on somatosensory–motor integration. In a recent study, Le Pera et al. in Italy reported that the amplitudes of LEPs elicited by CO_2 laser stimulation at vertex electrodes were attenuated in the time interval between a visual warning stimulus followed after 1 s by an imperative stimulus (S1–S2 paradigms) (Le Pera et al., 2007). In their experiment, the attenuation was found even if the subjects counted the number of imperative stimuli in the paradigm instead of motor tasks, and a noxious stimulus to evoke the LEPs was irrelevant to the subject's movement task. Thus, their data might include not only movement-related activity but also effects of cognition and attention, on the attenuation of LEPs.

In the current study, to clarify the centrifugal mechanisms of pain–motor integration before voluntary movement, we recorded the MEG and EEG responses simultaneously to noxious stimulation used as a task-relevant imperative signal to trigger voluntary movement in a forewarned reaction time paradigm. Several studies have attempted to clarify the centrifugal modulation of task-relevant tactile inputs, utilizing a forewarned reaction time paradigm where the tactile stimulation used to elicit the SEPs/SEFs was also used as an imperative signal (Shimazu et al., 1999; Murase et al., 2000; Asanuma et al., 2003; Kida et al., 2004, 2006a,b,c). The application of this paradigm allows one to examine how neural activities just before the task-relevant signal modulate neural responses to that signal. We hypothesized that the neural responses on LEPs and/or LEFs are modulated when noxious stimulation triggers a voluntary movement in a forewarned reaction time paradigm.

Materials and methods

Participants

Ten normal right-handed males (mean age 31.7 years, range 25–44 years) participated in this study. The subjects did not have a history of any neurological or psychiatric disorders. Informed consent was obtained from all participants. The study was approved by the Ethical Committee of the National Institute for Physiological Sciences, Okazaki, Japan.

Experimental paradigm

The subjects performed a warning stimulus (S1)–imperative stimulus (S2) paradigm. A pair of S1 and S2 stimuli was given to the subjects at an interval of 2–3 s The S1–S1 interval was 10 s to avoid habituation of evoked pain-related cortical responses (Raij et al., 2003). S1 was an auditory pure tone (60 dB SPL, 50 ms duration), presented through a speaker. For S2, a thulium:YAG laser beam (Neurolaser, BAASEL Lasertech, Germany) was applied to the dorsum of the left hand as noxious stimulation. The wavelength was 2000 nm, pulse duration was 1 ms, and spot diameter was 6 mm. To determine the intensity of painful stimulation, we used a visual analogue scale (VAS), in which 0 represented 'not painful' and 10 represented 'an intensity which subjects could not tolerate'. Subjects were asked to rate the intensity of the perceived pain, and a stimulus intensity of VAS 8 was used in each subject for the recording. In addition, subjects were requested to orally provide one adjective from a list of seven descriptors: 'not perceived', 'light touch', 'touch', 'tingling', 'warm', 'pricking', and 'burning'. All subjects reported 'pricking' for the intensity of VAS 8. This method for assessing quality of perception followed some previous studies (Opsommer et al., 2001; Mouraux and Plaghki, 2007). There were two reasons why we selected an intensity of VAS 8. First, because a strong stimulus would evoke clear and large cortical responses (Timmermann et al., 2001), we wanted to select the strongest intensity for each subject. Second, if the stimulus intensity was more than VAS 8, it was expected that subjects could not tolerate all painful stimuli during recordings. The mean intensity across all subjects was 194 mJ. Since the laser stimulator caused large magnetic artifacts, it was set outside of the shielded room, and the laser beam was conducted through optical fibers, approximately 6.5 m in length, into the shielded room. In order to maintain the distance between the laser outlet and the skin surface, a cable of optical fiber was attached to the MEG device, but the irradiated points were slightly moved by the experimenter for each stimulus to avoid tissue damage and habituation of the receptors (Kakigi et al., 1995b). 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. The subjects were wearing earplugs to avoid hearing sounds from the stimulator, and non-magnetic goggles for safety.

The recordings were conducted in three conditions. Condition 1 was the resting control (Control). The subjects were asked to relax and rest quietly with no task. In condition 2 (Movement), the subjects extended the left index finger as quickly as possible, when the S2 noxious stimuli were presented. In condition 3 (Count), the subjects were asked to count the number of S2 stimuli silently. To avoid the effect of habituation, only 5 stimuli were applied in one session. Each session consisted of one of three conditions, and the order of these three conditions was random. Ten sessions were conducted for each condition, and consequently 50 stimuli in total for each condition were applied.

EEG recordings and analysis

EEGs were recorded with Ag/AgCl disk electrodes placed on the scalp at Fz, Cz, Pz, C3, and C4, according to the International 10–20 System (Jasper, 1958). Each scalp electrode was referenced to linked earlobes. To eliminate eye movements or blinks exceeding 150 μV, an electrooculogram (EOG) was recorded bipolarly with a pair of electrodes placed 2 cm lateral to the lateral canthus of the left eye and 2 cm above the upper edge of the left orbit. The impedance was maintained at less than 5 k ohm. All of the EEG signals were collected in a signal processor (Neurofax EEG1100, Nihon-Kohden, Tokyo, Japan). The analysis epoch for ERPs was 800 ms including a prestimulus baseline period of 100 ms. The bandpass filter was set at 0.1–100 Hz and the sampling rate was 995 Hz. The peak amplitudes and latencies of N2 and P2 were measured at 170–250 ms, 280–380 ms, respectively. The amplitudes were measured baseline-to-peak. In addition, to clarify the difference in amplitude between N2 and P2, we calculated the N2–P2 component with a peak-to-peak measurement. No digital filter was applied off-line, and all ERP analyses were based on unfiltered data.

For the analysis of each component, the data on peak amplitude and latency was submitted to analyses of variance (ANOVAs) with repeated measures using as within-subject factors, Condition (Control, Movement, and Count), and Electrode (Fz, Cz, Pz, C3 and C4). For all repeated measures factors with more than two levels, it was tested whether Mauchly's sphericity assumption was violated. If the result of Mauchly's test was significant and the assumption of sphericity was violated, the Greenhouse–Geisser adjustment was used to correct for the sphericity altering the degrees of freedom using a correction

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coefficient epsilon. Normalization to assess topographical differences was not applied (Urbach and Kutas, 2002). When significant effects were identified, the Tukey HSD post hoc multiple-comparison was adjusted to identify the specific differences among conditions. Statistical significance was set at $p<0.05$.

MEG recordings and analysis

LEFs 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. In the present study, we analyzed MEG signals from 204-channel planar-type gradiometers, because the data on magnetometers were usually susceptive to global magnetic noises such as changes in geomagnetic field (Hämäläinen et al., 1993) (these noises can be successfully cancelled out in recording with planar sensors). These planar-type sensors can detect the signals just above local cerebral sources (Nishitani and Hari, 2002, Noguchi and Kakigi, 2005). The signals were recorded with a bandpass of 0.1–200 Hz and digitized at 995 Hz, rejecting noise, blinks, and eye movements from the analysis automatically. The analysis period of 800 ms included a prestimulus baseline of 100 ms. The signals recorded from the 204 gradiometers were used for source localization. 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 T MRI system (Allegra scanner, Siemens, Erlangen, Germany). A three-dimensional structural brain image of each subject was obtained using an MP-RAGE sequence with the following parameters: TR=2500 ms, TE=4.38 ms, FA=8°, FOV=230 mm, matrix size=256×256 mm, voxel dimension=0.9×0.9×1.0 mm. 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 (Nakata et al., 2004; Noguchi et al., 2004).

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 achieved by squaring MEG signals of gradiometer pairs, summing these signals together, and then recalculating the square root of this sum, following our previous studies (Kida et al., 2006c, 2007; Nakata et al., 2008). The calculation was carried out for all 102 sensors' locations to make an isocontour map of amplitude. Then, we calculated root-mean-square (RMS), in the set of sensors in each hemisphere (96 sensors) to compare the global field power among the three conditions (Hoshiyama et al., 2007). In addition, we analyzed the areal mean signals (AMS) of four gradiometer pairs that showed the largest response to measure amplitude and latency in the regions of interest. Finally, we calculated group averages across subjects. This method of data analysis followed previous studies using the same MEG system as the present study (Tarkiainen et al., 2003; Nakata et al., 2005, 2008; Bonte et al., 2006; Akatsuka et al., 2007a,b).

To identify the sources of the evoked activities, the equivalent current dipole (ECD), which best explains the measured data, was computed by using a least-squares search. Before estimating the ECDs, we examined the magnetic field pattern in 2-ms steps visually to identify all local and stable dipole field patterns. This procedure provided an initial estimate of the number of sources activated during the analysis period (Forss et al., 1999; Avikainen et al., 2002). Then, to select the ECD source, we first identified 3–4 channels, which detected large responses around the central sulcus and the Sylvian fissure (Nguyen et al., 2004; Nakata et al., 2005; Wasaka et al., 2005c, 2007; Kida et al., 2006c, 2007), and selected 16–18 channels around those channels with the large responses. A subset was employed for the estimation of ECDs. This number of channels has been used to cover around the signal maxima channels over somatosensory cortices, following previous studies using the same Neuromag system (Forss et al., 1996, 1999; Lin et al., 2000; Avikainen et al., 2002; Raij et al., 2003; Nguyen et al., 2004; Möttönen et al., 2005; Nakata et al., 2005, 2008; Wasaka et al., 2005c, 2007; Nevalainen et al., 2006; Sakamoto et al., 2008a,b). 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 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 85% of the field variance at selected periods of time were used for further analysis. The analysis period was extended to the entire time 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. If signals from any brain regions were insufficiently explained by the model, we re-analyzed the data to estimate more precise regions. The data acquisition and analysis followed Hämäläinen et al. (1993). In addition, the source location was transformed into the Talairach standard brain source (Talairach and Tournoux, 1988), following previous studies (Nishitani et al., 1999; Ploner et al., 2000; Nakata et al., 2005).

For the analysis of RMS from both hemispheres, the data on peak amplitude and latency was submitted to analyses of variance (ANOVAs) with repeated measures using as within-subject factors, Condition (Control, Movement, and Count), and Hemisphere (Left and Right). Data for the peak amplitude and latency of AMS were also submitted to two-way repeated measure ANOVA with Condition and Area. In addition, after confirmation of the dipole moments among the three different conditions, the dipole strengths and peak latencies were submitted to a two-way repeated measure ANOVA with Condition and Source of the dipole. For all repeated measures factors with more than two levels, it was tested whether Mauchly's sphericity assumption was violated. If the result of Mauchly's test was significant and the assumption of sphericity was violated, the Greenhouse–Geisser adjustment was used to correct for the sphericity altering the degrees of freedom using a correction coefficient epsilon. In addition, Tukey HSD post hoc multiple-comparison tests were adjusted for differences of the dipole strengths and peak latencies. Statistical significance was set at $p<0.05$.

Supplementary experiment

To clarify the effect of centrifugal modulation in detail, we performed a supplementary study. We recorded LEPs from eight subjects following noxious stimulation of the left hand dorsum, and three conditions were used. Condition 1 was Control. In condition 2 (Right Hand), the subjects extended the right index finger as quickly as possible after the S2 noxious stimuli. In condition 3 (Left Foot), the subjects were asked to perform ankle dorsiflexion of the left foot. Six sessions were conducted for each condition, and consequently 30 stimuli for each condition were applied. EEGs were recorded at Fz, Cz, Pz, C3, and C4, and all EEG signals were collected on a signal processor (Neuropack MEB-2200 system, Nihon-Kohden, Tokyo, Japan). The analysis epoch was 1000 ms, including a prestimulus baseline period of 100 ms, the bandpass filter was set at 0.1–50 Hz, and the sampling rate was 1000 Hz. To judge whether subjects responded to noxious S2

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stimuli precisely, an electromyogram (EMG) was also recorded from a pair of electrodes about 3 cm apart on the skin overlying the contraction muscle in the right forearm (Condition 2) and left anterior tibial muscle (Condition 3). The procedure for data analysis was the same as the main experiment.

Results

Behavioral and EEG data

The mean reaction time (RT) in Movement was 472 ms (standard error: SE 39 ms).

Fig. 1 displays the grand-averaged LEP waveforms in each condition across all subjects. Clear N2 and P2 components were recorded in all conditions after noxious stimulation. Judging from the morphology, the peak amplitude of N2 was smaller in Movement than Control and Count. This notion was supported by results of ANOVAs.

The ANOVAs for the amplitude of N2 revealed a significant main effect of Condition ($F(2, 18)=6.092$, $p<0.01$). The Tukey HSD post hoc test indicated that the amplitudes were significantly smaller in Movement than Control at Cz, Pz, C3 and C4 ($p<0.05$, $p<0.01$, $p<0.01$, and $p<0.01$, respectively) (Fig. 2A). These results suggest that voluntary movement in a preparatory period reduces the peak amplitude of the N2 component. There was also a significant main effect of Electrode ($F(4, 36)=9.030$, $p<0.01$, $\varepsilon=0.542$), and post hoc testing with collapsing Condition revealed that the amplitude of Cz was significantly larger than that of Fz, Pz, C3, and C4 ($p<0.05$, $p<0.001$, $p<0.01$, and $p<0.01$, respectively).

With regard to the peak amplitude of P2, there was a significant effect of Condition–Electrode interaction ($F(8, 72)=4.056$, $p<0.05$, $\varepsilon=0.410$), and a main effect of Electrode ($F(4, 36)=17.271$, $p<0.001$, $\varepsilon=0.483$). A post hoc test with collapsing Condition indicated that the amplitude of Cz was significantly larger than that of Fz, C3, and C4 ($p<0.001$, respectively), and the amplitude of Pz was also significantly larger than that of Fz, C3, and C4 ($p<0.001$, $p<0.01$, and $p<0.01$, respectively). In Fig. 2B, the post hoc test did not reach the significant level for differences between conditions per electrode, although the average value was smaller in Movement than Control at Cz ($p>0.05$).

The ANOVAs for the peak-to-peak amplitude of N2–P2 confirmed a significant effect of Condition–Electrode interaction ($F(8, 72)=3.704$, $p<0.05$, $\varepsilon=0.574$), and main effects of Condition ($F(2, 18)=3.818$,

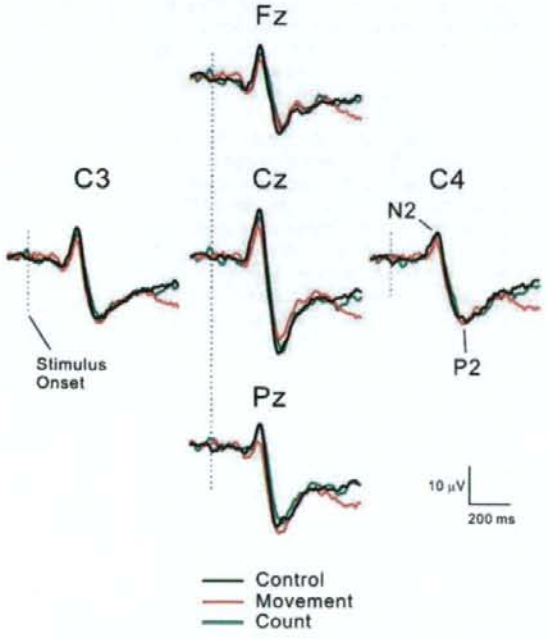

Fig. 1. Grand-averaged laser-evoked potentials (LEPs) in each condition following noxious YAG laser stimulation applied to the dorsum of the left hand. Clear N2 and P2 components were recorded in all conditions. Black, red, and green lines indicate waveforms of Control, Movement, and Count, respectively. The vertical line indicates the stimulus onset.

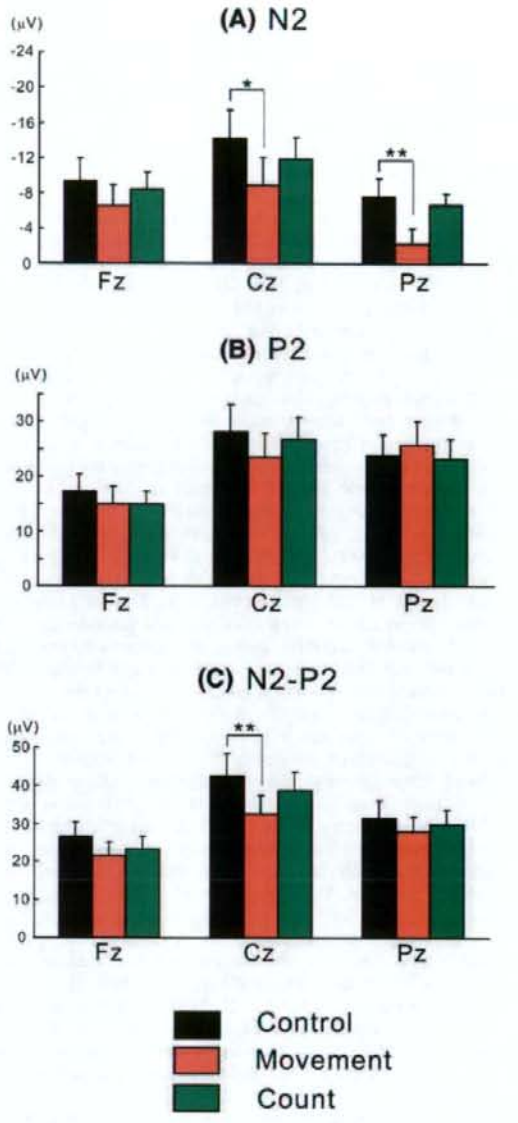

Fig. 2. Mean values of N2, P2, and N2–P2 amplitudes at the midline electrode, Fz, Cz, and Pz. A post hoc test indicated that the N2 amplitude at Cz and Pz was significantly smaller in Movement than Control ($p<0.05$, and $p<0.01$, respectively). The peak-to-peak amplitude of N2–P2 at Cz was significantly smaller in Movement than Control ($p<0.01$). Vertical lines indicate standard errors (S.E.). *$p<0.05$, **$p<0.01$.

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Table 1
Mean peak latency of N2 and P2 components for each condition with S.E.

	Fz	Cz	Pz	C3	C4
N2					
Control	222.7 (4.9)	211.9 (6.0)	217.7 (7.3)	220.6 (3.9)	211.6 (6.8)
Movement	229.2 (4.9)	218.1 (6.0)	216.4 (7.3)	220.0 (3.9)	212.3 (6.8)
Count	230.9 (6.2)	220.4 (4.1)	224.1 (4.4)	227.3 (4.0)	222.9 (4.5)
P2					
Control	313.4 (6.3)	312.1 (5.4)	312.6 (6.3)	311.2 (7.4)	326.9 (9.2)
Movement	313.6 (7.5)	313.5 (4.1)	314.2 (6.3)	313.9 (5.6)	322.2 (9.9)
Count	323.1 (5.9)	316.5 (6.6)	321.4 (6.9)	319.2 (7.7)	333.2 (12.0)

$p<0.05$) and Electrode ($F(4, 36)=18.138$, $p<0.001$). Post hoc testing showed that the amplitude was significantly smaller in Movement than Control at Cz, and C3 ($p<0.01$, $p<0.05$, respectively) (Fig. 2C). A post hoc test with collapsing Condition indicated that the amplitude of Cz was significantly larger than that of Fz, Pz, C3, and C4 ($p<0.001$, $p<0.01$, $p<0.001$, and $p<0.001$, respectively), and the amplitude of Pz was also significantly larger than that of Fz ($p<0.05$).

ANOVAs for the peak latency of N2 indicated a significant effect of Electrode ($F(4, 36)=7.189$, $p<0.001$), and post hoc testing with collapsing Condition demonstrated that the N2 latency was significantly later at Fz than Cz, Pz, and C4 ($p<0.01$, $p<0.05$, and $p<0.001$, respectively). There were no significant main effect and interaction for the P2 latency. Group averages of peak latencies across all subjects are listed in Table 1, and mean and earliest RTs for individual subjects are shown in Table 2.

MEG data

Fig. 3A shows the group averages of LEFs across all subjects in the Control condition. A clear and consistent component was recorded in three cortical areas, A, B and C. Fig. 3B shows the isocontour maps in this period in three representative subjects. Just like the grand-averaged LEFs, these isocontour maps revealed distinct neural responses in regions A, B, and C. By ECD analysis, A was estimated to lie between the posterior wall of the central sulcus and superior end of the postcentral fissure contralateral to the stimulation, corresponding to SI or posterior parietal cortex (PPC), and B and C were estimated to be located in the upper bank of the Sylvian fissure, corresponding to SII, in the right and left hemisphere, respectively (Fig. 4). Therefore, we termed them, SI/PPC, cSII (contralateral SII) and iSII (ipsilateral SII). In the Control and Count conditions, these three dipoles were estimated in all subjects, but in Movement, a dipole from SI/PPC could not be estimated in one subject. Their x, y and z coordinates and peak latencies are shown in Tables 3 and 4.

Fig. 5A shows the sensor layout of the MEG to calculate the RMS from the left and right hemispheres. The mean values of RMS peak latency from both hemispheres were recorded between 160–190 ms

Table 2
Mean and earliest reaction times, and peak latencies of N2 and P2 at Cz in the Movement condition for individual subjects (ms)

Subject	Mean RT	Earliest RT	N2 peak latency	P2 peak latency
A	663	317	223.4	304.0
B	390	238	227.2	312.7
C	486	354	217.3	338.1
D	351	233	242.2	309.2
E	617	286	219.1	318.5
F	496	313	203.8	312.8
G	505	264	233.1	300.0
H	555	333	209.0	293.6
I	269	231	206.7	322.5
J	383	229	199.6	323.7
Mean	472	280	218.1	313.5
SE	39	15	4.3	4.1

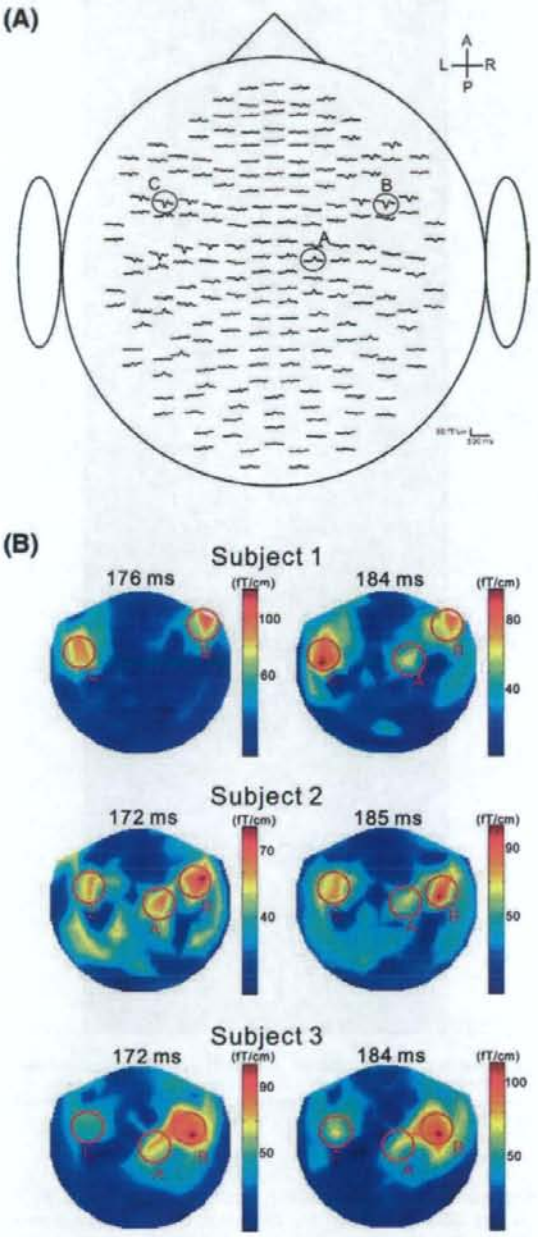

Fig. 3. (A) Grand-averaged laser-evoked magnetic fields (LEFs) over 204 planar coils in Control. The head is viewed from the top, and in each response pair, the upper trace illustrates the field derivate along the latitude and the lower trace that along the longitude. All data were digitally filtered (0.1–40 Hz bandpass) for display purposes. (B) The isocontour maps for Control at several time points in three representative subjects.

in each condition, which were clearly earlier than those of N2 component from Cz on EEG (Fig. 5B and Table 1). This result indicated that the MEG and EEG recorded different neural activities at different time period. ANOVA for RMS peak amplitude revealed no significant main effect of Condition and interaction, showing that there were no

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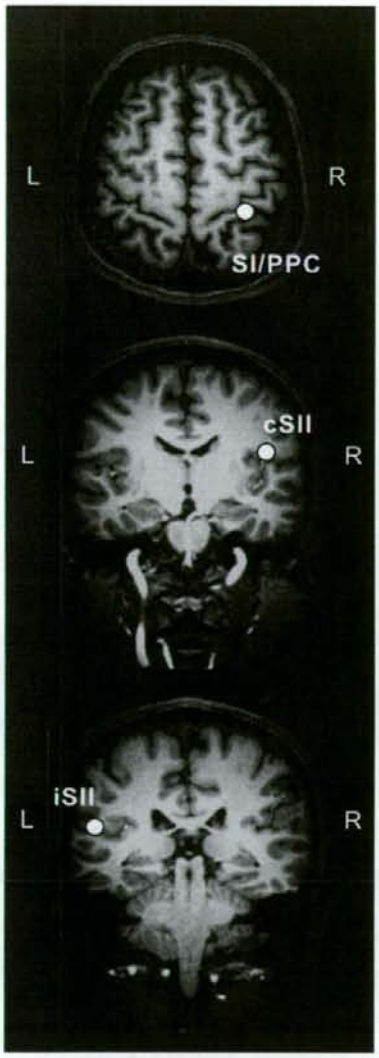

Fig. 4. Location of ECDs superimposed on a 2D MRI scan in a representative subject. L=left, R=right, SI=primary somatosensory cortex, PPC=posterior parietal cortex, cSII=secondary somatosensory cortex contralateral to the stimulation, iSII=secondary somatosensory cortex ipsilateral to the stimulation.

significant differences of amplitudes among the three conditions (Fig. 5B and Table 5). ANOVA for RMS peak latency demonstrated a significant main effect of Hemisphere ($F(1, 9)=13.848$, $p<0.01$), indicating that the peak latency was earlier in the right hemisphere than the left hemisphere. There were no effect of Condition and interaction for the latency.

Then, we calculated AMS in the regions of interest for all conditions (Fig. 6A). ANOVA for the peak amplitude of AMS revealed a significant main effect of Area ($F(2, 18)=8.959$, $p<0.01$), but there were no significant main effects of Condition and interaction (Fig. 6B and Table 5). Post hoc testing with collapsing Condition revealed that SI/PPC was significantly smaller than cSII and iSII ($p<0.01$, respectively), but there was no significant difference between cSII and iSII. As for peak latency, there was a significant main effect of Area ($F(2, 18)=7.740$, $p<0.01$), and post hoc analysis showed that cSII was significantly earlier than SI/PPC ($p<0.05$).

Table 3
Mean Talairach coordinates of the sources with S.E. for each condition

		x (mm)	y (mm)	z (mm)
Control	SI/PPC	22.1 (4.4)	−35.9 (1.9)	53.2 (1.7)
	cSII	47.8 (1.1)	−8.4 (1.1)	15.8 (1.1)
	iSII	−48.7 (0.9)	−14.3 (2.0)	17.8 (1.3)
Movement	SI/PPC	21.8 (3.3)	−36.2 (2.8)	56.8 (1.0)
	cSII	49.0 (1.2)	−8.4 (1.2)	16.0 (1.0)
	iSII	−48.9 (1.0)	−13.1 (2.7)	14.8 (1.1)
Count	SI/PPC	22.4 (2.5)	−35.5 (1.9)	55.3 (1.8)
	cSII	48.6 (0.9)	−8.9 (2.6)	16.5 (1.4)
	iSII	−50.6 (1.3)	−12.7 (2.1)	15.7 (1.3)

There were no significant differences among the conditions. Data are expressed as the mean (S.E.). SI=primary somatosensory cortex, PPC=posterior parietal cortex, cSII=secondary somatosensory cortex contralateral to the stimulation, iSII=secondary somatosensory cortex ipsilateral to the stimulation.

With two-way ANOVAs concerning Condition (Control, Movement, Count) and Source (SI/PPC, cSII, iSII), a significant main effect of Source was found for dipole strength ($F(2, 16)=15.401$, $p<0.001$). There was no significant main effect of Condition and Condition–Source interaction, suggesting that ECD strengths were not changed among conditions. This notion was supported by Fig. 7, showing similar ECDs of SI/PPC, cSII and iSII activities. Post hoc testing with collapsing Condition revealed that SI/PPC was significantly smaller than cSII and iSII ($p<0.001$, respectively), but there was no significant difference between cSII and iSII. In addition, there was a significant main effect of Source on the peak latency of ECD ($F(2, 16)=9.078$, $p<0.05$, $\varepsilon=0.552$). Post hoc analysis demonstrated that cSII was significantly earlier than SI/PPC and iSII ($p<0.001$, and $p<0.05$, respectively) (Table 4).

A one-way ANOVA revealed no significant effects on the x, y and z coordinates of ECDs. That is, the source locations of ECDs in SI/PPC, cSII, and iSII did not differ significantly among the conditions (Table 3).

The results of ANOVAs for the peak amplitudes of N2 and P2, RMS, AMS, and ECD strengths are listed in Table 5.

Based on N2 component data, we re-analyzed the ECD around 170–250 ms after noxious stimulation using all 306 channels of MEG to investigate which brain regions were responsible for generator mechanisms of N2. First, we calculated the AMS of five gradiometer pairs (Fig. 8A), showing that peaks were found around 160–230 ms (Fig. 8B). The morphology of the waveforms was clearly different from the results of other areas, which are shown in Fig. 6. Then, we determined the peak amplitude and latency in each condition, and performed one-way ANOVA to investigate differences among the three conditions. ANOVA for the amplitude demonstrated a significant main effect ($F(2, 18)=3.557$, $p<0.05$), and post hoc testing revealed that the amplitude was significantly smaller in Movement than Control (Fig. 8C). There was no significant difference in peak latency among conditions. The mean values of the peak latency were 197.4 ms (SE±4.8), 198.6 ms (±6.5), and 207.9 ms (±4.4) in the Control, Movement, and Count conditions, respectively.

The ECD for this area was estimated to be located on the anterior cingulate cortex (ACC) from the six, five, and five subjects in the

Table 4
Mean peak latencies of the sources with S.E. for each condition

	SI/PPC	cSII	iSII
Control	185.0 (5.3)	169.5 (5.0)	179.7 (4.3)
Movement	181.8 (5.1)	164.7 (4.9)	175.5 (4.0)
Count	185.0 (4.7)	162.4 (3.3)	176.2 (4.3)

There was a significant main effect of Source ($F(2, 16)=9.078$, $p<0.05$, $\varepsilon=0.552$), and post hoc analysis demonstrated that cSII occurred significantly earlier than SI/PPC and iSII ($p<0.001$, and $p<0.05$, respectively).

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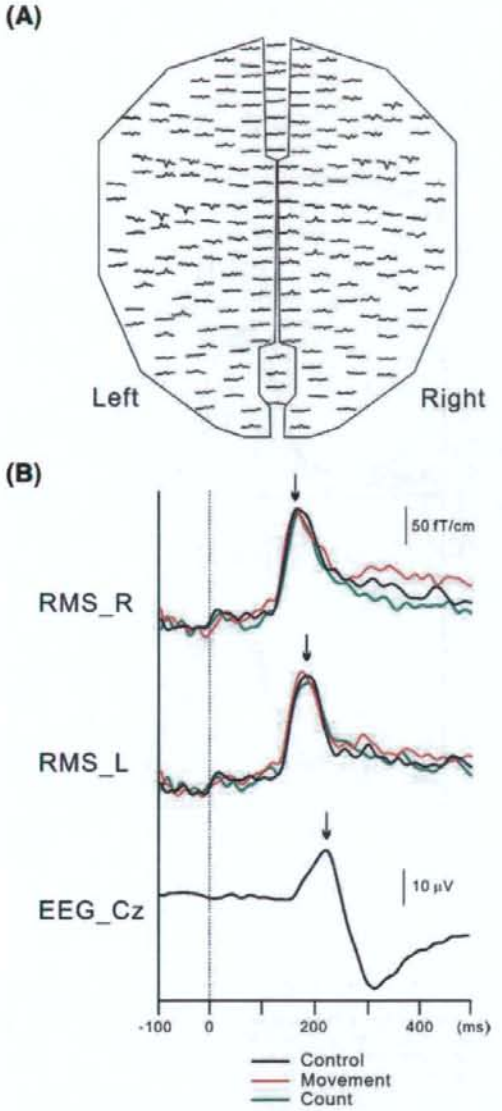

Fig. 5. (A) Sensor layout of the MEG to calculate the root-mean-square (RMS). (B) Change of the grand-averaged RMS waveforms from the right and left hemispheres. The peak amplitudes of RMS in each hemisphere not significantly changed among conditions. Black, red, and green lines indicate waveforms of Control, Movement, and Count, respectively. RMS_R = root-mean-square in the right hemisphere, RMS_L = root-mean-square in the left hemisphere, EEG_Cz = Cz electrode in electroencephalography.

Control, Movement, and Count conditions, respectively (Fig. 9A and Table 6). Fig. 9B indicates the change of the grand-averaged ECD strength waveforms of ACC. In the waveform of Control, two peaks were found at 160 and 210 ms, respectively. In Movement and Count, a single peak was identified around 210 ms, which was consistent with the peak of N2. Thus, we mainly focused on and analyzed this peak. Indeed, since ACC activity was not estimated from all subjects, we could not perform ANOVA, but the average values of the ECD strength was clearly smaller in Movement than Control and Count (Fig. 9C). These results suggest that voluntary movement in a preparatory period reduces the ECD strength of ACC.

Data of a supplementary experiment

Fig. 10 displays grand-averaged LEP waveforms in each condition across all subjects. Clear N2 and P2 components were recorded in all conditions after noxious stimulation.

ANOVAs for the amplitude of N2 revealed a significant main effect of Electrode ($F(4, 28) = 10.371$, $p < 0.01$, $\varepsilon = 0.413$), and a significant effect of Condition–Electrode interaction ($F(8, 56) = 5.288$, $p < 0.001$). Tukey HSD post hoc testing with collapsing Condition revealed that the amplitude was significantly larger at Cz than Fz, Pz, and C4 ($p < 0.05$, $p < 0.001$, and $p < 0.01$, respectively), and C3 than C4 ($p < 0.05$). There was no significant main effect of Condition ($F(2, 14) = 0.991$, $p > 0.05$), and post hoc test did not show differences in values between conditions per electrode (Fig. 11A). These results suggest that voluntary movements with the right hand and left foot did not significantly affect the peak amplitude of the N2.

In ANOVAs for the peak amplitude of P2, there was a significant effect of Condition–Electrode interaction ($F(8, 56) = 9.882$, $p < 0.001$), and a main effect of Condition ($F(2, 14) = 9.058$, $p < 0.01$), and Electrode ($F(4, 28) = 13.240$, $p < 0.01$, $\varepsilon = 0.493$). Post hoc testing showed that the P2 amplitude was significantly larger in Control than in Right Hand, and Left Foot at Fz ($p < 0.05$, and $p < 0.001$, respectively), Cz ($p < 0.001$, and $p < 0.01$, respectively), and C3 ($p < 0.05$, respectively). These findings suggest that both different types of movement, including the right hand and left foot reduced the P2 amplitude (Fig. 11B). In addition, a post hoc test with collapsing Condition indicated that the amplitude was significantly larger at Cz than Fz, and C3 ($p < 0.001$, respectively), Pz than Fz and C3 ($p < 0.001$, and $p < 0.01$, respectively), and C4 than Fz ($p < 0.05$).

ANOVAs for the peak-to-peak amplitude of N2–P2 revealed a significant effect of Condition–Electrode interaction ($F(8, 56) = 6.681$, $p < 0.001$), and main effects of Condition ($F(2, 14) = 10.153$, $p < 0.01$) and Electrode ($F(4, 28) = 11.547$, $p < 0.001$). Post hoc testing showed that the amplitude was significantly larger in Control than Right Hand at Fz, Cz, and C3 ($p < 0.05$, $p < 0.01$, and $p < 0.05$), and Control than Left Foot at Cz, Pz, C3, and C4 ($p < 0.01$, $p < 0.05$, $p < 0.05$, and $p < 0.05$) (Fig. 11C). A post hoc test with collapsing Condition indicated that the amplitude was significantly larger at Cz than Fz, Pz, C3, and C4 ($p < 0.001$, $p < 0.01$, $p < 0.001$, and $p < 0.001$, respectively).

ANOVAs for the peak latency of N2 indicated a significant effect of Electrode ($F(4, 28) = 3.884$, $p < 0.05$, $\varepsilon = 0.528$). Post hoc testing with

Table 5
Results of ANOVAs for the amplitudes of N2, P2, root-mean-square (RMS), and areal mean signals (AMS), and equivalent current dipole (ECD) strength

Component	Factor	*df*	*F*	ε	*P*
N2	C	2, 18	6.092		<0.01
	E	4, 36	9.030	0.542	<0.01
	C×E	8, 72	1.436		
P2	C	2, 18	0.342		
	E	4, 36	17.271	0.483	<0.001
	C×E	8, 72	4.056	0.410	<0.05
N2–P2	C	2, 18	3.818		<0.05
	E	4, 36	18.138		<0.001
	C×E	8, 72	3.704	0.574	<0.05
RMS	C	2, 18	0.918		
	H	1, 9	0.980		
	C×H	2, 18	0.938		
AMS	C	2, 18	0.715		
	A	2, 18	8.959		<0.01
	C×A	4, 36	0.832		
ECD	C	2, 16	0.672		
	S	2, 16	15.401		<0.001
	C×S	4, 32	0.058		

C = Condition, E = Electrode, S = Source, H = Hemisphere, A = Area ε = epsilon.

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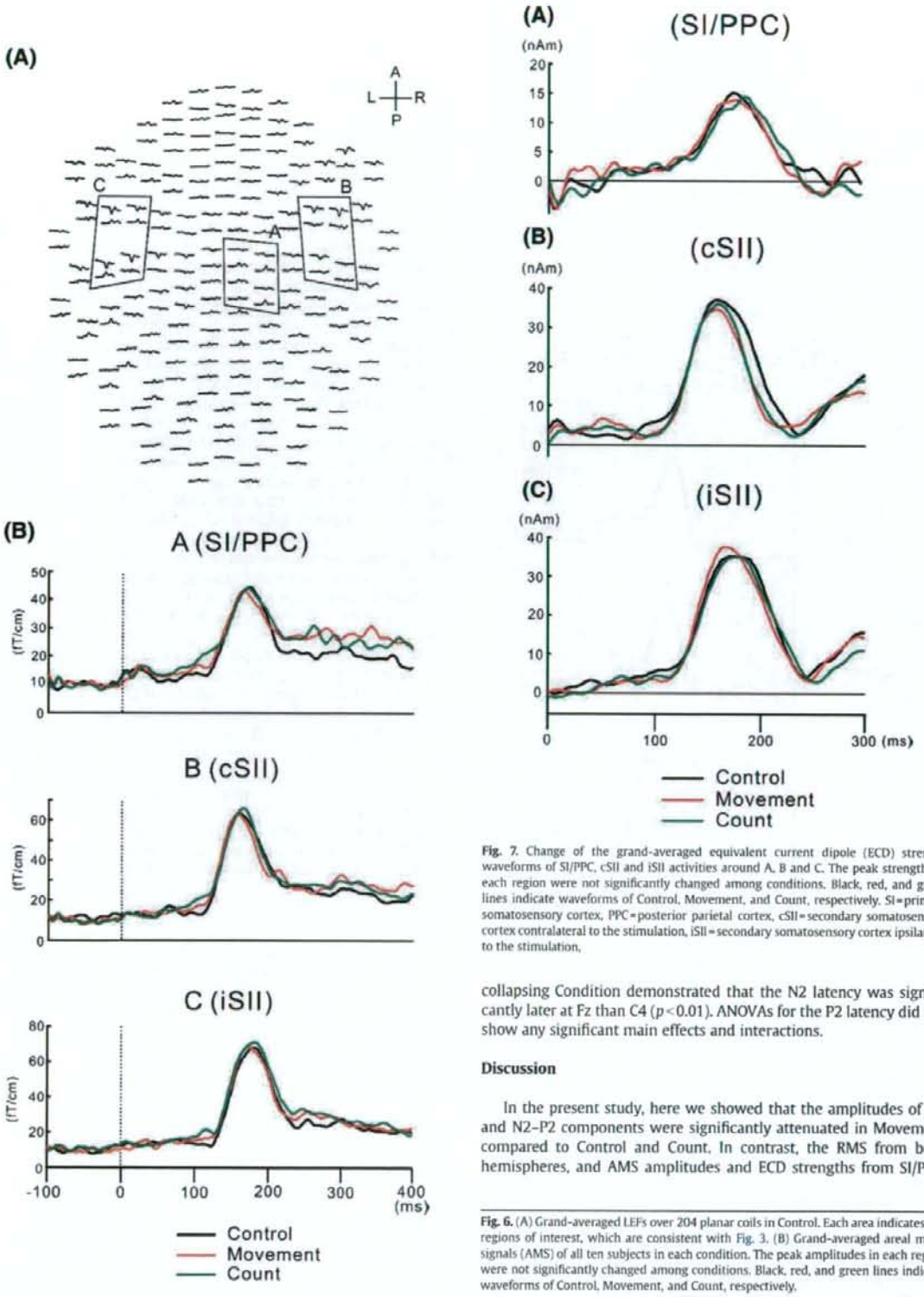

Fig. 7. Change of the grand-averaged equivalent current dipole (ECD) strength waveforms of SI/PPC, cSII and iSII activities around A, B and C. The peak strengths in each region were not significantly changed among conditions. Black, red, and green lines indicate waveforms of Control, Movement, and Count, respectively. SI = primary somatosensory cortex, PPC = posterior parietal cortex, cSII = secondary somatosensory cortex contralateral to the stimulation, iSII = secondary somatosensory cortex ipsilateral to the stimulation.

collapsing Condition demonstrated that the N2 latency was significantly later at Fz than C4 ($p < 0.01$). ANOVAs for the P2 latency did not show any significant main effects and interactions.

Discussion

In the present study, here we showed that the amplitudes of N2 and N2–P2 components were significantly attenuated in Movement compared to Control and Count. In contrast, the RMS from both hemispheres, and AMS amplitudes and ECD strengths from SI/PPC,

Fig. 6. (A) Grand-averaged LEFs over 204 planar coils in Control. Each area indicates the regions of interest, which are consistent with Fig. 3. (B) Grand-averaged areal mean signals (AMS) of all ten subjects in each condition. The peak amplitudes in each region were not significantly changed among conditions. Black, red, and green lines indicate waveforms of Control, Movement, and Count, respectively.

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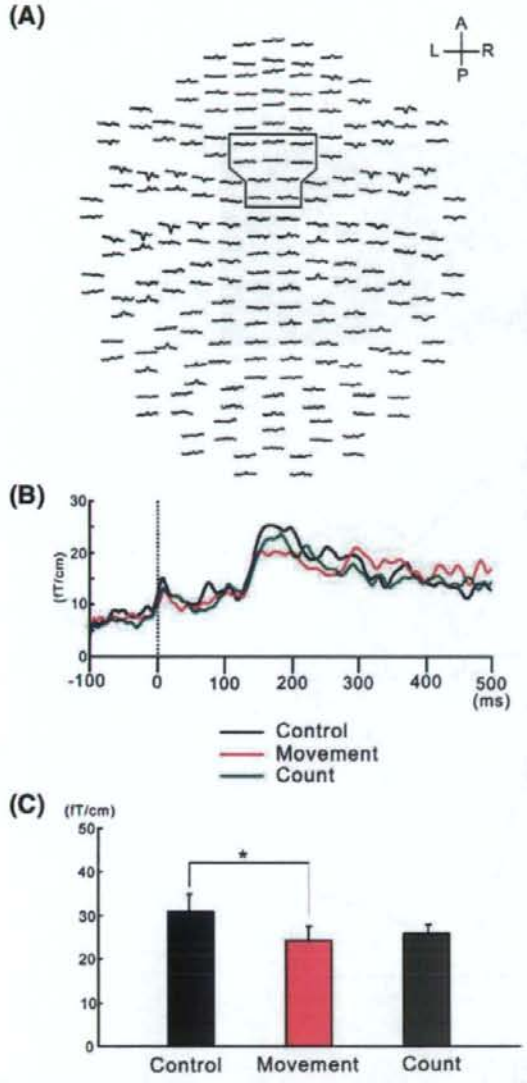

Fig. 8. (A) Grand-averaged LEFs over 204 planar coils in Control. The area indicates the regions of interest to detect activity in the anterior cingulate cortex (ACC). (B) Grand-averaged areal mean signals (AMS) of all ten subjects in each condition. Peaks were found at 160–230 ms after noxious stimulation. Black, red, and green lines indicate waveforms of Control, Movement, and Count, respectively. (C) Mean values of AMS amplitudes. Post hoc test indicated that amplitudes were significantly smaller in Movement than Control ($p<0.05$). Vertical lines indicate standard errors (S.E.). *$p<0.05$.

cSII, and iSII recorded by MEG were not significantly different among the three conditions. The AMS amplitudes and ECD strengths from ACC, which showed a similar peak to the N2 component, were significantly or clearly smaller in Movement than Control and Count. There were no effects of Count on LEPs and LEFs. These results indicated that the attenuation of LEP components and the neural activity of ACC started before voluntary movement, and this attenuation was related to the centrifugal effects caused by movement-related neural activities during a movement preparatory period.

N2 and P2 components

In general, N2 and P2 components are maximal at vertex electrodes, and spread widely after laser stimulation at any of site of the body. The mean peak latencies of N2 and P2 after laser stimulation of the hand are approximately 200 to 240 and 300 to 360 ms, respectively. The early N1 and P1 components are found before N2 and P2, and considered to be generated in the bilateral SII/Insula (reviewed in Kakigi et al., 2000).

Some previous studies reported that the amplitudes of N2 and P2 were attenuated during voluntary movement (Kakigi and Shibasaki, 1992; Kakigi et al., 1993), and pre-movement (Le Pera et al., 2007), which were consistent with our findings. Furthermore, there have been several papers examining the effects of attention/distraction on pain perception. They reported that the amplitudes of N2 and P2 on LEPs were enhanced by attention and attenuated by distraction (Beydoun et al., 1993; Siedenberg and Treede, 1996; García-Larrea et al., 1997; Yamasaki et al., 1999; Legrain et al., 2002, 2003a,b, 2005; Ohara et al., 2004a; Le Pera et al., 2007). In the present experimental design, since we used a task-relevant reaction time paradigm, the subjects were instructed to pay attention to the noxious stimuli due to respond to it or count in Movement and Count, respectively. As a result, modulation of the N2 and N2–P2 amplitudes was found only in Movement, not in Count. Thus, directing attention to the stimulation itself may not be a main factor causing the attenuation of the L2 and N2–P2 amplitudes in Movement, and other mechanisms should be considered.

We discuss the possibility that this finding was caused by overlapping of motor-related potentials. Motor-related activity can be recorded as MRCPs (movement-related cortical potentials) in scalp recordings, showing negative potentials. In particular, MP (motor potential), which consists of a short negative component, appears in the contralateral sensorimotor area (Shibasaki et al., 1980; Hallett, 1994). In the present study, the average values of P2 amplitude were smaller in Movement than Control and Count at Cz (Fig. 2B), and the mean RT across all subjects was 472 ms, and data from some subjects overlapped for the peak latency of P2 (Table 2). Thus, P2 amplitude in Movement may be influenced by this overlapping potential, which distorts the true P2 component. This notion was supported by the data of a supplementary experiment. That is, the amplitude of P2 was significantly smaller in Right Hand and Left Foot than Control (Figs. 10 and 11), indicating that attenuation of the P2 amplitude was affected by overlapping of MP, rather than centrifugal effects during a movement preparatory period.

In contrast, this possibility can be excluded for the N2 component, because, even though the negativity of MP overlapped on LEPs, this phenomenon cannot explain attenuation of the N2 amplitude. In addition, in a supplementary experiment, the N2 amplitude was not influenced by other body movements, such as the right hand and left foot; therefore, we should consider other mechanisms for attenuation of the N2 amplitude.

Our findings suggested that centrifugal effects were found on the N2 amplitude during the movement preparatory period, when the stimulated hand and movement hand were matched. Moreover, based on data of a supplementary experiment, hand movement contralateral to the noxious stimulation (i.e. right hand movement) did not affect the N2 amplitude, and other movement on the same body side to the noxious stimulation (i.e. left foot movement) also did not modulate the N2 amplitude. These results confirmed the result of Le Pera et al. (2007), which showed that hand movement contralateral to the noxious stimulation did not reduce the amplitude of LEPs.

SI/PPC, bilateral SII, ACC activities on LEFs

In the present study, the RMS, AMS, and ECDs peaks of LEFs generated in the contralateral SI/PPC bilateral SII were clearly

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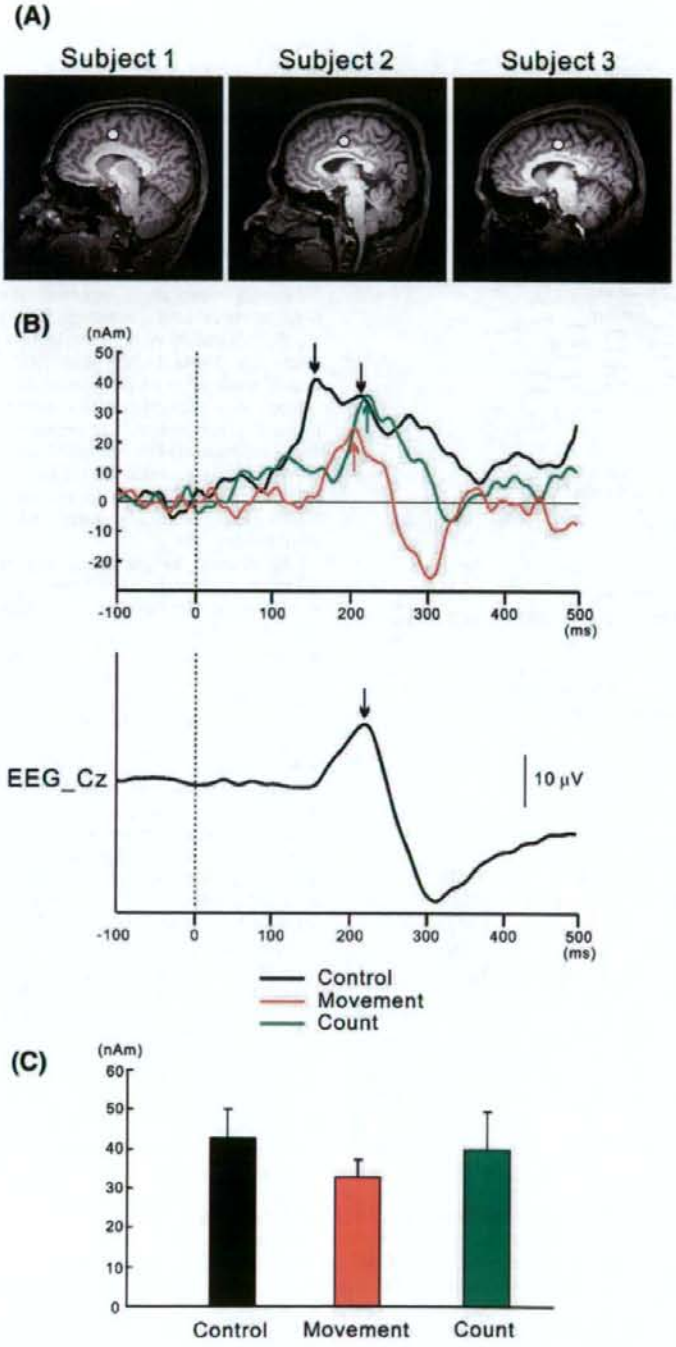

Fig. 9. (A) Location of ECDs for ACC superimposed on a 2D MRI scan in three representative subjects. (B) Change of the grand-averaged ECD strength waveforms of ACC. Black, red, and green lines indicate waveforms of Control, Movement, and Count, respectively. Arrows indicated the peak of the waveform, and peak strengths were smaller in Movement than Control and Count. (C) Mean values of ECD strengths for ACC. Vertical lines indicate standard errors (S.E.).

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Table 6
Mean Talairach coordinates and peak latency of the ACC source for each condition

	n	x (mm)	y (mm)	z (mm)	Latency
Control	6	[8.4] (2.0)	−0.9 (4.9)	38.8 (0.8)	216.5 (7.1)
Movement	5	[7.0] (1.9)	−0.1 (5.4)	38.8 (0.6)	201.6 (8.5)
Count	5	[9.3] (1.4)	−2.6 (4.3)	36.4 (1.2)	222.4 (2.2)

Data are expressed as the mean (SE). n = number of subjects, which was identified in the dipole analysis, [ ] = absolute value.

identified earlier than N2 and P2 peaks of LEPs (Fig. 5B and Table 1). They peaked between 160–190 ms after noxious stimulation, while N2 component of LEPs peaked about 220 ms. This difference indicated that LEPs and LEFs recorded different neural activities at different time periods. In addition, since the modulations of the RMS and AMS during the three conditions showed similar results to that of ECDs analysis, the RMS and AMS included mainly neural activities from SI/PPC and bilateral SII.

Some MEG studies using axial type coils reported small MEG activities in ACC following strong electrical stimulation (Kitamura et al., 1995), laser stimulation (Bromm et al., 1996) and noxious stimulation caused by specialized intra-epidermal needle electrode (Inui et al., 2003). In the present study, we found ACC activities, estimated by using all 306-channel analysis involving magnetometers, from six, five, and five subjects in Control, Movement, and Count, respectively (Fig. 9 and Table 6). The average values of ECD strength, and AMS amplitudes were clearly or significantly smaller in Movement than Control and Count (Figs. 8 and 9). Judging from the peak latency and modulation of the ECD strengths for ACC, the N2 component should be related to neural activity of ACC. Traditionally, the cingulate cortex has been regarded as part of the limbic system, and was associated with the motivational–affective component of pain (reviewed in Schnitzler and Ploner, 2000). Several LEP studies using dipole modeling reported a close relationship between generator mechanisms of N2 and ACC (Tarkka and Treede, 1993; Valeriani et al., 1996, 2000; Garcia-Larrea et al., 2003; Iannetti et al., 2003; Schlereth et al., 2003; Tsuji et al., 2006). In addition, there is anatomical evidence that motor-related cortical areas, especially the primary motor area (MI), are strongly connected with ACC (Dum and Strick, 1991; Morecraft and Van Hoesen, 1992), and a functional relation between these areas was also demonstrated in neurophysiological (Tamura et al., 2004a,b) and neuroimaging studies (Koski and Paus, 2000; Siebner et al., 2001). Taking these previous studies into consideration, it is likely that the neural activity of ACC was inhibited by movement-related neural activities, mainly in the MI, during a movement preparatory period.

However, we should reconsider that the activity of ACC could not be recorded from all subjects, and the number of subjects, identified by ECD analysis, was almost half of the participants (Table 6). Generally, it is difficult for MEG to detect dipoles generated in deep areas compared with EEG (reviewed in Hari et al., 2000), and thus many previous studies using the same Neuromag MEG system mainly

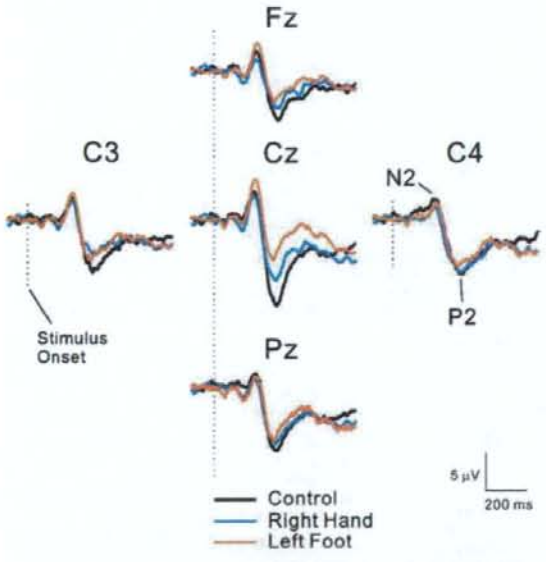

Fig. 10. Grand-averaged LEPs in a supplementary experiment. Noxious YAG laser stimulation was applied to the dorsum of the left hand in each condition. Black, blue, and orange lines indicate waveforms of Control, Right hand, and Left Foot, respectively. Vertical line indicates stimulus onset.

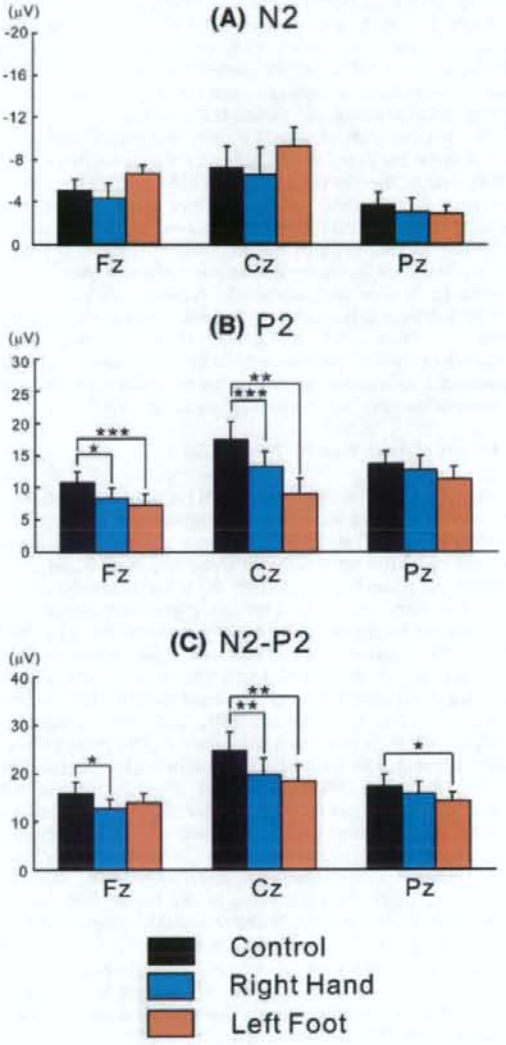

Fig. 11. Mean values of N2, P2, and N2–P2 amplitudes in a supplementary experiment. Vertical lines indicate standard errors (S.E.). *p<0.05, **p<0.01, ***p<0.001

analyzed ECDs from SI, PPC, and bilateral SII (Ploner et al., 1999, 2000; Kanda et al., 2000; Timmermann et al., 2001; Raij et al., 2003; Nakata et al., 2004, 2008; Forss et al., 2005). Based on the advantages and disadvantages of MEG, further studies are needed to clarify the characteristics of ACC activity in pain processing, for instance, a study with simultaneous MEG and a multi-EEG recording.

Our previous study using MEG showed that neural activities of SI and SII were attenuated during voluntary movement (Nakata et al., 2004), but in the current study, the AMS amplitudes and ECD strengths of SI/PPC and bilateral SII were not modulated before voluntary movement in a forewarned reaction time task. These differences for LEFs may infer that centrifugal modulation on sensory–motor integration is smaller during pre-movement than voluntary movement. In some MEG studies, SII responses elicited by tactile stimulation were enhanced in both hemispheres during voluntary movement (Forss and Jousmäki, 1998; Lin et al., 2000), but the enhancement was significant only in the contralateral SII before movement (Wasaka et al., 2005c). Such small modulation during pre-movement may also apply to pain–motor integration.

Differences of results between LEPs and LEFs

We considered the reason why the N2 and N2–P2 amplitudes of LEPs were modulated during motor preparation processing, but AMS amplitudes and ECD strengths of LEF were not changed. A possible explanation for this result is the difference of generator mechanisms between the N2 and P2 components of LEPs and LEFs. A number of EEG studies have demonstrated the pain-related cortical regions such as SI, bilateral SII, the insula, the ACC, the midcingulate cortex (MCC), the posterior cingulate cortex (PCC), and medial temporal regions including the amygdale and hippocampus using dipole source modeling (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al., 1996, 2000; Bentley et al., 2001, 2002, 2003; Garcia-Larrea, 2002; Garcia-Larrea et al., 2003; Iannetti et al., 2003; Schlereth et al., 2003; Tsuji et al., 2006), and intracranial recordings (Lenz et al., 1998a, b, 2000; Ohara et al., 2004a,b,c; Frot et al., 2008). On the other hand, MEG studies have shown that LEF components recorded about 170 ms after noxious laser stimulation of the hand were generated from SI, PPC, and bilateral SII (Ploner et al., 1999, 2000; Kanda et al., 2000; Timmermann et al., 2001; Raij et al., 2003; Nakata et al., 2004, 2008, Forss et al., 2005). Pain processing in the human brain has two different nociceptive systems, lateral and medial (reviewed in Treede et al., 1999). SI and SII cortices belong to the lateral system, while ACC and the insula belong to the medial system. Taking the studies mentioned above into consideration, LEF components from SI, PPC, and bilateral SII are related to the lateral system, and N2 and P2 components on LEPs, the medial system.

In one previous study recording LEPs and LEFs simultaneously, Yamasaki et al. (1999) reported that the N2 and P2 amplitudes were attenuated during calculation and memorization tasks, but SII responses of LEFs were unchanged. Moreover, Le Pera et al. (2007) analyzed both N1–P1 and N2–P2, and found that the N1–P1 amplitude remained unchanged during the pre-movement period, but the N2–P2 amplitude was attenuated. These results were consistent with our findings.

Conclusion

The N2 and N2–P2 components of LEPs following a task-relevant noxious stimulation were modulated through a centrifugal mechanism when the signal triggered a voluntary movement. This effect was not found in Count. In addition, ECD strengths and AMS amplitudes of ACC, which showed a similar peak to the N2 component, were clearly smaller in Movement than Control and Count. We therefore suspect that neural activities related to the generator mechanisms of N2, especially those in the ACC, are inhibited by movement-related neural activities during the preparatory period. In addition, since the N2 amplitude was not affected by the right hand and left foot in a supplementary experiment, we consider that centrifugal effects occur on the N2 amplitude during the movement preparatory period, when the stimulated hand and movement hand are matched.

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