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Neural codes for somatosensory two-point discrimination in inferior parietal lobule: An fMRI study

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This is the first functional magnetic resonance imaging (fMRI) study to investigate the hemodynamic response related to somatosensory spatial discrimination, so-called two-point discrimination. During scanning, we examined two discrimination tasks using four types of electrical stimuli applied to one or two points with strong or weak intensity on the right and left forearm, respectively. In the two-point discrimination task (TPD), subjects reported whether they thought the stimulus was applied to one point or two. In the intensity discrimination task (ID), subjects were required to judge whether the stimulus was strong or weak. In each task, they pressed a button to report their choice. Comparing TPD with the control, we found activated regions in the inferior parietal lobule (IPL) around the supramarginal gyrus (SMG) (Brodmann's area 40) and anterior cingulate cortex (ACC). These areas were significantly activated irrespective of the forearm stimulated. Comparing ID with the control, there were no significantly activated regions. By comparing the TPD and ID, we identified that the left IPL was significantly activated, specifically in TPD, irrespective of the forearm stimulated. In contrast, there were no significantly activated regions in the ID task. Therefore, the left IPL is considered to play an important role in two-point discrimination.

Introduction

The discrimination of stimuli is necessary in daily life and involves the peripheral and central nervous system. Recent fMRI studies involved different brain systems, ranging from unimodal somatosensory to higher order cognitive brain areas, and evolved with different time windows (Stoeckel et al., 2003; Kaas et al., 2007; Pleger et al., 2006) using various discrimination tasks, such as frequency (Pleger et al., 2006), grating orientation (Kitada et al., 2006; Van Boven et al., 2005), or Braille tactile (Harada et al., 2004) in humans. However, the regions activated are different with each task. For example, Li Hegner et al. (2007) found that blood-oxygen-level-dependent (BOLD) adaptation is initiated in the contralateral primary somatosensory cortex (SI) and superior temporal gyrus (STG) using a tactile frequency discrimination task. On the other hand, Zhang et al. (2005) reported that a tactile grating orientation task activated regions around the postcentral sulcus and intraparietal sulcus (IPS). However, to our knowledge, there have been no fMRI studies focusing on the somatosensory two-point discrimination (TPD) task that required the discrimination of stimuli whether applied to one or two points. Therefore, the TPD task would help us to reveal which cortical regions are activated by discriminating simultaneous stimuli at different locations.

TPD is an important and frequently used clinical test of the higher function of somatosensory perception. TPD is based on the slowly adapting type I afferent fiber system, one of four afferent fiber systems in the skin. Our group investigated the cortical cognitive processes during TPD in a reaction time task (Tamura et al., 2003, 2004) and suggested the presence of a cortical cognitive process in TPD. Therefore, TPD is considered to reflect cognitive functions taking place in the central nervous system, but its underlying mechanisms have still not been clarified. One major problem with this test is that it is very subjective, being dependent on the examiners' skills and subjects' reactions.

To solve these problems, we recently reported automatic detection systems for somatosensory spatial and temporal discrimination using electroencephalography (EEG) and magnetoen-

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cephalography (MEG). In the EEG study, we applied paired stimuli to the same region of the skin with a different inter stimulus interval (ISI) between the standard and deviant stimuli, that is, a temporal discrimination task. Then, we succeeded in recording somatosensory mismatch responses, N60 and P150, elicited by deviant stimuli (Akatsuka et al., 2005). In the MEG study, we applied a two-point stimulus to the dorsal surface of the right hand with a different two-point distance as the standard and deviant stimuli, that is, TPD. Then, we succeeded in recording the components peaking around 30–70 ms and 150–250 ms following deviant stimuli, which were significantly larger than those following standard stimuli (Akatsuka et al., 2007). On the other hand, as already mentioned, no fMRI studies had investigated the neural mechanisms involved in somatosensory TPD.

In the present study, therefore, we investigated the areas of the brain specifically involved in somatosensory spatial TPD using fMRI. We performed TPD with a simple detection control task. In addition, we performed intensity discrimination (ID) with a simple detection control task using the same stimulus parameter as for the TPD task. By comparing the two discrimination tasks between TPD and ID, we identified the regions specifically involved in TPD.

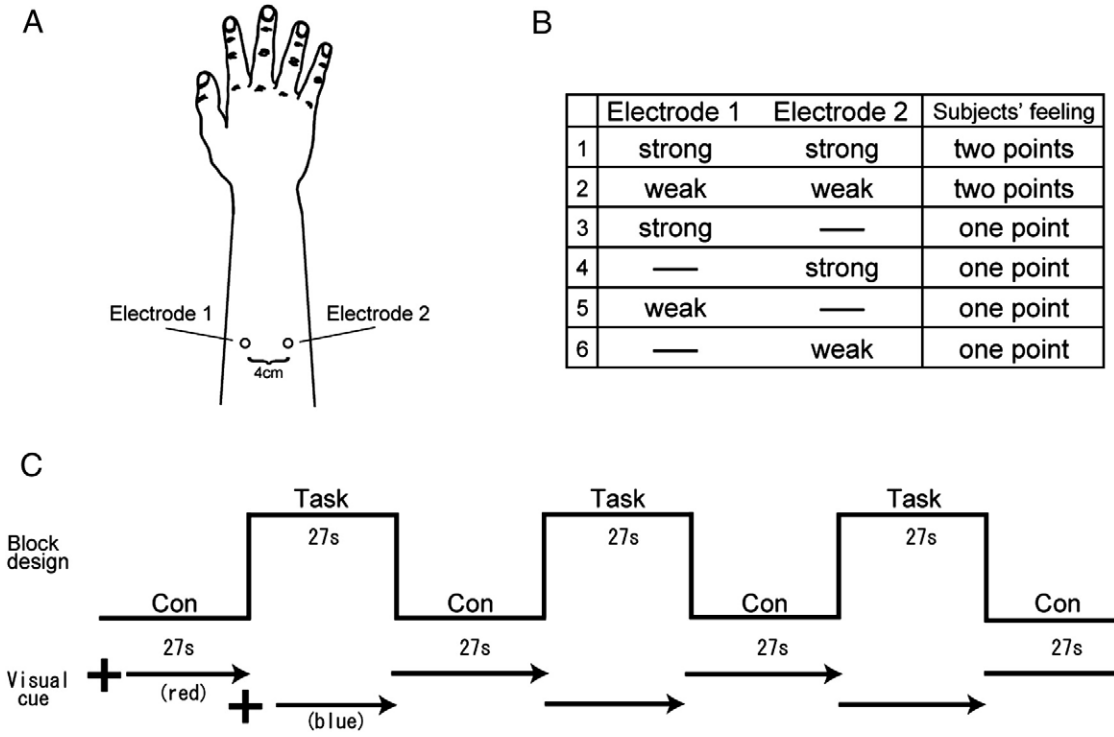
Materials and methods

Subjects

Fifteen individuals (four women, eleven men; mean age± S.D.=29.9±5.9) participated in this study. The subjects were all right handed and did not have neurological disorders. Informed consent was obtained from each participant. Approval for the experimental protocols was obtained from the ethics committee of the National Institute for Physiological Sciences, Okazaki, Japan.

Stimulation and procedure

Four types of stimulus (strong one point, strong two points, weak one point and weak two points) were presented to the subjects using a ball-shaped Ag electrode (2 mm in diameter, anode 2 mm from cathode) which was placed on the right and left forearm skin of the flexor middle, independently (Fig. 1). The inter-stimulus interval (ISI) was 3 s. First, we set two Ag electrodes on the right and left forearms with a distance of 4 cm between them. When we presented one-point stimuli to the subjects, we stimulated either one of the two electrodes. In contrast, we stimulated both electrodes simultaneously as a two-point stimulus. Second, we determined the type of electrical intensity, strong or weak. The intensity of the strong and weak stimuli was 2.5 times and 1.5 times the sensory threshold in each subject, respectively. When we applied one point stimulus, we stimulated either one of the two electrodes, therefore, four kinds of stimulus set were used: strong (electrode 1)–none (electrode 2) and vice versa, and weak (electrode 1)–none (electrode 2) and vice versa. When we applied two-point stimuli, two kinds of stimulus set were used: strong–strong and weak–weak, therefore, strong (electrode 1)–weak (electrode 2) or vice versa were not used. The same stimulus sets were used for each TPD and ID task. Each right and left forearm



	Electrode 1	Electrode 2	Subjects' feeling
1	strong	strong	two points
2	weak	weak	two points
3	strong	—	one point
4	—	strong	one point
5	weak	—	one point
6	—	weak	one point

Fig. 1. (A) Schematic illustrations of the two electrode locations in the right forearm stimulated condition. (B) Four types of stimulus patterns (strong one point, strong two points, weak one point, and weak two points). (C) Experimental design. We used a conventional block design. In the control blocks, subjects were required to only push the button when they felt stimuli during both TPD and ID. In the discrimination blocks, TPD or ID, subjects were required to discriminate whether it was one- or two-point (TPD), and strong or weak (ID).

stimulus session was performed independently. The order of the session was counterbalanced among subjects. All subjects practiced at correctly discriminating the four types of stimulus before the experiment.

Discrimination task

Spatial two-point discrimination (TPD)

A conventional block design was used. Four types of electrical stimulus with a 3-s ISI were delivered at two electrodes on the forearm. A session consisted of four controls and three TPD tasks, each 27 s in duration, with the order of the control and task blocks alternated. Each block consisted of eight trials, and two sessions were performed for each subject. At the beginning of the control and task block, the fixation point was shown by a red and blue cue, respectively, in the central visual field. In the TPD task, subjects reported whether they felt a one-point stimulus or two-point stimulus by pressing a button. When subjects felt an electrical stimulus as one point or two points, they were required to push a button with their right or left index finger, respectively as quickly as possible. Subjects were not required to perform any discrimination during the Control task, but they were required to push the button as quickly as possible when they felt any stimulus.

Intensity discrimination (ID)

Subjects were required to report whether they felt a weak or strong stimulus in each trial of the task blocks. When subjects felt an electrical stimulus as strong or weak, they were required to push a button with their right or left index finger, respectively. Other experimental conditions were the same as for the TPD task.

MR parameters

Imaging was performed using a 3 T head scanner (Allegra; Siemens, Erlangen, Germany). A time course series of 68 volumes was acquired in 1 session, but the first 5 volumes of each fMRI session were discarded due to unsteady magnetization. The remaining 63 volumes per subject were used for the analysis. Using a gradient echo-planar imaging (EPI) sequence [repetition time (TR), 3000 ms; echo time (TE), 30 ms; flip angle, 85°; field of view, 192×192 mm^2; resolution, 3×3 mm^2], over 48 slices of 3 mm thickness with 0 mm gap were scanned to cover the entire brain volume. To normalize individual brains into a standard brain, a three-dimensional structural brain image of each subject was also obtained using an MP-RAGE sequence (Mugler and Brookeman, 1990) with the following parameters: TR, 2500 ms; TE, 4.38 ms; flip angle, 8°; field of view, 230×230 mm^2; resolution, 0.9×0.9 mm^2.

Data analysis

Data analyses were performed using SPM2 (statistical parametric mapping software; Wellcome Department of Imaging Neuroscience, London, UK) on MATLAB (Math Works, Natick, MA). First, the functional volume data for each subject in multiple runs were realigned to the first image. No participants displayed more than 3 mm movement or 1° rotation from the reference image. After realignment, all images were coregistered to the high-resolution three-dimensional T2-weighted MRI using anatomical MRI with T2-weighted spin-echo sequences from identical locations to the fMRI image. Each individual brain was normalized to the standard brain space defined by the Montreal Neurological Institute with re-sampling of 2 mm using bilinear interpolation. Normalized data were then spatially smoothed using an isotropic Gaussian kernel of 8 mm full width at half maximum (FWHM). Temporal filters were also applied and low frequency noise and global changes in the signal were removed. Specific effects for two types of discrimination were estimated for each subject using a general linear model with a boxcar waveform convolved with a canonical hemodynamic response function (Friston et al., 1998).

The main objective of the present study was to investigate the neural system specifically involved in TPD, irrespective of the forearm stimulated. Therefore, we did not analyze the data of right or left forearm stimulation independently, but instead performed the following two main comparisons. As the first comparison, we tested for the overall effect of each discrimination task (TPD or ID) versus the Control, irrespective of the forearm stimulated. This contrast highlights areas of the brain involved in each type of discrimination. Group analysis (random-effect model) of each contrast was then performed by entering contrast images into a one-sample t test. The statistical threshold was set at a familywise error (FWE) of $P<0.05$, corrected for multiple comparisons. As the second comparison, we compared brain activity during TPD versus ID. In this comparison, we could investigate the specific brain regions involved in TPD and ID, irrespective of the forearm stimulated. Using the contrast of first comparison (TPD versus Control) as an inclusive mask (FWE of $P<0.05$, corrected), group analysis (random-effect model) was then performed by entering contrast images into one-way ANOVA, and regions activated more during TPD than ID were identified with an FWE of $P<0.05$, corrected. In a similar manner, we investigated specifically activated regions during ID than during TPD, irrespective of the forearm stimulated.

Results

Experimental conditions and behavioral data

The intensity of the strong and weak stimulus of the right forearm was 2.5±0.15 mA (mean±S.E) and 1.37±0.08 mA, while that of the left forearm was 2.42±0.14 mA and 1.35±0.07 mA, respectively (Table 1). Behavioral accuracy of the right TPD and ID was 69.7%±3.7% and 74.7%±3.3% while that of the left TPD and ID was 71.7%±3.9% and 82.2%±2.9%, respectively. There was no significant difference between these scores for the right forearm stimulus ($p>0.05$; paired t test), but TPD of the left forearm stimulus was significantly more difficult than ID ($p<0.05$; paired t test), that is, we could not perfectly control the difficulty of the left forearm stimulated condition (Fig. 2). However, since stimulus conditions should be consistent through all the experiments for fMRI to compare results, we did not change the

Table 1
The intensity of stimulus used in this study

	Strong stimuli	Weak stimuli
Right hand	2.5±0.15 mA	1.37±0.08 mA
Left hand	2.42±0.14 mA	1.35±0.07 mA

Data are expressed as mean±S.E.

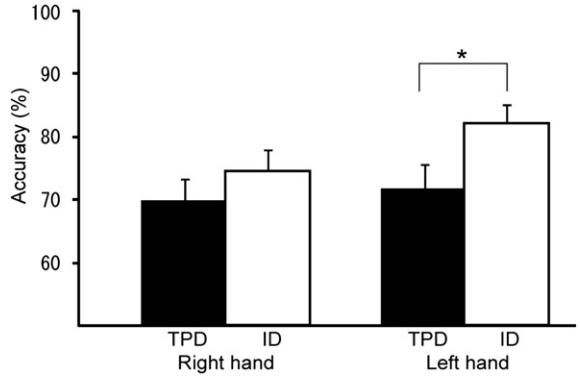


Fig. 2. Behavioral accuracy of TPD and ID in the right and left hand. TPD of the left forearm stimulus was significantly more difficult than ID. *$p<0.05$ (paired t test).

conditions for two-point and intensity for the left forearm stimulation. In fact, if we tried to change the intensity, the accuracy for TPD would be changed according to the change.

Functional imaging results for each discrimination task and Control

Comparing TPD with the Control, we found significantly activated regions in the inferior parietal lobule (IPL) around the supramarginal gyrus (SMG) (Brodmann's area 40) and anterior cingulate cortex (ACC) (FWE of $P<0.05$, corrected) (Table 2). The IPL around SMG, pre-frontal gyrus (PFG), inferior frontal gyrus (IFG), ACC, left primary somatosensory cortex (SI), anterior insula, striatum, and the anterior lobe of the cerebellar vermis (ALV) were also activated, when the threshold was set at a false discovery rate (FDR) of $P<0.05$ (corrected) (Figs. 3 and 4). FDR of $P<0.05$ (corrected) was not considered significant in this study, and this result is shown as reference data. Comparing ID with the control, there were no significantly activated regions. The IPL around SMG, PFG, IFG, ACC, left SI, anterior insula, striatum, and the ALV were also activated, when the threshold was set at FDR of $P<0.05$ (corrected).

Functional imaging results for the TPD versus ID

We identified significantly activated regions specifically involved in TPD, irrespective of the forearm stimulated. The left IPL (x, y, $z=-46$, -40, 48; Z-score$=3.00$) showed significantly stronger activity during TPD than ID (FWE of $P<0.05$, corrected) (Fig. 5). This region appeared to be involved in the TPD task specifically. There were no significantly activated regions in the ID task.

Discussion

In this study, we investigated the areas of the brain specifically activated while subjects discriminated whether stimuli affected one point or two. We used the same stimulus parameter and motor response for TPD and ID. We stimulated the right and left forearm independently, and identified significantly activated regions, which were specifically involved in TPD, irrespective of the forearm stimulated.

Activated areas specifically involved in TPD task

To identify the cerebral areas specifically activated during TPD, we contrasted the activation pattern during TPD with that during ID. We found significantly more activated areas in the IPL during TPD than during ID. In the TPD and ID tasks, we used the same stimulus sequence and type of response. Therefore, the area significantly activated during TPD was influenced only by the TPD task that discriminated whether a stimulus was delivered to one point or two.

In this study, we found increased activity in IPL during TPD than during ID; however, Pastor et al. (2004) reported that the pre-SMA and ACC were activated during a temporal discrimination task. They used a random series of paired stimuli with variable inter-stimulus intervals (5–110 ms) presented at different sites on one forearm (8–64 mm from the midline), and then the subjects judged whether they felt one stimulus or a pair of distinct pulse. In addition, they reported that the same regions were activated during an auditory temporal discrimination task (Pastor et al., 2006). They suggested that these areas were strategically placed for a pivotal role in temporal processing across sensory modalities. Concerning the task difference between ours and theirs, it was the same to discriminate stimuli whether subjects felt one or two, but crucial difference was that our task involved spatial comparison whereas the task of Pastor et al. (2006) involved temporal integration.

Several recent studies have shown participation of the parietal region in somatosensory discrimination. Hillis et al. (2006) investigated the neural correlates of modality-specific spatial extinction using patients with supratentorial stroke. They suggested that tactile extinction was most associated with neural dysfunction in the IPL including SMG. The SMG is a part of the IPL which belonged to Brodmann's area 40. In addition, Bodegard et al. (2001) investigated activated regions in the anterior part of the SMG elicited by active and passive shape discrimination. They suggested that process takes place in a set of somatosensory areas: 3b and 1 in the first stages, area 2 in the intermediated stage, and IPS and SMG in the final stages. Stoeckel et al. (2004) suggested that the left superior parietal cortex related to the maintenance of tactile information of subsequent object discrimination. Their task was to discriminate a second object from the first object, therefore, subjects had to retain tactile information about the first object. However, our task was to discriminate the stimulus itself during each task condition without comparing the stimuli given before or after. We think that the activation of the left superior parietal cortex, which Stoeckel et al. (2004) indicated, was different from the activation of left IPL found in our study in terms of the underlying mechanism, although the role of these two closed regions may overlap to some degree. Therefore, we believe that higher order somatosensory discrimination such as TPD should

Table 2
Activated regions in TPD versus Control

Brain region (side)		BA	x	y	z	Z-score
IPL	Left	40	−46	−40	48	5.32
ACC		32	10	29	26	5.25

BA, Brodmann's area.

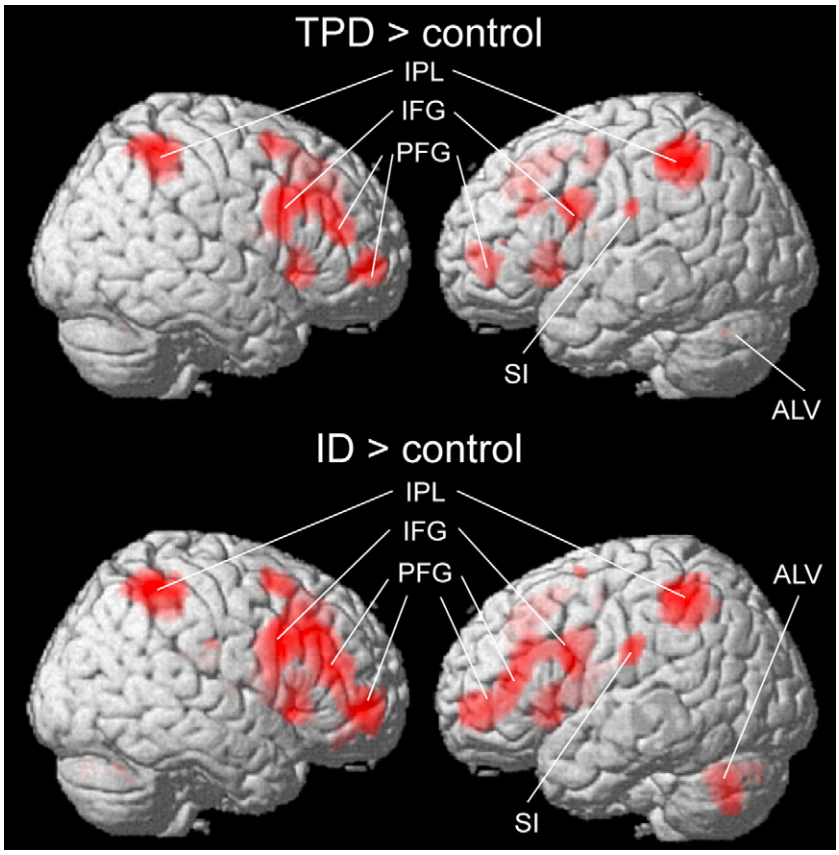


Fig. 3. Cortical regions where differences were identified between each discrimination task (TPD and ID) and Control task, irrespective of the forearm stimulated. Left inferior parietal lobule was significantly activated during TPD than Control (FWE of $p<0.05$, corrected). Although our statistical threshold was FWE of $p<0.05$ (corrected), the threshold was lowered at FDR of $p<0.05$ (corrected) for display purposes.

take place in the IPL. In addition, clinical studies reported that tactile object recognition was impaired by focal lesions in the SMG even though normal sensations were spared (Caselli, 1993; Reed et al., 1996). Therefore, the IPL would also play some important role in the discrimination and recognition of somatosensory tactile stimuli.

Hopfinger et al. (2000) suggested that IPL played a role in attentional control mechanisms, which may include shifting attention or working memory processes engaged to support task performance. Additionally, Oshiro et al. (2007) showed that IPL was activated during spatial discrimination and spatial memory using pain stimulation. Taking into account all of the above

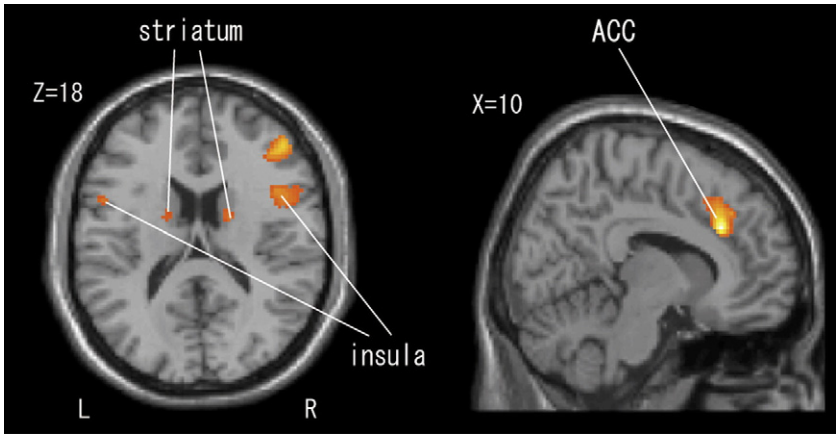


Fig. 4. Subcortical regions where differences were identified between TPD and Control, irrespective of the forearm stimulated. Anterior cingulate cortex was significantly activated during TPD than Control (FWE of $p<0.05$, corrected). Although our statistical threshold was FWE of $p<0.05$ (corrected), the threshold was lowered at FDR of $p<0.05$ (corrected) for display purposes.

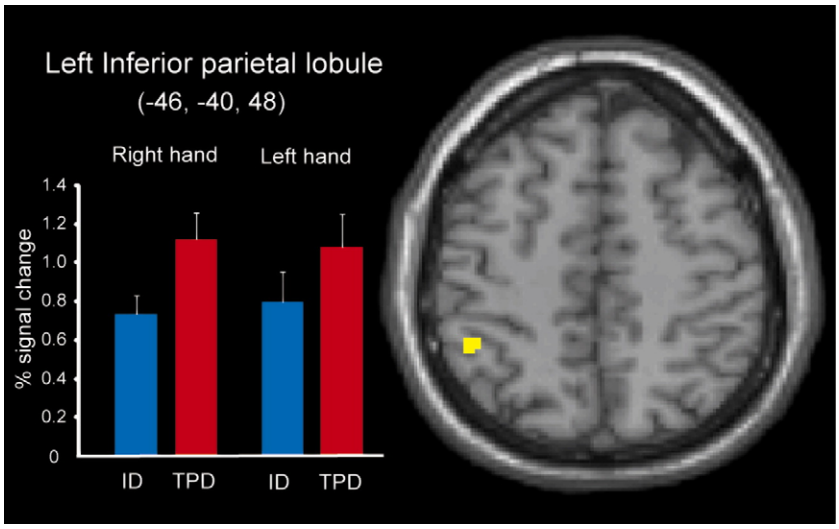


Fig. 5. Significantly activated cortical region during TPD versus ID, irrespective of the forearm stimulated. Initially, we sought regions showing significantly stronger activity in TPD than Control, irrespective of the forearm stimulated (FWE of $p<0.05$, corrected). Using this contrast as an inclusive mask, regions activated more during TPD than ID were then identified (FWE of $p<0.05$, corrected).

findings, therefore, we could hypothesize that TPD requires IPL activation much more than ID.

In our previous MEG study (Akatsuka et al., 2007), we found that the SI and secondary somatosensory cortex (SII) played an important role in the automatic detection of whether it was two point stimulation or one point stimulation in the early stage of discrimination within 200 ms following the stimulation. Therefore, we presume that the early automatic discrimination of TPD takes place in the SI and SII and the next judgment process takes place in the IPL.

We used a conventional block design to investigate the areas of the brain involved in TPD, since the amount of BOLD signal change related to such a higher function process is frequently smaller than event-related design, and block design has some advantages to store trial effects than event-related design. However, the block design could not distinguish pre-stimulus, inter-stimulus, and post-stimulus processing. Pre-stimulus effects are known to affect the processing of sensory stimuli (Linkenkaer-hansen et al., 2004; Boly et al., 2007). Also sustained inter-stimulus processing is likely during discrimination tasks. We considered that event-related design might be more appropriate to investigate the details of pre-stimulus, inter-stimulus, and post-stimulus processing.

In conclusion, we showed that TPD processing was significantly related to neural responses in the IPL. The analysis of common regions between right and left TPD showed significant activation in the left IPL. Therefore, we think that the left IPL plays an important role in two-point discrimination. This is the first study to clarify the regions responsible for two-point discrimination, which has been vague until now. To our knowledge, there have been no clinical studies of patients whose TPD was impaired but general tactile perception was not impaired by the left IPL lesion, but more careful examination will find such patients.

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