

**Asymmetrical Neural Substrates of Tactile
Discrimination in Humans: A Functional Magnetic
Resonance Imaging Study**

Tokiko HARADA

DOCTOR OF PHILOSOPHY

Department of Physiological Sciences

School of Life Sciences

The Graduate University for Advanced Studies

2004

ABSTRACT

The left-hand advantage seen during tactile discrimination tasks suggests hemispheric-processing asymmetry, although its neural substrates are not well known. We used functional magnetic resonance imaging to evaluate the laterality of the neural substrates involved in tactile discrimination in 19 normal volunteers. Passive tactile discrimination tasks, along with appropriate control tasks, were performed with both the right and left hands to evaluate the effects of the hand used and hemispheric effects (i.e., laterality of the activation pattern). Regardless of the hand used, the right dorsolateral prefrontal cortex, posterior parietal cortex, pre-supplementary motor area, and rostral portion of the dorsal premotor cortex (PMdr) were activated asymmetrically during tactile discrimination. This confirms the previous finding of a right-sided asymmetry for tactile shape discrimination. Hand effects were found in the left caudal PMd (PMdc) adjacent to the central sulcus, which showed prominent activation during right-handed but not left-handed discrimination tasks. This asymmetric activation in the left PMdc might be related to the asymmetric interhemispheric interaction during right-handed tactile discrimination.

INTRODUCTION

It has been suggested that tactile pattern discrimination is a right hemisphere function (Carmon and Benton, 1969; Fontenot and Benton, 1971; Zaidel and Sperry, 1973). Fontenot and Benton found that patients with left hemisphere lesions were deficient in the perception of the direction of tactile stimulation of the right hand, whereas patients with right hemisphere lesions showed a bilateral impairment. This idea is consistent with previous studies of patients with complete cerebral commissurotomy, which showed a left-hand advantage for nonverbal tactile tasks (Milner and Taylor, 1972; Kumar, 1977; Dodds, 1978). Using a cross-modal geometric matching task, Dodds (1978) found that the right hemisphere is superior in terms of both speed and accuracy. Using a tactile modification of the Memory for Designs Test, Kumar (1977) found that processing in the right hemisphere was markedly superior to the left hemisphere, indicating independent right hemisphere-based memories of spatial configurations. Because this right hemisphere superiority is not evident in subjects with an intact or remnant corpus callosum, interhemispheric transfer probably equalizes the performance by either hand. This implies that the neural substrates of tactile spatial processing might be right lateralized even if the left-hand advantage is not evident; furthermore, the right-hand process might be more demanding than the left-hand process because of inter-hemispheric transfer. However, the neural substrates of this compensatory workload are unknown.

Recent advances in neuroimaging techniques allow the visualization of task-related neural circuits using blood flow changes as an indirect index of neural activity. In the present study, we hypothesized that the difference between the neural substrates for tactile discrimination by the right and left hands might represent those regions necessary for interhemispheric transfer. To test this hypothesis, we conducted a functional magnetic resonance imaging (fMRI) study. A Braille letter discrimination task was performed by sighted subjects with no knowledge of Braille reading and hence regarded as a non-lexical tactile discrimination task. To exclude any exploratory movements during tactile discrimination, the tactile stimuli were presented passively. To visualize the neural substrates of tactile discrimination, the discrimination task was contrasted with a nondiscrimination task; this allowed us to control for somatosensory input and motor responses. These tasks were performed using both the right and left hands. The hemisphere effect (i.e., laterality of the activation pattern), hand effect, and the interaction between these two were evaluated.

SUBJECTS AND METHODS

Subjects

We studied a total of 19 healthy right-handed subjects, 8 females and 11 males, with a mean age of 24.8 ± 3.6 years. The subjects were all right-handed according to the Edinburgh handedness inventory (Oldfield, 1971). There was no history of neurological or psychiatric illness in any of the subjects, and none had any neurological deficits. All participants were naïve to Braille reading. The protocol was approved by the ethical committee of Fukui Medical University and the National Institute for Physiological Sciences, Japan, and all subjects gave their written informed consent. Eight of the participants had taken part in previous studies that used identical tasks (Sadato et al., 2002).

Magnetic resonance imaging

A time-course series of 126 volumes was acquired using T2*-weighted, gradient echo, echo planar imaging (EPI) sequences with a 3.0 Tesla MR imager (Signa Horizon; General Electric, Milwaukee, WI). Each volume consisted of 36 slices, with a slice thickness of 3.5 mm and a 0.5 mm gap, which included the entire cerebral and cerebellar cortices. The timeinterval between two successive acquisitions of the same image was 3000 msec, and the echo time was 30 msec. The flip angle (FA) was 90 degrees. The field of view (FOV) was 22 cm. The in-plane matrix size was 64×64 pixels with a pixel dimension of 3.44×3.44 mm. Tight, but

comfortable, foam padding was placed around each subject's head to minimize head movement.

For anatomical reference, T2-weighted fast-spin echo images were obtained from each subject with location variables identical to those of the EPIs. In addition, high-resolution whole-brain MRIs were obtained with a conventional T2-weighted fast-spin echo sequence. A total of 112 transaxial images were obtained. The in-plane matrix size was 256×256 pixels, the slice thickness was 1.5 mm, and the pixel size was 0.859×0.859 mm.

Tactile tasks

We used the same passive Braille tactile tasks as those used by Sadato et al. (2002) (see Fig. 1).

Right hand

Passive Braille tactile discrimination task

A session consisted of six task and six rest periods, each 30 sec in duration, and alternating the task and rest periods. Braille stimuli were presented passively using a plastic rail on which different pairs of two-dot standard Braille characters (center-to-center distance, 5 mm) were printed. The rail was 1.7 m long. The rail was moved manually by an examiner from outside of the MRI gantry by a skid (1 m in length), which was fixed on the left side of the subject's body. The subject placed their right arm across their chest, rested their thumb and four fingers

at a fixed position on the skid, and placed their right index finger so that the finger pad rested on the rail (Sadato et al., 2002). The initial position of the rail was set so that the subject's right index finger was located between two consecutive pairs of Braille characters. The subject's left hand was placed on a button box connected to a microcomputer for recording the subject's response.

A pacemaking cue was projected onto a semitransparent screen hung approximately 1.5 m from the subject's eyes. For this, a liquid crystal display projector (ELP-7200L; Epson, Tokyo, Japan) was connected to a personal computer (Dynabook with Windows95; Toshiba, Tokyo, Japan), on which in-house software generated a visual cue (a small filled circle). To maintain eye position, the subject was requested to fixate on the cue circle throughout the session. For 18 sec before a session, a yellow cue was presented to allow the subject time to position both hands. Then, during the tactile discrimination task, red and green cues, each 3 sec in duration, were given alternately for 30 sec. When the red cue was on, the examiner slowly moved the rail to present passively a pair of two-dot Braille characters to the subject's finger pad. The rail was moved three times in 3 sec: 30 mm in the head-to-foot direction for 1 sec, 30 mm in the foot-to-head direction in the next second, and 30 mm again in the head-to-foot direction in the final second. The speed of presentation was approximately 30 mm/sec. The rail moved quietly without making any task-related sound. The examiner also confirmed that the subject did not move the right index finger for exploration. When the green cue was on, the rail

stopped moving, and the subject responded by pushing a button with their left index finger if the pair of characters was the same, or with their middle finger if the characters were different. Reaction times were not measured. A 30 sec rest condition followed, in which red and green cues were given alternately, as in the task condition. When the red cue was on, no tactile stimulus was presented. When the green cue was on, the subject pushed buttons with their left index and middle finger alternately. The comparison of neuroimages collected during the discrimination task versus those during rest periods thus allowed the correction for the effects of the cue and response movements.

Passive Braille tactile nondiscrimination task

In the tactile nondiscrimination task, which was used to control for sensorimotor effects, six-dot (instead of two-dot) Braille characters were presented when the red cue was given. When the green cue was on, the subject pushed buttons with the left index and middle finger alternately. The other variables were identical to those in the Braille tactile discrimination task.

Left hand

The aforementioned tasks also were performed with the left hand.

The order of the conditions was counterbalanced within the group. Before scanning, outside of the MRI room, the subjects sufficiently practiced the tactile discrimination task using different sets of two-dot Braille characters than those used in each task.

Data analysis

The first six volumes of each fMRI session were discarded due to unsteady magnetization, and the remaining 120 volumes per session (480 volumes per subject) were used for analysis. The data were analyzed using statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Sherborn, MA) (Friston et al., 1994, 1995a,b). After realignment, all images were coregistered to the high-resolution three-dimensional (3D) T2-weighted MRI with use of the anatomical MRI with T2-weighted spin-echo sequences from identical locations to the fMRI images. The parameters for affine and nonlinear transformation into a template of T2-weighted images that was already fit for a standard stereotaxic space (Montreal Neurological Institute template) (Evans et al., 1994) were estimated based on the high-resolution 3D T2-weighted MRI using least-squares means (Friston et al., 1995a). The parameters were applied to the coregistered fMRI data. The anatomically normalized fMRI data were filtered using a Gaussian kernel of 10 mm (full width at half maximum) in the x , y and z axes.

Statistical analysis

Statistical analysis was conducted at two levels. First, individual task-related activation was evaluated. Second, to make inferences at a population level, individual data were summarized and incorporated into a random effect model (Friston et al., 1999).

Individual analysis

The signal was scaled proportionally by setting the whole-brain mean value to 100 arbitrary units. The signal time course of each subject, with 480 time points, was modeled with four boxcar functions convolved with a hemodynamic response function, high-pass filtering (120 sec), and session effects. To test hypotheses about regionally specific condition effects, the estimates for each condition were compared by means of the linear contrasts shown in Table 1. The resulting set of voxel values for each comparison constituted a statistical parametric map (SPM) of the t statistic [SPM $\{t\}$]. The threshold for the SPM $\{t\}$ was set at a false-discovery rate (FDR) of $p < 0.01$ (Genovese et al., 2002). FDR is the proportion of false positives (incorrect rejections of the null hypothesis) among multiple voxel-wise tests for which the null hypothesis is rejected, and hence the procedure controls the family-wise error rate (Genovese et al., 2002). The activation foci depicted by this height threshold were then tested by their spatial extent, based on the theory of Gaussian random field considering clusters as “rare events” that occur in a whole brain according to the Poisson’s distribution (Friston et al.

1996). Statistical threshold for the spatial extent test was set at $p < .05$ (Friston et al., 1996).

When evaluating the neural substrates of the tactile discrimination processes, we controlled for nonspecific somatosensory processes (D-N), hand effect [right(R) versus left(L)], and hemispheric effects. To evaluate the effects of hand use, comparison of (R-L)(D-N) (Table 1) were performed within the areas activated during the right-handed (D-N) condition ($p < 0.05$; spatial extent test). The threshold for the SPM{t} was set at an FDR of $p < 0.01$ for clusters larger than 40 voxels (Genovese et al., 2002). We omitted the spatial extent test (Friston et al. 1996) because the spatial extent test is valid only for large search regions (Worsley et al. 1996).

Group analysis with random-effect model

The weighted sum of the parameter estimates in the individual analysis constituted “contrast” images, which were used for the group analysis (Friston et al., 1999). The contrast images obtained by individual analyses represent the normalized task-related increment of the MR signal of each subject [i.e., the discrimination task vs rest period (D), the nondiscrimination task vs rest period (N), and the discrimination vs nondiscrimination tasks (D-N)]. A total of 19 subjects with three contrasts (discrimination, nondiscrimination and discrimination-nondiscrimination) each for the right- and left-hand conditions were used for analysis. The resulting set of voxel values for each contrast constituted an SPM{t}. The

SPM $\{t\}$ was transformed to normal distribution units [SPM $\{Z\}$]. The threshold for the SPM $\{t\}$ was set at an FDR of $p < 0.01$ (Genovese et al., 2002). Statistical threshold for the spatial extent test on the clusters was set at $p < 0.05$ (Friston et al., 1996), as in the individual analysis.

To evaluate the effects of hand use, contrast images of the (D-N) (one image per subject) for the right-hand condition [R(D-N)] (Table 1) were compared with those for the left-hand condition [L(D-N)] (Table 1). We did this in a pairwise manner fashion within the areas activated during the right-handed (D-N) condition ($P < 0.05$, spatial extent test). To evaluate the hemisphere effects on tactile discrimination, contrast images of (L+R)(D-N) (Table 1) were flipped in the horizontal (right-left) direction. Asymmetric involvement of the neural substrates for the discrimination task, regardless of the hand used, was shown by the comparison between unflipped and flipped groups in a pair-wise manner. The test was performed within the regions that showed activation during this task when either hand was used. The threshold for the SPM $\{t\}$ was set at an FDR of $p < 0.01$ for clusters larger than 40 voxels (Genovese et al., 2002).

RESULTS

Task performance

The passive tactile discrimination tasks were performed equally well by the subjects when using either the right hand or the left hand. Right-handed accuracy was 67.4 ± 7.6 %, and left-handed accuracy was 64.0 ± 12.5 %, with no significant difference between these scores ($N = 19$, $P = 0.24$, paired t-test).

Group analysis with random-effect model

Nondiscrimination

The passive nondiscrimination tasks activated the contralateral primary sensory motor area (SM1) and the dorsal portion of the lateral premotor area, the bilateral secondary somatosensory area (SII) extending to the postcentral gyrus (GPoC), the anterior intraparietal sulcus (IPA), the ipsilateral superior parietal lobule (LPs), and the cerebellum, regardless of the hand used (Fig. 1, Table 2). The supplementary motor area (SMA) was active with right-handed passive tactile stimulation, but this was not true when the left hand was used. The activation in the dorsal portion of the premotor cortex was designated as dorsal premotor cortex (PMd) according to the criteria of Rizzolatti et al. (2002) (Talairach's z-coordinate, > 50 mm).

Discrimination

The passive discrimination task activated bilateral SM1 and PMd extending to the SMA, SII extending to the GPoC, IPA extending to the posterior intraparietal sulcus (IPP), the frontal cortices, and the ipsilateral cerebellum, regardless of the hand used (Fig. 1, Table 3). The contralateral cerebellum was activated during right-handed processing.

Discrimination-nondiscrimination (D-N)

When the discrimination condition was contrasted with the nondiscrimination (D-N) task, with the exception of SMI and SII, the following areas that were activated by the nondiscrimination task showed increased activation regardless of the hand used: the bilateral IPA, cerebellum, and SMA (Figs. 2, 3). With the right hand, the PMd was activated bilaterally, whereas with the left hand, its task-related activity was right lateralized. In addition to the tactile-related areas defined by the nondiscrimination task, discrimination tasks activated bilateral prefrontal cortices regardless of the hand used, and the IPP was activated bilaterally with the right hand, whereas the right IPP was active when the left hand was used (Table 4).

Hemisphere effect

Right-lateralized activities were found in the IPP, rostral PMd, dorsolateral prefrontal cortex, anterior insula, and pre-SMA (Fig. 4). These areas showed consistent right-lateralized

activation during performance of the task with both the right and left hands. Left-lateralized activity was found in the rostral PMd.

Hand effect

Direct comparison between the task-related activation depicted by the D-N contrast with the right hand with that of the left hand showed more prominent activation in the left precentral gyrus, corresponding to the caudal PMd (Fig. 5). Reverse contrast did not show any significant activation. This hand effect was observed consistently in individual analyses. Three representative subjects are shown in Figure 6. There was no significant activation for the reverse contrast [i.e., L(D-N)-R(D-N)].

DISCUSSION

Nondiscrimination condition

Activation of the SM1, SII, PMd, SMA and cerebellum by passive tactile stimulation suggests that the cortical motor networks participate in somatosensory processing (Romo and Salinas, 2001). In the task epoch, the subjects were asked to respond to tactile stimuli by making a button press. In the rest epoch, the subjects pushed the button without tactile stimuli. Hence, the former contains a sensorimotor link that might account for the PMd and SMA activity.

D-N condition

IPA activation with absent SII activation during shape discrimination

This study showed that the passive nondiscriminatory tactile task activated SII, with no additional activation during the discriminatory task. However, the IPA bilaterally showed more activation during passive tactile discrimination compared with the nondiscrimination condition (Fig. 3). This is consistent with the findings of Roland et al. (1998) that roughness discrimination activated SII significantly more than length or shape discrimination. Conversely, shape and length discrimination activated the same cortical area lining the IPA more than roughness discrimination. They suggested that there are different cortical processing streams for somatosensory submodalities, such as microgeometry (texture) and macrogeometry (shape and length).

Cerebellum

The anterior lobe of the cerebellum showed more activation during the discrimination task than during the nondiscrimination task. Because this was observed during passive conditions, the cerebellar activation might be related to the nonmotor cognitive process of shape discrimination. Cognitive tasks are known to activate cerebellar structures (Petersen et al., 1988; Kim et al., 1994; Raichle et al., 1994; Fiez et al., 1996; Gao et al., 1996; Cabeza and Nyberg, 2000; Liu et al., 2000).

Hemisphere effect

This study revealed right-lateralized activation of the parietal, prefrontal and dorsal premotor cortices regardless of the hand performing the task.

Posterior intraparietal sulcus

We found right-lateralized activation in the IPP during tactile discrimination. The posterior parietal cortex [Brodmann area (BA) 7/40], particularly the intraparietal sulcus, consists of multiple subdivisions, each of which is involved in particular aspects of visual or somatosensory information processing. The posterior parietal cortex and BA 6 are connected in a specific pattern, forming several frontoparietal circuits (Rizzolatti et al., 1998; Geyer et al., 2000). These two cortical areas function in concert during cognitive operations, motor

control (Deiber et al., 1997) and voluntary attentional control (Hopfinger et al., 2000).

Dorsal premotor cortex (PMd)

The PMd is the dorsolateral subdivision of BA 6, which is defined as the agranular frontal cortex situated between the primary motor cortex (M1) and the prefrontal cortex. In stereotactic space, the boundary of the PMd and ventral premotor cortex (PMv) is said to be at $Z = +50$ (Rizzolatti et al., 2002). At the level of the hand, M1 is located around $Z = 50$; hence, the convolution of the precentral gyrus corresponds mostly to the caudal PMd (PMdc), because the representation of the hand in M1 is located in the central sulcus (Yousry et al., 1997). The rostral PMd (PMdr) is probably located anterior to the superior precentral sulcus (Rizzolatti et al., 1998). In addition, the vertical anterior-commissural plane was used as a landmark of the border between the PMdc and PMdr (Deiber et al., 1991). There might be functional segregation within PMd in a rostrocaudal direction in primates (Geyer et al., 2000). The PMdc is more closely related to motor execution, whereas the PMdr is involved more with the sensory components of motor tasks (Weinrich and Wise, 1982; Johnson et al., 1996; Shen and Alexander, 1997; Hanakawa et al., 2002). The PMd receives input from the somatosensory areas in the parietal cortex. Non-human primate studies showed that the PMdc receives input from area 5 in the dorsal bank of the intraparietal sulcus (Chavis and Pandya, 1976) and the caudal part of area 7. In contrast, PMdr receives inputs from areas 7m, 7ip and

the superior temporal sulcus (Kurata, 1991). Furthermore, the PMdr receives projections from the prefrontal cortex, which receives projections from the inferior parietal area 7a (Barbas and Pandya, 1987; Tanne et al., 1995), forming the parietal-prefrontal-premotor networks. These inputs presumably represent the sensory aspects of the set-related activity observed in the PMd, and are more dominant in the PMdr than PMdc (Tanne et al., 1995). Furthermore, recent functional neuroimaging studies indicate that the PMd might have nonmotor cognitive functions (Jonides et al., 1993; Deiber et al., 1998; Hanakawa et al., 2002, 2003).

Right lateralization

A previous PET study (Sadato et al., 1998) revealed that blind subjects showed activation of the right dorsal premotor cortex and the right prefrontal cortex during tactile discrimination tasks, regardless of the finger used for reading. O'Sullivan et al. (1994) suggested that the right PMd is involved in length discrimination, probably through the close interplay between sensory and motor regions during active touch. Gitelman et al. (1996) has shown that exploratory tasks with the right hand activate the right cingulate, dorsal premotor and posterior parietal areas; they attributed this to the spatial-attention requirements of the task. Because the right dorsal premotor, posterior parietal, and prefrontal cortices are related to visuospatial working memory (Jonides et al., 1993), they are components of a functional network for modality-independent extrapersonal spatial attention, which might be required for

exploratory finger movements. This study, however, revealed that without active exploratory movement, tactile discrimination activated the right-dominant parietal-premotor-prefrontal networks, regardless of the hand used to perform the task. This is consistent with a previous study showing that the right parietal-premotor-prefrontal network was activated by passive tactile discrimination performed with the right hand (Bodegard et al., 2001). Gitelman et al. (1999) showed that the right premotor and posterior parietal areas are specialized for spatial attention with stringent controls for response-related motor activity, motor inhibition, eye movements, and working memory. Hence, the right-lateralized neural substrates for spatial attention might contribute to the right-hemisphere dominance found during the tactile shape discrimination task.

Hand effects

This study revealed that the hand that performed the task influenced activity in the left PMdc only: this activation during use of the right hand was left lateralized and there was no activation while the left hand was used (Fig. 5). During nondiscrimination condition PMdc revealed the activation by the contralateral hand but not by the ipsilateral hand (Fig. 2), and hence the differential left-right hand effect occurs during the discrimination task. This activation pattern is unlikely to be related to movement control. First, the tactile stimuli were presented passively in both the discrimination and control conditions, eliminating any

exploratory movements of the stimulated fingers. Second, the responses by the hand contralateral to the stimulated side during the tactile discrimination task were controlled for by the nondiscrimination condition in which the subjects were required to alternate finger movements. It should be noted that the tactile discrimination task required that the button press was based on the tactile stimuli. This is conditional motor behavior guided by sensory cues, which is not included in the control condition. Both the PMdr and PMdc are important in conditional motor behavior guided by symbolic cues (Petrides, 1986; Passingham, 1988; Wise and Murray, 2000). This might represent an interface between the output of the sensory categorization process and the motor command used to indicate the movement choice (Romo and Salinas, 2001). However, asymmetric left PMdc activation cannot be explained by the conditional motor behavior as guided by tactile cues, because the button press was performed by the left hand during right-hand discrimination. If the PMdc activation were attributable to conditional motor behavior, it should have appeared in the PMdc ipsilateral to the stimulated hand. Hence, asymmetric left PMdc activation might represent nonmotor processing. Considering these anatomical and functional connections, the activation of the left PMdc only by right-handed discrimination may represent the output of the sensory categorization process; this might be part of the parieto-premotor networks in the left hemisphere that are driven by tactile information from the right hand.

Several lines of evidence suggest that the PMd is involved in the inter-hemispheric interaction.

The PMd has dense corticocortical connections with the SMA (Kurata, 1991), which, in turn, has dense and widespread transcortical connections with the contralateral SMA and the premotor cortex (Rouiller et al., 1994). The PMd is related to the interhemispheric interaction seen during the performance of bimanual coordinated movements (Sadato et al., 1997; Kermadi et al., 2000; Immisch et al., 2001; Gerloff and Andres, 2002). Certainly, this does not mean that the PMdc is the only area involved in the interhemispheric interaction during tactile tasks. Tactile information is represented bilaterally in the postcentral gyrus and its posterior extension (Iwamura, 1998). Partial callosotomy sparing the splenium of the corpus callosum did not induce right-hemisphere superiority, whereas complete callosotomy did (Kumar, 1977), suggesting that interhemispheric interaction occurs at the level of the parietal cortex. Hence, the increased activity of the left PMdc during right-hand discrimination might represent the additional workload necessary for the parieto-premotor network on the left to access the right-lateralized neural resources for spatial attention.

REFERENCES

Barbas H, Pandya DN (1987) Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. *J Comp Neurol* 256:211-228.

Bodegard A, Geyer S, Grefkes C, Zilles K, Roland PE (2001) Hierarchical processing of tactile shape in the human brain. *Neuron* 31:317-328.

Cabeza R, Nyberg L (2000) Imaging cognition. II. An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 12:1-47.

Carmon A, Benton AL (1969) Tactile perception of direction and number in patients with unilateral cerebral disease. *Neurology* 19:525-532.

Chavis DA, Pandya DN (1976) Further observations on corticofrontal connections in the rhesus monkey. *Brain Res* 117:369-386.

Deiber M-P, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RSJ (1991) Cortical areas and the selection of movement: a study with positron emission tomography. *Exp Brain Res* 84:393-402.

Deiber MP, Wise SP, Honda M, Catalan MJ, Grafman J, Hallett M (1997) Frontal and parietal networks for conditional motor learning: a positron emission tomography study. *J Neurophysiol* 78:977-991.

Deiber MP, Ibanez V, Honda M, Sadato N, Raman R, Hallett M (1998) Cerebral processes related to visuomotor imagery and generation of simple finger movements studied with positron emission tomography. *Neuroimage* 7:73-85.

Dodds AG (1978) Hemispheric differences in tactuo-spatial processing. *Neuropsychologia* 16:247-254.

Evans AC, Kamber M, Collins DL, MacDonald D (1994) An MRI-based probabilistic atlas of neuroanatomy. In: *Magnetic resonance scanning and epilepsy* (Shorvon SD, ed), pp 263-274. New York: Plenum Press.

Fiez JA, Raife EA, Balota DA, Schwarz JP, Raichle ME, Petersen SE (1996) A positron emission tomography study of the short-term maintenance of verbal information. *J Neurosci* 16:808-822.

Fontenot DJ, Benton AL (1971) Tactile perception of direction in relation to hemispheric locus of lesion. *Neuropsychologia* 9:83-88.

Friston KJ, Jezzard P, Turner R (1994) Analysis of functional MRI time-series. *Hum Brain Mapp* 1:153-171.

Friston KJ, Ashburner J, Frith CD, Heather JD, Frackowiak RSJ (1995a) Spatial registration and normalization of images. *Hum Brain Mapp* 2:165-189.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ (1995b) Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp* 2:189-210.

Friston KJ, Holmes A, Poline J-B, Price CJ, Frith CD (1996) Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage* 4:223-235.

Friston KJ, Holmes AP, Worsley KJ (1999) How many subjects constitute a study? *Neuroimage* 10:1-5.

Gao J-H, Parsons LM, Bower JM, Xiong J, Li J, Fox PT (1996) Cerebellum implicated in sensory acquisition and discrimination rather than motor control. *Science* 272:545-547.

Genovese CR, Lazar NA, Nichols T (2002) Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 15:870-878.

Gerloff C, Andres FG (2002) Bimanual coordination and interhemispheric interaction. *Acta Psychol (Amst)* 110:161-186.

Geyer S, Matelli M, Luppino G, Zilles K (2000) Functional neuroanatomy of the primate isocortical motor system. *Anat Embryol (Berl)* 202:443-474.

Gitelman DR, Alpert NM, Kosslyn S, Daffner K, Scinto L, Thompson W, Mesulam M-M (1996) Functional imaging of human right hemispheric activation for exploratory movements. *Ann Neurol* 39:174-179.

Gitelman DR, Nobre AC, Parrish TB, LaBar KS, Kim YH, Meyer JR, Mesulam M (1999) A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. *Brain* 122:1093-1106.

Hanakawa T, Honda M, Sawamoto N, Okada T, Yonekura Y, Fukuyama H, Shibasaki H (2002) The role of rostral Brodmann area 6 in mental-operation tasks: an integrative neuroimaging approach. *Cereb Cortex* 12:1157-1170.

Hanakawa T, Honda M, Okada T, Fukuyama H, Shibasaki H (2003) Differential activity in the premotor cortex subdivisions in humans during mental calculation and verbal rehearsal tasks: a functional magnetic resonance imaging study. *Neurosci Lett* 347:199-201.

Hopfinger JB, Buonocore MH, Mangun GR (2000) The neural mechanisms of top-down attentional control. *Nat Neurosci* 3:284-291.

Immisch I, Waldvogel D, van Gelderen P, Hallett M (2001) The role of the medial wall and its anatomical variations for bimanual antiphase and in-phase movements. *Neuroimage* 14:674-684.

Iwamura Y (1998) Hierarchical somatosensory processing. *Curr Opin Neurobiol* 8:522-528.

Johnson PB, Ferraina S, Bianchi L, Caminiti R (1996) Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. *Cereb*

Cortex 6:102-119.

Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun MA (1993) Spatial working memory in humans as revealed by PET [see comments]. *Nature* 363:623-625.

Kermadi I, Liu Y, Rouiller EM (2000) Do bimanual motor actions involve the dorsal premotor (PMd), cingulate (CMA) and posterior parietal (PPC) cortices? Comparison with primary and supplementary motor cortical areas. *Somatosens Mot Res* 17:255-271.

Kim SG, Ugurbil K, Strick PL (1994) Activation of a cerebellar output nucleus during cognitive processing. *Science* 265:949-951.

Kumar S (1977) Short term memory for a nonverbal tactual task after cerebral commissurotomy. *Cortex* 13:55-61.

Kurata K (1991) Corticocortical inputs to the dorsal and ventral aspects of the premotor cortex of macaque monkeys. *Neurosci Res* 12:263-280.

Liu Y, Pu Y, Gao J-H, Parsons L, Xiong J, Liotti M, Bower JM, Fox PT (2000) The human red nucleus and lateral cerebellum in supporting roles for sensory information processing. *Hum Brain Mapp* 10:147-159.

Milner B, Taylor L (1972) Right-hemisphere superiority in tactile pattern-recognition after cerebral commissurotomy: evidence for nonverbal memory. *Neuropsychologia* 10:1-15.

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97-113.

O'Sullivan BT, Roland PE, Kawashima R (1994) A PET study of somatosensory discrimination in man: microgeometry versus macrogeometry. *Eur J Neurosci* 6:137-148.

Passingham RE (1988) Premotor cortex and preparation for movement. *Exp Brain Res* 70:590-596.

Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME (1988) Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 331:585-589.

Petrides M (1986) The effect of periarculate lesions in the monkey on the performance of symmetrically and asymmetrically reinforced visual and auditory go, no-go tasks. *J Neurosci* 6:2054-2063.

Raichle ME, Fiez JA, Videen TO, MacLeod A-MK, Pardo JV, Fox PT, Petersen SE (1994) Practice-related changes in human brain functional anatomy during nonmotor learning. *Cereb Cortex* 4:8-26.

Rizzolatti G, Luppino G, Matelli M (1998) The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol* 106:283-296.

Rizzolatti G, Fogassi L, Gallese V (2002) Motor and cognitive functions of the ventral premotor cortex. *Curr Opin Neurobiol* 12:149-154.

Roland PE, O'Sullivan B, Kawashima R (1998) Shape and roughness activate different somatosensory areas in the human brain. *Proc Natl Acad Sci USA* 95:3295-3300.

Romo R, Salinas E (2001) Touch and go: decision-making mechanisms in somatosensation. *Ann Rev Neurosci* 24:107-137.

Rouiller EM, Balalian A, Kazennikov O, Moret V, Yu X-H, Wiesendanger M (1994)

Transcallosal connections of the distal forelimb representation of the primary and supplementary motor cortical areas in macaque monkeys. *Exp Brain Res* 102:227-243.

Sadato N, Yonekura Y, Waki A, Yamada H, Ishii Y (1997) Role of the supplementary motor area and the right premotor cortex in coordination of bimanual movements. *J Neurosci* 17:9667-9674.

Sadato N, Pascual-Leone A, Grafman J, Deiber MP, Ibanez V, Hallett M (1998) Neural networks for Braille reading by the blind. *Brain* 121:1213-1229.

Sadato N, Okada T, Honda M, Yonekura Y (2002) Critical period for cross-modal plasticity in blind humans: a functional MRI study. *Neuroimage* 16:389-400.

Shen L, Alexander GE (1997) Preferential representation of instructed target location versus limb trajectory in dorsal premotor area. *J Neurophysiol* 77:1195-1212.

Tanne J, Boussaoud D, Noelle B-Z, Rouiller EM (1995) Direct visual pathways for reaching movements in the macaque monkey. *Neuroreport* 7:267-272.

Weinrich M, Wise SP (1982) The premotor cortex of the monkey. *J Neurosci* 2:1329-1345.

Wise SP, Murray EA (2000) Arbitrary associations between antecedents and actions. *Trends Neurosci* 23:271-276.

Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996) A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping* 4:58-73.

Yousry T, Schmid U, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P (1997) Localization of the motor hand area to a knob on the precentral gyrus: a new landmark. *Brain* 120:141-157.

Zaidel D, Sperry RW (1973) Performance on the Raven's colored progressive matrices test by subjects with cerebral commissurotomy. *Cortex* 9:34-39.

Table 1. Predefined Contrasts.

Name of Contrasts	Conditions			
	Left hand		Right hand	
	Disc.	Non-disc.	Disc.	Non-disc.
LD	1	0	0	0
LN	0	1	0	0
RD	0	0	1	0
RN	0	0	0	1
L (D-N)	1	-1	0	0
R (D-N)	0	0	1	-1
(R-L)(D-N)	-1	1	1	-1
(R+L)(D-N)	1	-1	1	-1

Disc, Discrimination; Non-disc, nondiscrimination.

Table 2

Nondiscrimination task-rest							
Cluster level		x	y	z	Z value	Location	
<i>P</i> *	Size	(mm)	(mm)	(mm)		Side	Area
<i>Right hand</i>							
< 0.001	6444	-58	-16	36	6.29	Left	SMI
		-36	-38	50	6.22	Left	IPA
		-44	-20	52	6.12	Left	SM1
		-48	-24	20	6	Left	SII
		-44	-28	40	5.37	Left	GPoC
		-20	-10	56	4.95	Left	PMd
		0	-2	56	4.13		SMA
< 0.001	2355	68	-16	22	6	Right	GPoC
		54	-22	24	5.9	Right	SII
		34	-36	46	4.5	Right	IPA
		24	-48	64	3.32	Right	LPs
0.001	740	30	-50	-24	4.95	Right	Cerebellum
		18	-68	-20	4.97	Right	Cerebellum
<i>Left hand</i>							
< 0.001	5484	56	-10	44	6.41	Right	GPrC
		56	-10	15	5.44	Right	SII
		34	-36	56	5.13	Right	IPA
		40	-32	56	5.12	Right	GPoC
		40	-6	60	4.84	Right	PMd
		26	-30	70	4.25	Right	SMI
< 0.001	2990	36	-52	60	3.82	Right	LPs
		-62	-26	22	5.14	Left	GPoC
		-50	-26	18	5.11	Left	SII
		-56	-18	34	4.7	Left	GPoC
		-36	-52	56	4.54	Left	LPs
		-34	-36	40	3.95	Left	IPA
0.006	572	-22	-66	-22	5.03	Left	Cerebellum

Abbreviations: IPA, anterior portion of the intraparietal sulcus; DLPFC, dorsolateral prefrontal cortex; GPoC, postcentral gyrus; GPrC, precentral gyrus; IFG, inferior frontal gyrus; LPi, inferior parietal lobule; LPs, superior parietal lobule; MFG, middle frontal gyrus; IPP, posterior portion of the intraparietal sulcus; PMd, dorsal premotor area; SII, secondary somatosensory area; SMI, primary sensorimotor area; SMA, supplementary motor area. Coordinates are given in the x, y, and z dimensions in Talairach space. All *P* values are corrected for multiple comparisons at cluster level.

Table 3

Discrimination task-rest							
Cluster level		x	y	z	Z value	Location	
<i>P</i> *	Size	(mm)	(mm)	(mm)		Side	Area
<i>Right hand</i>							
< 0.001	10505	-46	-20	48	7.08	Left	SM1
		-58	-18	34	6.73	Left	SM1
		-20	-8	72	6.36	Left	PMd
		-34	-40	58	5.87	Left	IPA
		-62	-30	26	5.71	Left	LPi
		-48	-22	22	5.93	Left	SII
		0	10	50	5.43		SMA
< 0.001	4769	30	-2	56	4.66	Right	PMd
		-18	-60	56	4.65	Left	IPP
		60	-12	36	6.64	Right	SMI
		68	-12	24	6.15	Right	GPoC
		36	-34	42	5.82	Right	IPA
		36	-52	60	5.04	Right	LPs
		54	-22	22	4.98	Right	SII
0.002	940	-50	8	30	6.23	Left	DLPFC
< 0.001	1732	26	-54	-20	6.17	Right	Cerebellum
		-16	-70	-26	3.5	Left	Cerebellum
< 0.001	3300	46	52	10	5.08	Right	MFG
		36	24	2	4.92	Right	IFG
		54	18	30	4.87	Right	DLPFC
0.008	672	-8	-18	12	4.19	Left	Thalamus
<i>Left hand</i>							
< 0.001	10846	64	-12	22	6.42	Right	GPoC
		60	-12	20	6.19	Right	SII
		60	-14	34	6.11	Right	SM1
		36	-4	58	5.98	Right	PMd
		50	-18	46	5.75	Right	SM1
		4	6	58	5.74	Right	SMA
		38	-34	44	5.61	Right	GPoC
		36	-54	58	5.19	Right	IPA
		-26	-6	58	4.93	Left	PMd

		24	-62	54	4.15	Right	IPP
< 0.001	3290	-56	-18	34	6.33	Left	SMI
		-38	-44	54	5.56	Left	IPA
		-30	-60	54	3.94	Left	IPP
< 0.001	3727	56	18	8	5.86	Right	IFG
		54	18	28	6	Right	DLPFC
		36	42	22	4.82	Right	MEG
< 0.001	1431	-18	-64	-26	5.19	Left	Cerebellum
< 0.001	1873	-52	10	28	5.03	Left	DLPFC
		-52	-22	20	4.69	Left	SII
		-40	42	10	4.68	Left	MFG
		-30	24	4	4.56	Left	Insula
		-32	30	14	4.45	Left	IFG
0.004	799	16	-16	8	4.48	Right	Thalamus

Abbreviations: IPA, anterior portion of the intraparietal sulcus; DLPFC, dorsolateral prefrontal cortex; GPoC, postcentral gyrus; GPrC, precentral gyrus; IFG, inferior frontal gyrus; LPi, inferior parietal lobule; LPs, superior parietal lobule; MFG, middle frontal gyrus; IPP, posterior portion of the intraparietal sulcus; PMd, dorsal premotor area; SII, secondary somatosensory area; SMI, primary sensorimotor area; SMA, supplementary motor area. Coordinates are given in the x, y, and z dimensions in Talairach space. All *P* values are corrected for multiple comparisons at cluster level.

Table 4

Discrimination task-nondiscrimination task							
Cluster level		x	y	z	Z value	Location	
<i>P</i> *	Size	(mm)	(mm)	(mm)		Side	Area
<i>Right hand</i>							
< 0.001	3501	62	-14	40	5.48	Right	GPrC
		42	-28	58	5.39	Right	GPrC
		34	-38	56	5.15	Right	IPA
		24	-62	44	3.87	Right	IPP
< 0.001	7322	-54	-24	38	5.47	Left	LPi
		6	8	56	5.36	Left	SMA
		-22	-12	56	4.7	Left	PMd
		-40	-20	46	4.63	Left	GPoC
		-32	-44	54	4.44	Left	IPA
		-24	-58	58	3.9	Left	IPP
< 0.001	1472	-46	8	28	5.39	Left	DLPFC
		-34	18	10	4.83	Left	Insula
< 0.001	6561	48	42	20	5.11	Right	MFG
		50	16	30	4.93	Right	DLPFC
		36	-2	54	4.48	Right	PMd
< 0.001	1483	22	-60	-24	5.13	Right	Cerebellum
		2	-76	-32	3.26	Left	Cerebellum
<i>Left hand</i>							
0.001	573	38	-4	60	5.32	Right	PMd
< 0.001	1132	56	18	30	4.78	Right	DLPFC
		46	22	-2	4.57	Right	IFG
		46	30	26	3.86	Right	MFG
0.022	247	-36	40	14	4.77	Left	IFG
< 0.001	755	-26	-72	-24	4.72	Left	Cerebellum
		24	-62	-24	4.53	Right	Cerebellum
		-4	-70	-16	3.81	Left	Cerebellum
< 0.001	809	34	-50	60	4.49	Right	LPs
		64	-12	30	3.98	Right	LPi
		36	-44	42	3.62	Right	IPA
		56	-20	48	3.6	Right	LPi
		24	-66	54	3.22	Right	IPP

< 0.001	656	4	2	56	4.04	Right	SMA
0.031	218	-54	-22	46	4	Left	LPI
		-36	-40	60	3.78	Left	IPA
		-44	-28	38	3.68	Left	LPI

Abbreviations: IPA, anterior portion of the intraparietal sulcus; DLPFC, dorsolateral prefrontal cortex; GPoC, postcentral gyrus; GPrC, precentral gyrus; IFG, inferior frontal gyrus; LPI, inferior parietal lobule; LPS, superior parietal lobule; MFG, middle frontal gyrus; IPP, posterior portion of the intraparietal sulcus; PMd, dorsal premotor area; SII, secondary somatosensory area; SM1, primary sensorimotor area; SMA, supplementary motor area. Coordinates are given in the x, y, and z dimensions in Talairach space. All *P* values are corrected for multiple comparisons at cluster level.

FIGURE LEGENDS

Figure 1.

Task design. During the discrimination task, pairs of two-dot standard Braille characters were presented passively to the index finger of one hand when the red cue was on. When the green cue was on, the subject responded by pushing a button with their other index finger (I) if the pairwise characters were the same, or with their middle finger (M) if the characters were different. During the rest condition, no tactile stimulus was presented. When the green cue was on, the subject pushed buttons with their left index and middle finger alternately. During the nondiscrimination session, pairs of six-dot standard Braille characters were presented, and no discrimination was requested.

Figure 2.

Statistical parametric maps of the average neural activity within the group during the discrimination task (left) and the nondiscrimination task (middle) compared with those during each rest period. D-N (right) is the subtraction of the images taken during the discrimination task compared with those taken during the nondiscrimination task. The top and bottom rows indicate activations during task performance with the left hand (LH) and the right hand (RH), respectively. The 3D information was collapsed into 2D sagittal, coronal and transverse images (i.e., maximum intensity projections viewed from the right, back and top of the brain).

Figure 3.

Statistical parametric map of the average neural activity within the group during the discrimination task compared with the activity during the nondiscrimination task (D-N). The activities while performing the task with the left (blue) and right (red) hands were superimposed on surface-rendered high-resolution MRIs unrelated to the subjects of the present study, viewed from the left and right. Bottom left, the averaged percent signal change of D-N in the bilateral IPA (+/-36, -40, 50). Lower right, the averaged percentage of signal changes in the bilateral SII (-50, -24, 20) and (56, -16, 20). Percentage of signal change was calculated individually within spherical volumes of interest with a diameter of 10 mm placed at the center of the volume. These data were presented as the mean \pm SEM of 19 subjects. Lt, left.

Figure 4.

Asymmetric neural representation of tactile discrimination by either hand. The contrast images of (D-N) were compared with those flipped in the horizontal (right-left) direction in a pairwise fashion (see Table 1). The test was performed within the areas that revealed activation by the (D-N) condition with either hand. The SPM was superimposed on a surface-rendered high-resolution MRI unrelated to the subjects of the present study, and is also shown in standard anatomical space (center). The 3D information was collapsed into 2D

sagittal, coronal and transverse images viewed from the right (top left), back (top middle) and top of the brain (middle row, left). The percentage of signal changes in DLPFC (+/-50, 26, 30) (bottom right), pre-SMA (+/-10, 22, 48) (middle row, right), IPP (+/-42, -48, 42) (bottom left), and PMdr (+/-32, 8, 52) (bottom middle) and (+/-20, -10, 56) (top right) were presented as the mean \pm SEM of 19 subjects.

Figure 5.

The SPM of the average neural activity in the (D-N) condition with the right hand compared with the left hand, within the activated areas in the (D-N) condition with the right hand. The focus of activation was superimposed on the transaxial plane ($Z = 48, 52, 56$ mm) of the T2-weighted high-resolution MRIs of the subjects who participated in this study. The T score is as indicated by the color bar; statistical significance increases as red proceeds to white. The arrowhead indicates the central sulcus with the inverted-omega shape that is a landmark of the hand area. The averaged percentage of signal change in the precentral gyrus (+/-32, -20, 52). The data were presented as the mean \pm SEM of 19 subjects. Tactile discrimination by the right hand activated the left precentral gyrus more prominently than discrimination by the left hand (*, $t = 5.98$, paired Student's t -test, $df = 18$). Its right counterpart was not active during tactile discrimination by either hand. There was significant hand by hemisphere interaction in this area (paired Student's t -test, $t = 5.4$, $df = 18$). Lt, left.

Figure 6.

Individual analysis of the hand effect on the passive tactile discrimination. The foci with more prominent activation during tactile discrimination with the right hand than with the left hand (left column), indicated by means of the comparison of (R-L)(D-N), were superimposed on the high resolution T2-weighted MRI of each individual. The arrowheads indicate the central sulcus. The activated foci are on the left precentral gyrus. The Talairach's coordinates of the area with maximum intensity change are shown. The task-related activation of the left PMdc (middle column) and the right PMdc (right column) during the task phase (shaded; 30 sec in duration) when compared with the following rest phase (nonshaded; 30 sec). The percentage of signal changes averaged across the six repeated task-rest periods of the discrimination session (blue line) and the nondiscrimination session (green line) were plotted. LH, left hand; RH, right hand; Lt, left.

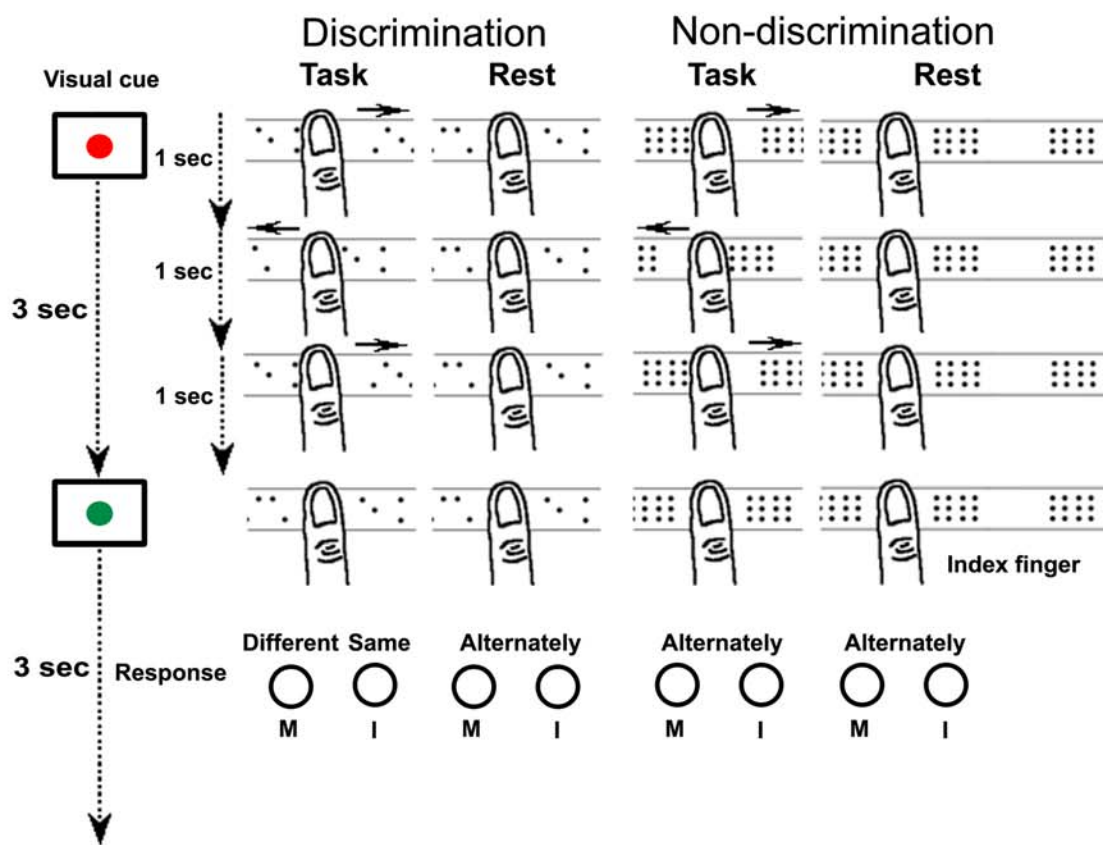


Fig. 1

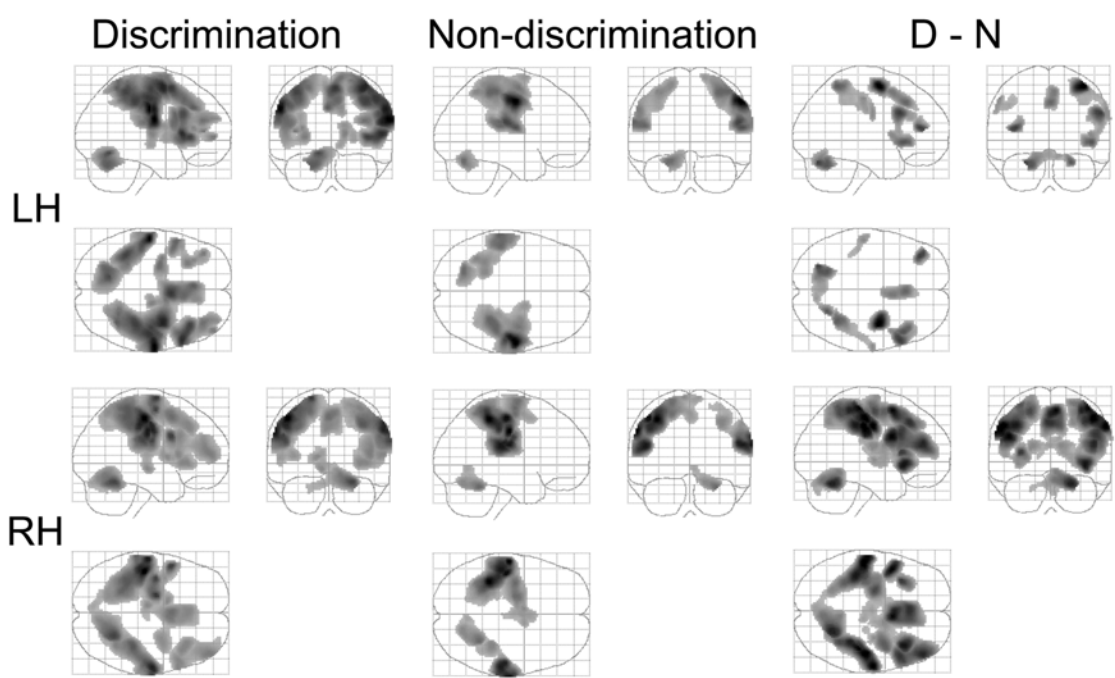


Fig. 2

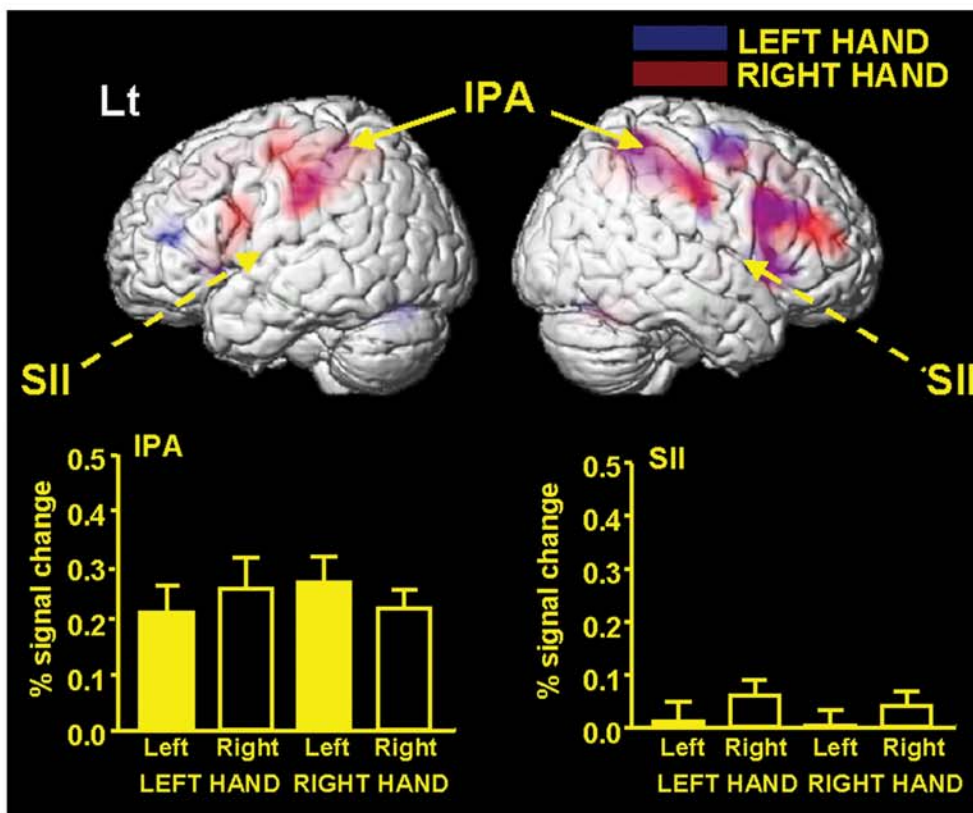


Fig. 3

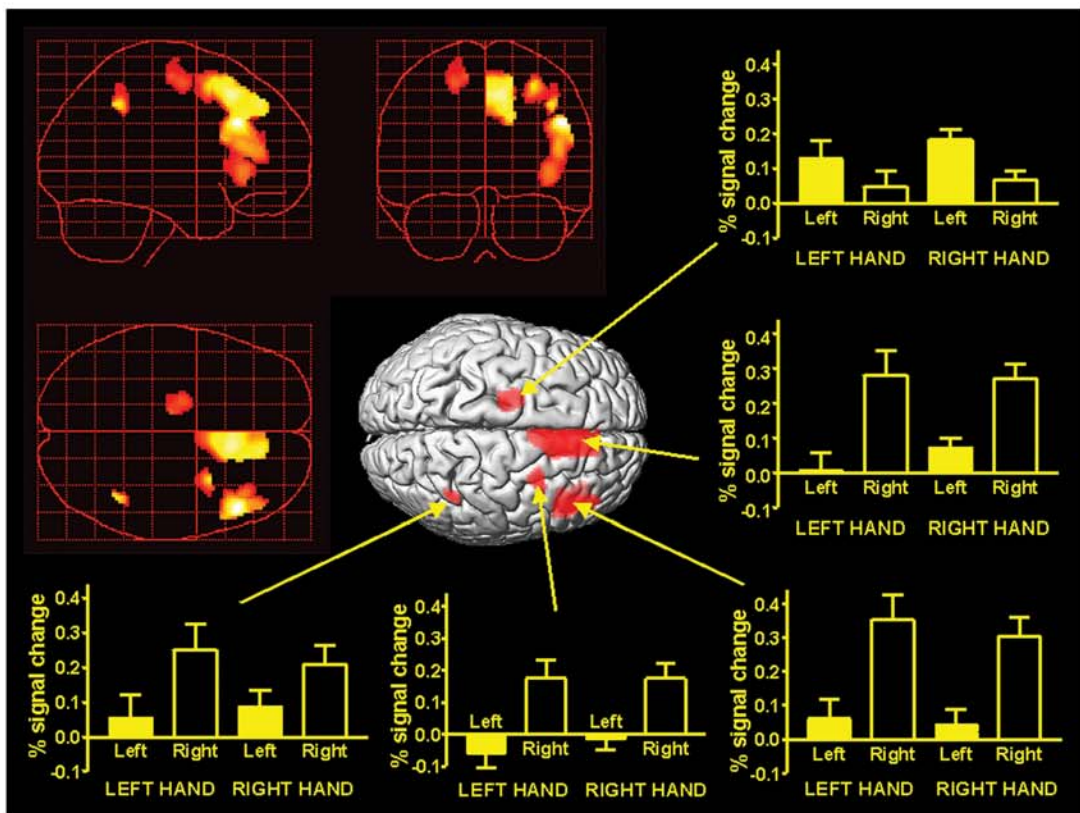


Fig. 4

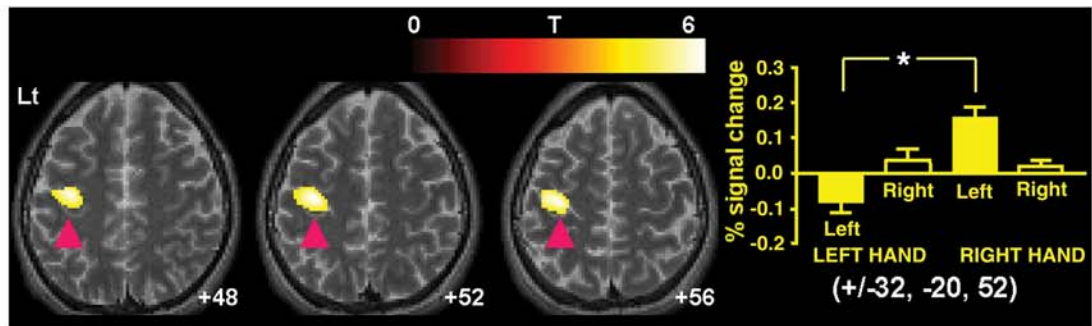


Fig. 5

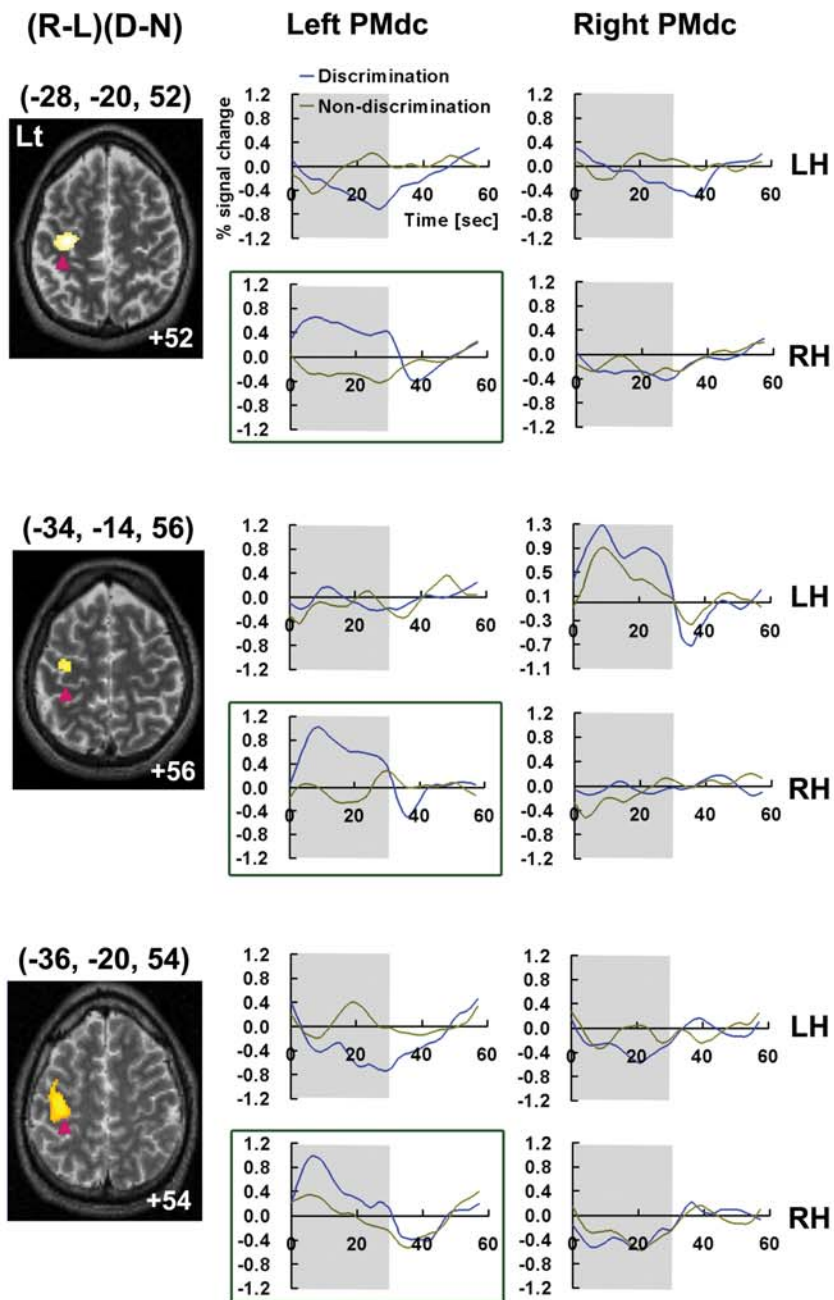


Fig. 6

ACKNOWLEDGEMENTS

This study was supported in part by Grant-in Aid for Scientific Research B#14380380 (NS) from Japan Society for the Promotion of Science, and Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology, the Japanese Government.