

Gender Difference in Premotor Activity during Active Tactile Discrimination

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Received August 3, 1999

To investigate possible gender differences in tactile discrimination tasks, we measured cerebral blood flow of seven men and seven women using positron emission tomography and ^{15}O water during tactile tasks performed with the right index finger. A nondiscrimination, somatosensory control task activated the left primary sensorimotor cortex and the left parietal operculum extending to the posterior insula without any gender difference. Compared with the control task, discrimination tasks activated the superior and inferior parietal lobules bilaterally, right dorsal pre-motor cortex, and dorsolateral prefrontal cortex in both genders, consistent with the notion of right hemisphere involvement during exploratory attentional movements. In both genders, symmetric activation of the superior and inferior parietal lobules and asymmetric activation of the right dorsolateral prefrontal cortex were confirmed. The former is consistent with the spatial representation of the tactile input and the latter with the spatial working memory. However, activation of the dorsal pre-motor cortex was asymmetric in men, whereas it was symmetric in women, the gender difference being statistically significant. This may suggest gender differences in motor programs for exploration in manipulospatial tasks such as tactile discrimination with active touch, possibly by greater interhemispheric interaction through the dorsal pre-motor cortices in women than in men. © 2000 Academic Press

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INTRODUCTION

Sexual dimorphism in the human brain could be due to genomic factors influenced by sex differences in early social experience or to the expression of neural processes mediated by sex hormones or both (Breedlove, 1994). In animals, structural sex differences exist in regions controlling sexual dimorphism as well as in those not directly related to reproductive function (Allen and Gorski, 1991), nearly all of which are influ-

enced by perinatal gonadal hormone levels (Allen and Gorski, 1991). In humans, there are significant sex differences in the shape of the midsagittal structures of the brain: the splenium of the corpus callosum tends to be more bulbous in females (Allen *et al.*, 1991); the anterior commissure and massa intermedia of the thalamus are larger in women (Allen and Gorski, 1991). Functionally, sex differences in performance such as the slight male superiority in tests of spatial reasoning and the female superiority in verbal fluency have been reported (Breedlove, 1994; Levy and Heller, 1992). There is a prevalence of developmental language disorders in boys compared to girls (Hier, 1979). With regard to functional lateralization, the incidence of left-handedness is generally higher in males (Oldfield, 1971). Among right-handed individuals, verbal information is usually processed more rapidly and accurately when presented to the left cerebral hemisphere while spatial information is better processed when presented to the right hemisphere. The discrepancy in performance when information is presented to one side or the other is slightly greater in men (Breedlove, 1994; McGlone, 1980), suggesting more functional lateralization in men. There is evidence that cognitive functions not directly related to reproductive function may be influenced by sex hormones. Androgen metabolites can masculinize cognitive function (Hines, 1982); early exposure to androgens has lasting effects on problem-solving behavior (Resnick *et al.*, 1986; Collaer and Hines, 1995; Hampton, 1995). Moreover, fluctuations in sex hormones in both sexes are associated with changes in cognitive pattern (Hampton, 1990a,b; Kimura, 1996).

Tactile discrimination processes such as Braille reading are better performed by the left hand in both sexes in both adults (Carmon and Benton, 1969; Fontenot and Benton, 1970; Zaidel and Sperry, 1973) and children (Rudel *et al.*, 1974; Klein and Rosenfield, 1980). This suggests right hemispheric predominance, although the preferred hand appears to depend on the

reading strategy and task demands (Millar, 1984, 1987, 1994). Highly proficient reading depends mainly on verbal strategies and skill (right hand/left hemisphere advantage) while less proficient reading demands attention to spatial coding of the physical characteristics (left hand/right hemisphere advantage). Left-hand superiority is different between genders while learning Braille, which is the less proficient reading phase (Rudel *et al.*, 1974). The effect of the order in which hands were trained on the difference between left and right hand performance was greater for girls than boys, which was interpreted as implying more left hemisphere mediation in females (Rudel *et al.*, 1974).

The neuroanatomic substrates of the differences in men and women are poorly understood. To investigate the gender difference in the neuroanatomic pathways for tactile discrimination, we measured cerebral blood flow (CBF) with ^{15}O water and positron emission tomography (PET).

SUBJECTS AND METHODS

We studied 14 normal volunteers (7 men, age 32.6 ± 8.6 years; 7 women, age 27.4 ± 7.2 years), all right handed by the Edinburgh Inventory (Oldfield, 1971). All women and 3 men were included in the previous studies of blind Braille reading as a control group (Sadato *et al.*, 1996a, 1998). The protocol was approved by the Institutional Review Board, and all subject gave their written informed consent for the study. The task design, previously described (Sadato *et al.*, 1996a, 1998), consisted of five conditions: rest, angle discrimination, width discrimination, non-Braille character discrimination, and a somatosensory nondiscrimination control task. In the rest condition, subjects lay quietly with no task. In task conditions, subjects were asked to place their index finger on a window in which different patterns appeared every 5 s. Subjects were instructed to scan all patterns with their index finger from left-to-right and right-to-left. In the somatosensory control condition, subjects were asked to sweep the rough surface homogeneously covered with Braille dots with no discrimination or response. In the angle discrimination condition, two grooves with the same width were presented in pairs. Subjects were asked to respond when the angles were the same. In the width discrimination condition, subjects were asked to respond when the widths of paired vertical grooves were the same. In the character discrimination condition, three uppercase English letters embossed with Braille dots were presented together. Subjects were asked to respond if all the characters were the same. In each condition, the "identical" trials consisted of 10% of the total presentation (3/30).

PET scanning was performed with a Scanditronix PC 2048-15B (Uppsala, Sweden) 15-slice tomograph with interslice spacing of 6.5 mm. Images were recon-

structed to a full width at half maximum (FWHM) of 6.5 mm. CBF images were obtained by summing the activity occurring during the 60-s period following the initial increase in cerebral radioactivity after an intravenous bolus injection of 30 mCi of ^{15}O -labeled water (Fox *et al.*, 1984; Fox and Mintun, 1989). Each condition began 30 s before the tracer injection and continued for the duration of the scan. The task duration was approximately 150 s for each condition. Each condition was performed twice with the right index finger only. The order of presentation sets was counterbalanced within sets and across individuals. The initial and final scans of the series of 10 were done with the subject at rest. During the intervening 8 scans, the tasks were performed.

The data were analyzed with statistical parametric mapping (SPM95/96, from the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc., Sherborn, MA) (Friston *et al.*, 1990, 1994, 1995a,b). The scans from each subject were realigned using the first image as a reference. Following realignment all images were transformed into a standard stereotaxic space (Talairach and Tournoux, 1988) by matching each scan to a reference image that already conformed to the standard space. The transformation was performed with 12 linear and 6 quadratic parameters to minimize the sum of squares between the sample PET data and the template image (Friston *et al.*, 1995a). Utilizing only PET data without detailed anatomical MR images, this method was validated to be as effective in spatial normalization as other methods utilizing anatomical MRI (Sugiura *et al.*, 1999). The variance of the central sulcus normalized by SPM95 was approximately 3 mm (Sugiura *et al.*, 1999). After the anatomical normalization, smoothing using a 10-mm FWHM isotropic Gaussian kernel followed. The following general linear model was applied on voxel-by-voxel basis to explore the effect of condition-gender interaction.

Let Y_{igt}^k denote the rCBF at voxel k for the condition q of the i th subject in group t ($q = 1, \dots, 10$; $i = 1, \dots, 7$; $t = 1, 2$), thus

$$Y_{igt}^k = \alpha\varphi_{qt}^k + \gamma_{it}^k + \xi_t^k(g_{igt} - g_{t..}) + \epsilon_{igt}^k, \quad (1)$$

where $\alpha\varphi_{qt}^k$ is the interaction effect for condition q of group t (the condition-by-group effect), γ_{it}^k is the subject effect, ξ_t^k is the global regression effect of group t , g_{igt} is the global CBF (gCBF) of the i th subject in group t of condition q , and $g_{t..}$ is the mean of the gCBF over 10 conditions of 7 subjects of group t . To test hypotheses about region-specific condition and gender effects, the estimates were compared using linear contrasts (Table 1). The resulting set of voxel values for each contrast constituted a statistical parametric map of the t statistic $\text{SPM}\{t\}$. The $\text{SPM}\{t\}$ was transformed to the unit

TABLE 1
Layout of Comparisons

Condition:	1	2	3	4	5	6	7	8	9	10
Men ($n = 7$)	MR1	MR2	MS1	MS2	MA1	MA2	MC1	MC2	MW1	MW2
Women ($n = 7$)	FR1	FR2	FS1	FS2	FA1	FA2	FC1	FC2	FW1	FW2
Effect of somatosensory control task										
Men			(1) $(MS1 + MS2) - (MR1 + MR2)$							
Women			(2) $(FS1 + FS2) - (FR1 + FR2)$							
Men - Women			(2) - (1)							
Women - Men			(1) - (2)							
Effect of tactile discrimination compared with somatosensory control task										
Men			(3) $(MA1 + MA2 + MC1 + MC2 + MW1 + MW2) - (MS1 + MS2) \times 3$							
Women			(4) $(FA1 + FA2 + FC1 + FC2 + FW1 + FW2) - (FS1 + FS2) \times 3$							
Men - Women			(4) - (3)							
Women - Men			(3) - (4)							

Note. MR, male rest; MS, male somatosensory control; MA, male angle discrimination; MC, male character discrimination; MW, male width discrimination; FR, female rest; FS, female somatosensory control; FA, female angle discrimination; FC, female character discrimination; FW, female width discrimination.

normal distribution (SPM(Z)). To evaluate common activation between genders, conjunction analysis was utilized (Price and Friston, 1997). This approach tests a set of two hypotheses, asking whether the activations by somatosensory control task compared with rest condition (somatosensory control–rest) in the Men group (contrast 1) and those in the Women group (contrast 2) are equally significant. The conjunction analysis has two steps (Price and Friston, 1997). First is the elimination of the regions that show significant differences in the task-related activity (somatosensory control–rest) between the women and the men by F test with an appropriate threshold ($P < 0.05$, uncorrected for multiple comparisons). Second is the statistical inference test for the main effect using the standard procedure based on the theory of Gaussian random fields (with the threshold of $Z > 3.09$ and $P < 0.05$ with a correction for multiple comparisons at cluster level) (Friston *et al.*, 1995b). Eliminating regions where there is significant interaction decreases search volume, thereby rendering the correction for multiple comparisons less severe and the analysis more sensitive (Price and Friston, 1997), but less conservative. Conjunction analysis attributes Z scores and related corrected P values to the co-occurrence of activation and does not directly address the occurrence of the activation specified by each contrast. To ensure that those voxels depicted by conjunction have a significant effect in each of the contrasts independently, we utilized masking. The masking procedure with contrast 1 and contrast 2 depicts the voxels, which are significant in the main effect revealed by conjunction analysis, also significant in each mask contrast (i.e., contrasts 1 and 2) independently. In other words, any voxels that are not signifi-

cant in both mask contrasts are eliminated. The threshold for the mask was $P < 0.01$, uncorrected for multiple comparisons. The same procedures were performed for the comparisons of the tactile discrimination condition with somatosensory control condition (discrimination–somatosensory control).

Similarly, to evaluate the hemispheric effect on pixel-by-pixel basis in each gender group, image datasets were flipped in the horizontal (right–left) direction. Symmetric involvement of the neural substrates for each task was depicted as common activation between flipped and unflipped groups assessed by conjunction analysis with the same statistical threshold and masking procedure as described above.

As the comparison of tactile discrimination and somatosensory control revealed asymmetric activation patterns in the right premotor cortex and the dorsolateral prefrontal cortex, which were common to both genders, the interaction between hemispheric effect (asymmetry), gender effect, and condition effect was evaluated in these predefined areas. First, to test if there were any effects of interest (i.e., condition effect and gender effect) in their counterparts in the contralateral hemisphere, an F test was applied to the general linear model (Eq. (1)) with an appropriate threshold ($P < 0.05$, uncorrected for multiple comparisons). This procedure evaluates the omnibus significance, by testing the null hypothesis that including the effect of interest does not significantly reduce the error variance (Friston *et al.*, 1995a). This is called the omnibus test because it does not address any specific condition. If the counterpart voxel to the activated focus fails to pass this test with relatively low threshold ($P < 0.05$), it is likely that there is no condition

TABLE 2
Common Activation by Tactile Tasks in Both Men and Women Groups

Cluster size	P^a	Talairach's coordinates			Z^b	% Δ CBF		Location ^c
		x	y	z		Women	Men	
Somatosensory control–rest								
1531	<0.001	-28	-34	56	7.80	10.01	6.41	It GpoC
		-40	-40	52	7.70	8.16	7.00	It LPi (40)
		-40	-32	48	7.51	8.49	6.78	It GpoC
		-30	-22	60	6.52	8.74	4.68	It SM1
		-24	-16	60	6.39	6.78	5.27	It PMd (6)
		-48	-30	16	6.22	5.23	3.65	It GTs (22)
		4	-6	56	6.19	4.41	4.73	rt SMA (6)
		-6	-10	44	5.69	3.28	4.73	It ACG (24)
Discrimination–somatosensory control								
410	<0.001	24	-72	44	7.34	6.59	7.70	rt PCu (7)
		36	-52	44	6.54	4.03	7.95	rt LPi (40)
		42	-48	36	5.68	4.92	7.54	rt Gsm (40)
140	<0.001	32	-16	56	7.18	5.16	6.02	rt PMd (6)
362	<0.001	-20	-76	44	6.01	5.46	6.07	It PCu (7)
		-42	-34	44	5.06	3.54	5.03	It LPi (40)
92	0.002	32	32	28	5.08	3.11	3.94	rt GFm (46)

Note. ACG, anterior cingulate gyrus; GFm, middle frontal gyrus; GFs, superior frontal gyrus; GpoC, postcentral gyrus; Gsm, supramarginal gyrus; GTm, middle temporal gyrus; GTs, superior temporal gyrus; LPi, inferior parietal lobule; LPs, superior parietal lobule; PCu, precuneus; PMd, dorsal premotor cortex; SM1, primary sensorimotor area; SMA, supplementary motor area.

^a P value at cluster level with correction for multiple comparisons.

^b Z scores correspond to $P < 0.01$ at voxel level with a correction for multiple comparisons.

^c Brodmann area according to Talairach and Tournoux (1988).

effect in the counterpart, hence the activation is asymmetric. Actually, only right dorsal premotor cortex (PMd) (-32, -16, 56) had its counterpart (32, -16, 56) which revealed a condition effect. With rCBF values of bilateral PMd, adjusted for global CBF by Eq. (1) (Friston *et al.*, 1990), the following general linear model was applied. Adjusted rCBF is a value relative to the whole-brain mean (global CBF), which we assumed to be 50. Let Y_{iqmt} denote the adjusted rCBF at the PMd on the side m for the condition q of the i th subject in group t ($m = 1, 2$; $q = 1, \dots, 10$; $i = 1, \dots, 7$; $t = 1, 2$), thus

$$Y_{iqmt} = \alpha\beta\phi_{qmt} + \gamma_{it} + \epsilon_{iqmt},$$

where $\alpha\beta\phi_{qmt}$ is the interaction effect for side m in condition q of group t (the side-by-condition-by-gender effect), γ_{it} is the subject effect, and ϵ_{iqmt} is an error term which is an independent, normally distributed random variable with zero means. Note that this combines the discrimination tasks (angle, character, and width) in one condition of discrimination. To test the gender difference in asymmetric activation by tactile discrimination compared with the somatosensory control, we used the contrast

$$\begin{aligned} & (\text{WRD} - \text{WRS}) - (\text{WLD} - \text{WLS}) \\ & - \{(\text{MRD} - \text{MRS}) - (\text{MLD} - \text{MLS})\} \end{aligned}$$

where WLS is the adjusted rCBF in the PMd on the left in women during somatosensory control condition; WLD, left in women during discrimination; WRS, right in women during somatosensory control; WRD, right in women during discrimination; MLS, left in men during somatosensory control; MLD, left in men during discrimination; MRS, right in men during somatosensory control; and MRD, right in men during discrimination.

RESULTS

Task Performance

Task performance was equivalent between men (Men) and women (Women) (accuracy: Men $88.9 \pm 8.8\%$; Women $89.1 \pm 7.6\%$, $P > 0.9$, ANOVA).

Condition Effect

For both Men and Women separately, there were no differences among the discrimination tasks; the results from these tasks are combined in the rest of the article.

In both Men and Women (Table 2, Fig. 1), the sensorimotor control task activated the left primary sensorimotor area (SM1), inferior parietal lobule (LPi) extending to the medial portion of the temporal gyrus, and posterior supplementary motor area (SMA proper). There was no significant gender difference during the sensorimotor control condition compared with rest.

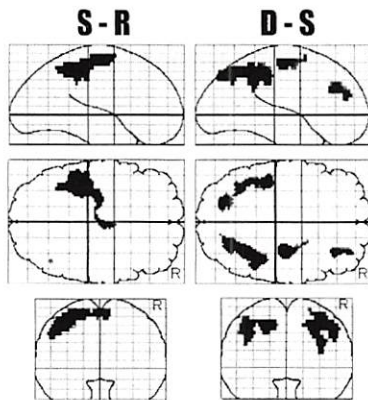


FIG. 1. Activation common to both Men and Women groups. Activated areas during sensorimotor control task compared with rest (S-R, left column) and tactile discrimination compared with somatosensory control condition (D-S, right column) are shown. Significantly activated voxels ($P < 0.05$ with a correction for multiple comparisons at cluster level) are displayed in the sagittal (upper row), transverse (middle row), and coronal (bottom row) projections with the maximal pixel value along with "line of sight."

In both Men and Women, compared with the sensorimotor control condition, discrimination tasks activated the superior parietal lobule (LPs) extending to precuneus (PCu) and LPi bilaterally, right PMd, and right middle frontal gyrus (Table 2, Fig. 1). In Men, conjunction analysis with flipped and nonflipped dataset revealed symmetric activation of the PCu. In Women, symmetrical activation extended more anteriorly than in Men, including the PMd (Fig. 2). The activation in the right middle frontal gyrus, at the Talairach coordinates of (32, 32, 28), was asymmetric in both gender groups, because the left counterpart showed no condition effect. In the PMd (+32, -16, 56), located in the precentral gyrus (Fig. 3), interaction between condition, hemisphere, and gender effects was

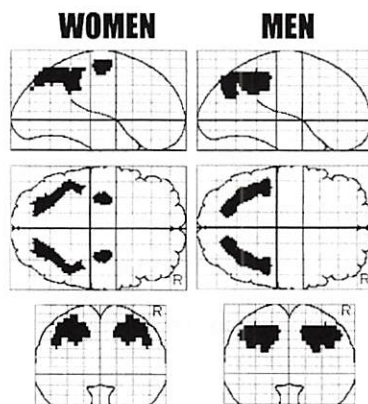


FIG. 2. Symmetric activation in Women (left column) and Men (right column) during tactile discrimination compared with somatosensory control condition. Significantly activated voxels ($P < 0.05$ with a correction for multiple comparisons at cluster level) are displayed with the same format as in Fig. 1.

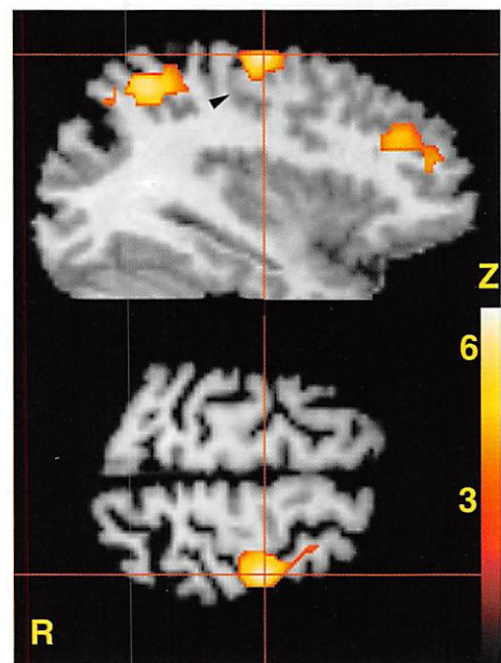


FIG. 3. Activation of the right PMd during tactile discrimination compared with somatosensory control condition, common to both Men and Women, on the typical high-resolution MRI unrelated to the studied groups. The red lines indicate the projections of each section that cross the center of the right PMd at the specified Talairach coordinates of (-32, -16, 56). The activated cluster is anterior to the central sulcus (arrowhead), mainly in the precentral gyrus.

significant ($F(256, 10) = 32.5$, $P = 0.0001$). Asymmetric activation of the right PMd was significantly more prominent in Men than in Women ($F(256, 1) = 26.62$, $P = 0.0001$, Fig. 4). Percentage increase of rCBF of the PMd in Women was 4.70 on the right and 3.63 on the left, whereas in Men it was 6.02 on the right and 0.89 on the left.

DISCUSSION

As activation patterns of the comparisons common to genders were similar to those reported previously (Sadato *et al.*, 1998), discussion will be focused mainly on the gender difference, which was observed in the comparison between discrimination condition and somatosensory control condition.

To investigate the gender difference in tactile discrimination, we used active touch, because exploratory finger movement is an essential component of Braille reading. The manipulospatial function is neither motor nor perceptual per se, but is the mechanism by which a spatial context is mapped onto the perceptual and motor activities of the hands (LeDoux *et al.*, 1977). To control confounding factors such as movement force, velocity of strokes, and amount of skin compression, we utilized the somatosensory control task, although complete control of these motor components is difficult

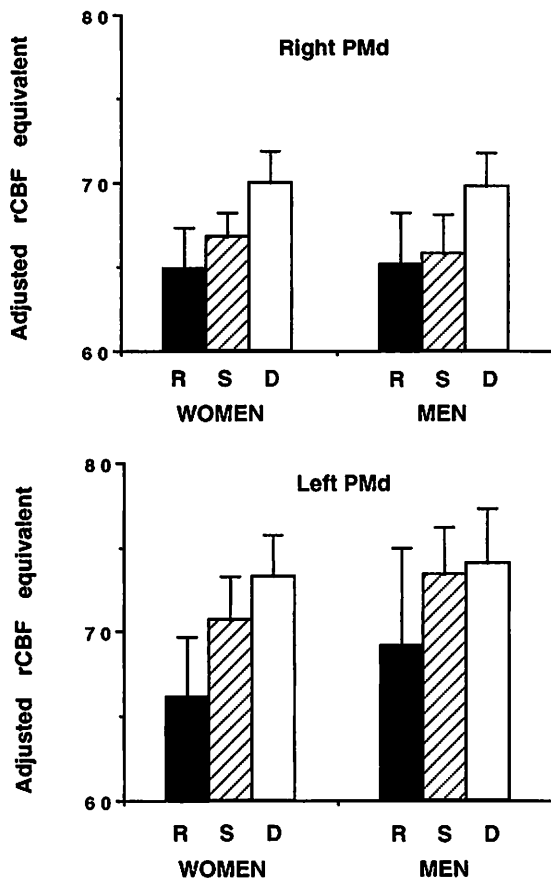


FIG. 4. Adjusted rCBF equivalent of the right (top) and left (bottom) PMd (+32, -16, 56) during rest condition (R), somatosensory control condition (S), and tactile discrimination condition (D) of Women (left) and Men (right). Error bars indicate standard deviation of each condition. Regional CBF was adjusted assuming global CBF to be 50.

because of the nature of active touch. However, speed, force, and frequency of the movement are well known to influence the primary motor cortex of the side contralateral to the used finger (Dettmers *et al.*, 1995; Sadato *et al.*, 1996b, 1997). As the comparisons of (somatosensory control–rest) and (discrimination–somatosensory control) clearly separate the neural substrates (the left SM1 in particular was activated only in the former comparison) we believe that these primitive motor components were similar between the somatosensory control and the discrimination conditions. Hence the comparison between tactile discrimination and somatosensory control condition represents the exploratory component of the manipulospatial function, i.e., tactile discrimination by active touch.

This study was motivated by the previous study on gender–hand interaction while learning Braille (Rudel *et al.*, 1974), expecting that the neural substrate for exploratory movement would be different between genders with regard to hemispheric interaction. For this

reason we investigated the gender difference in symmetric activation.

Tactile discrimination tasks compared with the somatosensory control condition activated the LPs and LPi bilaterally and the right dorsal premotor cortex and dorsolateral prefrontal cortex in both gender groups. These areas are well known to be critical nodal points for access to and processing of attentional information within extrapersonal space (Mesulam, 1981, 1990; Gitelman *et al.*, 1996): premotor cortex for exploratory movements and posterior parietal cortex for spatial representation (Gitelman *et al.*, 1996; Deiber *et al.*, 1996). The posterior parietal cortex includes mainly Brodmann area 7 in the superior parietal lobule and the precuneus. Area 7 of macaque monkeys is said to be homologous to Brodmann area 7 of humans (Haxby *et al.*, 1991), although this view remains controversial. The dorsolateral prefrontal cortex (DLPFC) is related to working memory probably by monitoring and actively manipulating information within working memory storage (Owen *et al.*, 1998), hence it is responsible for the updating function of the central executive (Salmon *et al.*, 1996). Right lateralized asymmetric activation of the DLPFC by spatial working memory task was reported (Jonides *et al.*, 1993).

The present study showed gender difference in asymmetric activation of the dorsal premotor cortex during tactile discrimination tasks compared with the somatosensory control task. According to the Talairach atlas (Talairach and Tournoux, 1988), the activated focus with the local maxima at (32, -16, 56) is 8 mm anterior to the central sulcus. As the variation of the left central sulcus normalized with SPM95 (the same method used in the present study) was reported to be approximately 3 mm (Sugiura *et al.*, 1999), the activation focus is in the precentral gyrus close to the precentral sulcus. Although the activated foci include the central sulcus, probably because of relatively large spatial smoothness (filtered with $10 \times 10 \times 10$ mm Gaussian kernel, the spatial smoothnesses of the images were $\text{FWHM}_x = 10.3$ mm, $\text{FWHM}_y = 11.5$ mm, and $\text{FWHM}_z = 14$ mm), the local maximum is anterior to the central sulcus. Despite the relatively low spatial resolution, local maximum sampling can detect the activation focus with precision above image resolution (Fox *et al.*, 1988).

The “premotor cortex” is a term originally applied to the lateral portion of the frontal agranular cortex rostral to the primary motor cortex (Dum and Strick, 1991). The premotor cortex in the primate is heterogeneous and composed of multiple areas including the PMd and the PMv (Dum and Strick, 1991; He *et al.*, 1993). PMd is located around the precentral dimple of the monkey, and PMv is in the postarcuate region. The PMd can be further divided into two parts rostrocaudally, PMdr and PMdc, the border of which is the genu of the arcuate sulcus (Preuss *et al.*, 1996). In humans,

PMdc is presumably on the precentral gyrus and PMdr is immediately anterior to the precentral sulcus (Preuss *et al.*, 1996). PMdc reciprocally connects with M1 (Wise *et al.*, 1997). Corticospinal cells extend well beyond the limits of M1 into PMdc (He *et al.*, 1993). PMdr, which probably does not project directly to the spinal cord, receives its frontal information mainly from the prefrontal cortex but not extensively from M1 (Wise *et al.*, 1997). The right premotor cortex, which showed activation during tactile discrimination compared with somatosensory control task in the present study, may be equivalent to the PMdc because of its dorsal and caudal location and because of its proximity to the central sulcus.

Premotor lesions can be characterized by the disintegration of the dynamics of the motor act and skilled movements (Kleist, 1907; Luria, 1966). Although some types of apraxia have been related mainly to left premotor lesions, a role for the right premotor area has occasionally been described (Halsband *et al.*, 1993). Fine perceptual discrimination with fingertips during tactile discrimination is likely to be closely related to praxic function. Furthermore, PMd may have a critical role in manipulospatial function such as tactile discrimination, because PMd is critical in making arbitrary stimulus-to-response linkage (Wise, 1996). On-line monitoring of sensorimotor input from the fingertip is necessary for exploratory movement, which is essential for manipulospatial function. In nonhuman primates, PMd and the posterior parietal lobe (especially area 7b) appear to form a system for the coding of near extrapersonal space for guidance of movement within that space (Graziano *et al.*, 1994). Brodmann area 7 is involved in multimodal integration of external information, and it provides a sensory representation of extrapersonal space (Leinonen *et al.*, 1979). By exchanging information with posterior parietal regions during spatial processing, PMd may encode a spatial environment in its descriptive and behavioral aspects for exploratory finger movement (Mellet *et al.*, 1996). Considering these characteristics of PMd, gender difference in the activation pattern of PMd may be related to interhemispheric interaction for exploratory motor control. Men showed asymmetric right PMd activation, whereas Women showed symmetric activation. PMd has dense corticocortical connections with SMA proper (Kurata, 1991). SMA proper has dense and widespread transcortical connections with its contralateral counterpart, the primary motor cortex, and with the premotor cortex (Rouiller *et al.*, 1994). These findings suggest that more interhemispheric interaction for tactile discrimination, probably through PMd, is necessary in women than in men. Future functional neuroimaging studies dealing with the gender difference in a larger population would be helpful to confirm the present interpretation.

Gender differences in interhemispheric interaction during tactile discrimination tasks have previously been suggested. To study hand difference in tactile discrimination, Nilsson and Geffen (1987) performed a tactile similarity judgment task with both hands. Men showed a left-hand advantage, whereas women were equally accurate at recognizing target shapes with either hand, equivalent to men's left-hand recognition accuracy. Decision time, however, was longer for women than for men. Nilsson and Geffen (1987) speculated that women might have compared the shapes in each hand, involving interhemispheric transfer of motor and sensory information. Potter and Graves (1988) reported that women showed better performance in comparing stimuli presented simultaneously on both sides of the body midline than men, suggesting that the better interhemispheric transfer performance by women may be related to the less strong lateralization of function.

Considering these findings, gender difference in accomplishment of left-hand superiority in early Braille reading training (Rudel *et al.*, 1974) could be explained as follows. Superiority of the left hand in women, as in men, is probably due to right hemispheric ability for spatial processing. In women, right-handed training for tactile discrimination might activate the left PMd more than in men. Hence, coactivation of bilateral PMd which appears to be important for women in tactile exploration, may be more primed by right-hand training. For the following left-hand performance, priming this area would be more beneficial for women because of the greater interhemispheric transfer through PMd. Clearly further examinations designed for evaluation of hand effect as well as of interhemispheric functional connectivity are necessary.

The present study indicates that the gender difference in tactile discrimination tasks may be derived from sensorimotor integration of active touch. This suggests the importance of neuroanatomic substrates when evaluating gender differences in higher cognitive functions.

ACKNOWLEDGMENTS

Dr. Sadato was supported in part by a research grant (JSPS-RFTF97L00203) from the "Research for the Future" Program of the Japan Society for the Promotion of Science. The authors thank the members of the Positron Emission Tomography Section, Nuclear Medicine Department, Clinical Center, NIH, for their expertise, and Devera G. Schoenberg, M. S., OCD, NINDS, for skillful editing.

REFERENCES

- Allen, L. S., and Gorski, R. A. 1991. Sexual dimorphism of the anterior commissure and massa intermedia of the human brain. *J. Comp. Neurol.* 312:97-104.
- Allen, L. S., Richey, M. F., Chai, Y. M., and Gorski, R. A. 1991. Sex differences in the corpus callosum of the living human being. *J. Neurosci.* 11:933-942.

- Breedlove, S. M. 1994. Sexual differentiation of the human nervous system. *Annu. Rev. Psychol.* 45:389–418.
- Carmon, A., and Benton, A. L. 1969. Tactile perception of direction and number in patients with unilateral cerebral disease. *Neurology* 19:525–532.
- Collaer, M. L., and Hines, M. 1995. Human behavioral sex differences: A role for gonadal hormones during early development? *Psychol. Bull.* 118:55–107.
- Deiber, M.-P., Ibañez, V., Sadato, N., and Hallett, M. 1996. Cerebral structures participating in motor preparation in humans: A positron emission tomography study. *J. Neurophysiol.* 75:233–247.
- Dettmers, C., Fink, G. R., Lemon, R. N., Stephan, K. M., Passingham, R. E., Silbersweig, D., Holmes, A., Ridling, M. C., Brooks, D. J., and Frackowiak, R. S. J. 1995. Relation between cerebral activity and force in the motor areas of the human brain. *J. Neurophysiol.* 74:802–815.
- Dum, R. P., and Strick, P. L. 1991. The origin of corticospinal projections from the premotor areas in the frontal lobe. *J. Neurosci.* 11:667–689.
- Fontenot, D. J., and Benton, A. L. 1971. Tactile perception of direction in relation to hemispheric locus of lesion. *Neuropsychologia* 9:83–88.
- Fox, P. T., and Mintun, M. A. 1989. Noninvasive functional brain mapping by change-distribution analysis of averaged PET images of $H_2^{16}O$ tissue activity. *J. Nucl. Med.* 30:141–149.
- Fox, P. T., Mintun, M. A., Raichle, M. E., and Herscovitch, P. 1984. A noninvasive approach to quantitative functional brain mapping with $H_2^{15}O$ and positron emission tomography. *J. Cereb. Blood Flow Metab.* 4:329–333.
- Fox, P. T., Mintun, M., Reiman, E., and Raichle, M. 1988. Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. *J. Cereb. Blood Flow Metab.* 8:642–653.
- Friston, K. J., Frith, C. D., Liddle, P. F., Dolan, R. J., Lammertsma, A. A., and Frackowiak, R. S. J. 1990. The relationship between global and local changes in PET scans. *J. Cereb. Blood Flow Metab.* 10:458–466.
- Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., and Evans, A. C. 1994. Assessing the significance of focal activations using their spatial extent. *Hum. Brain Mapp.* 1:210–220.
- Friston, K. J., Ashburner, J., Frith, C. D., Heather, J. D., and Frackowiak, R. S. J. 1995a. Spatial registration and normalization of images. *Hum. Brain Mapp.* 2:165–189.
- Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C. D., and Frackowiak, R. S. J. 1995b. Statistical parametric maps in functional imaging: A general linear approach. *Hum. Brain Mapp.* 2:189–210.
- Gitelman, D. R., Alpert, N. M., Kosslyn, S., Daffner, K., Scinto, L., Thompson, W., and Mesulam, M.-M. 1996. Functional imaging of human right hemispheric activation for exploratory movements. *Ann. Neurol.* 39:174–179.
- Graziano, M. S., Yap, G. S., and Gross, C. G. 1994. Coding of visual space by premotor neurons. *Science* 266:1054–1057.
- Halsband, U., Ito, N., Tanji, J., and Freund, H.-J. 1993. The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain* 116:243–266.
- Hampton, E. 1990a. Variations in sex-related cognitive abilities across the menstrual cycle. *Brain Cognit.* 14:26–43.
- Hampton, E. 1990b. Estrogen-related variations in human spatial and articulatory-motor skills. *Psychoneuroendocrinology* 15:97–111.
- Hampton, E. 1995. Spatial cognition in humans. Possible modulation by androgens and estrogens. *J. Psychiatry Neurosci.* 20:397–404.
- Haxby, J. V., Grady, C. L., Horwitz, B., Ungerleider, L. G., Mishkin, M., Carson, R. E., Herscovitch, P., Schapiro, M. B., and Rapoport, S. I. 1991. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proc. Natl. Acad. Sci. USA* 88:1621–1625.
- He, S. Q., Dum, R. P., and Strick, P. L. 1993. Topographic organization of corticospinal projections from the frontal lobe: Motor areas on the lateral surface of the hemisphere. *J. Neurosci.* 13:952–980.
- Hier, D. B. 1979. Sex differences in hemispheric specialization: Hypothesis for the excess of dyslexia in boys. *Bull. Orton. Soc.* 29:74–83.
- Hines, M. 1982. Prenatal gonadal hormones and sex differences in human behavior. *Psychol. Bull.* 92:56–80.
- Jonides, J., Smith, E. E., Koeppel, R. A., Awh, E., Minoshima, S., and Mintun, M. A. 1993. Spatial working memory in humans as revealed by PET. *Nature* 363:623–625.
- Kimura, D. 1996. Sex, sexual orientation and sex hormones influence human cognitive function. *Curr. Opin. Neurobiol.* 6:259–263.
- Klein, S. P., and Rosenfield, W. D. 1980. The hemispheric specialization for linguistic and non-linguistic tactile stimuli in third grade children. *Cortex* 16:205–212.
- Kleist, K. 1907. Corticale (innervatorische) apraxie. *Jahrbuch Psychiatr. Neurol.* 28:46–112.
- Kurata, K. 1991. Corticocortical inputs to the dorsal and ventral aspects of the premotor cortex of macaque monkeys. *Neurosci. Res.* 12:263–280.
- LeDoux, J. E., Wilson, D. H., and Gazzaniga, M. S. 1977. Manipulospacial aspects of cerebral lateralization: Clues to the origin of lateralization. *Neuropsychologia* 15:743–750.
- Leinonen, L., Hyvarinen, J., Nyman, G., and Linnankoski, I. 1979. I. Functional properties of neurons in lateral part of associative area 7 in awake monkeys. *Exp. Brain Res.* 34:299–320.
- Levy, J., and Heller, W. 1992. Gender differences in human neuropsychological function. In *Handbook of Behavioral Neurobiology* (A. A. Gerall, H. Moltz, and I. L. Ward, Eds.), pp. 245–273. Plenum, New York.
- Luria, A. R. 1966. *Higher Cortical Functions in Man*. Basic Books, New York.
- McGlone, J. 1980. Sex differences in human brain asymmetry: A critical survey. *Behav. Brain Sci.* 3:215–263.
- Mellet, E., Tzourio, N., Crivello, F., Joliot, M., Denis, M., and Mazoyer, B. 1996. Functional anatomy of spatial mental imagery generated from verbal instructions. *J. Neurosci.* 16:6504–6512.
- Mesulam, M.-M. 1981. A cortical network for directed attention and unilateral neglect. *Ann. Neurol.* 10:309–325.
- Mesulam, M.-M. 1990. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann. Neurol.* 28:597–613.
- Millar, S. 1984. Is there a “best hand” for Braille? *Cortex* 20:75–87.
- Millar, S. 1987. The perceptual “window” in two-handed Braille: Do the left and right hands process text simultaneously. *Cortex* 23:111–122.
- Millar, S. 1994. *Understanding and Representing Space*. Oxford Univ. Press, New York.
- Nilsson, J., and Geffen, G. 1987. Perception of similarity and laterality effects in tactile shape recognition. *Cortex* 23:599–614.
- Oldfield, R. C. 1971. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9:97–113.
- Owen, A. M., Stern, C. E., Look, R. B., Tracey, I., Rosen, B. R., and Petrides, M. 1998. Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. *Proc. Natl. Acad. Sci. USA* 95:7721–7726.
- Potter, S. M., and Graves, R. E. 1988. Is interhemispheric transfer related to handedness and gender? *Neuropsychologia* 26:319–325.

- Preuss, T. M., Stepniewska, I., and Kaas, J. H. 1996. Movement representation in the dorsal and ventral premotor areas of owl monkeys: A microstimulation study. *J. Comp. Neurol.* **371**:649–676.
- Price, C. J., and Friston, K. J. 1997. Cognitive conjunction: A new approach to brain activation experiments. *NeuroImage* **5**:261–270.
- Resnick, S. M., Berenbaum, S. A., Gottesman, I. J., and Bouchard, T. J. 1986. Early hormonal influences on cognitive functioning in congenital adrenal hyperplasia. *Dev. Psychol.* **22**:191–198.
- Rouiller, E. M., Balalian, A., Kazennikov, O., Moret, V., Yu, X.-H., and 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.
- Rudel, R., Denckla, M., and Spalten, E. 1974. The functional asymmetry of Braille letter learning in normal sighted children. *Neurology* **24**:733–738.
- Sadato, N., Pascual-Leone, A., Grafman, J., Ibañez, V., Deiber, M.-P., Dold, G., and Hallett, M. 1996a. Activation of the primary visual cortex by Braille reading in blind subjects. *Nature* **380**:526–528.
- Sadato, N., Ibañez, V., Deiber, M.-P., Campbell, G., Leonardo, M., and Hallett, M. 1996b. Frequency-dependent changes of regional cerebral blood flow during finger movements. *J. Cereb. Blood Flow Metab.* **16**:23–33.
- Sadato, N., Ibañez, V., Campbell, G., Deiber, M.-P., Le Bihan, D., and Hallett, M. 1997. Frequency dependent changes of regional cerebral blood flow during finger movements: Functional MRI compared with PET. *J. Cereb. Blood Flow Metab.* **17**:670–679.
- Sadato, N., Pascual-Leone, A., Grafman, J., Deiber, M.-P., Ibañez, V., and Hallett, M. 1998. Neural networks for Braille reading by the blind. *Brain* **121**:1213–1229.
- Salmon, E., Van der Linden, M., Collette, F., Delfiore, G., Maquet, P., Degueldre, C., Luxen, A., and Franck, G. 1996. Regional brain activity during working memory. *Brain* **119**:1617–1625.
- Sugiura, M., Kawashima, R., Sadato, N., Senda, M., Kanno, I., Oda, K., Inoue, K., Kinomura, S., Sato, K., and Fukuda, H. 1999. Anatomical validation of spatial normalization methods for PET. *J. Nucl. Med.* **40**:317–322.
- Talairach, J., and Tournoux, P. 1988. *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme, New York.
- Wise, S. P. 1996. Evolution of neuronal activity during conditional motor learning. In *The Acquisition of Motor Behavior in Vertebrates* (J. R. Bloedel, T. J. Ebner, and S. P. Wise, Eds.), pp. 261–286. MIT Press, Cambridge, MA.
- Wise, S. P., Boussaoud, D., Johnson, P. B., and Caminiti, R. 1997. Premotor and parietal cortex: Corticocortical connectivity and combinatorial computations. *Annu. Rev. Neurosci.* **20**:25–42.
- Zaidel, D., and Sperry, R. W. 1973. Performance on the Raven's colored progressive matrices test by subjects with cerebral commissurotomy. *Cortex* **9**:34–39.