

Merging of oculomotor and somatomotor space coding in the human right precentral gyrus

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Summary

Using PET and $H_2^{15}O$, we investigated the cortical areas that merge two different ways of coding space in the cerebral cortex, those concerned with the oculomotor and the somatomotor space. Normal subjects performed a visuomotor task that required the spatial coding of visual stimuli in oculomotor space and of motor responses in somatomotor space. We manipulated the mapping of oculomotor and somatomotor space by instructing subjects to respond in half of the PET scans with uncrossed hands, i.e. each hand was in the homonymous hemisphere (standard oculomotor–somatomotor mapping), and in the other half with crossed hands, i.e. with the left hand in the right hemisphere and the

right hand in the left hemisphere (nonstandard oculomotor–somatomotor mapping). Reaction times were slower for crossed hands than uncrossed hands. Crossed hands produced increases in blood flow in the precentral and postcentral gyri of the right hemisphere. Increases in blood flow in the precentral gyrus were correlated with increases in reaction time comparing the crossed-hand task with the uncrossed one, whereas the increases in blood flow in the postcentral gyrus were not. These findings suggest that the right precentral gyrus merges oculomotor and somatomotor space coding in the human brain.

Keywords: positron emission tomography; spatial compatibility; motor cortex; premotor cortex; parietal cortex

Abbreviations: ANOVA = analysis of variance; rCBF = regional cerebral blood-flow

Introduction

Brain lesions produce spatial deficits that concern different sectors of space. For instance, experimental data show that frontal eye field lesions are associated with spatial deficits in far space (Milner, 1987), whereas ventral premotor lesions produce spatial disorders in near space (Rizzolatti *et al.*, 1983). In humans, although the anatomical correlates are less defined, dissociable spatial disorders for near and far space have been observed after cerebral lesions (Bisiach *et al.*, 1986; Halligan and Marshall, 1991; Cowey *et al.*, 1994). This suggests that different space sectors are coded in different brain areas. Anatomical and physiological evidence converge in suggesting two ways of coding space in two separate parieto-frontal circuits. Oculomotor space coding is associated with far space, simple visual stimuli and eye movements, and is mainly subserved by a medial circuit connecting area 7a and the lateral intraparietal area with the dorsal premotor cortex (the superior colliculus is also involved

in this circuit) (Duhamel *et al.*, 1992; Andersen *et al.*, 1993; Rizzolatti *et al.*, 1994; Petit *et al.*, 1996). Somatomotor space coding is associated with peripersonal–personal space, with three-dimensional objects, and with arm, hand, face and mouth movements, and it is subserved by a lateral circuit connecting area 7b and the anterior intraparietal area with the ventral premotor cortex (Gentilucci *et al.*, 1983; Matelli *et al.*, 1986; Rizzolatti *et al.*, 1988, 1996; Sakata *et al.*, 1995; Grafton *et al.*, 1996a).

Space is coded differently in the oculomotor and somatomotor systems. Visual receptive field activity of oculomotor neurons is largely gaze-dependent and retinocentric (Goldberg *et al.*, 1990). In contrast, somatomotor neurons have gaze-independent bimodal receptive fields, with visual receptive fields usually located around tactile receptive fields (Fogassi *et al.*, 1992, 1996; Graziano *et al.*, 1994). A number of issues related to oculomotor and somatomotor

space coding, however, are still unsettled. For instance: (i) the role of newly recognized visual posterior parietal areas sending inputs to the dorsal premotor cortex (Caminiti *et al.*, 1996; Jackson and Husain, 1996; Johnson *et al.*, 1996; Wise *et al.*, 1997); (ii) whether spatial maps are necessary in the oculomotor circuit for programming eye movements (Andersen *et al.*, 1985), or, alternatively, if spatial locations in the oculomotor system can be computed from vector analyses based on target position and motor errors (Duhamel *et al.*, 1992); (iii) what is the role of neurons with gaze-dependent activity in an area such as the ventral premotor cortex (Boussaoud *et al.*, 1993; Boussaoud, 1995), where somatomotor neurons with gaze-independent, bimodal receptive fields are generally found (Graziano *et al.*, 1994; Fogassi *et al.*, 1996); (iv) why certain somatomotor neurons with bimodal receptive fields have visual receptive fields that are not located around their tactile receptive fields (Fogassi *et al.*, 1996).

In spite of these unsolved issues, the hypothesis of separate oculomotor and somatomotor ways of coding space fits the empirical evidence well. A fundamental question raised by this evidence is how and where the two different ways of coding space merge to give a unitary space percept and to subservise an integrated motor behaviour in space (Fogassi *et al.*, 1996). How the computational problem is solved, is a question that can be addressed by single-unit studies and by modelling approaches. The neural system that subserves the merging process, however, can be localized by neuroimaging techniques. To investigate the cortical localization of the merging process of oculomotor and somatomotor space coding, we used PET and a spatial stimulus–response compatibility task.

In spatial stimulus–response compatibility, contralateral (incompatible) motor responses to lateralized flashes are 40–80 ms slower than ipsilateral (compatible) responses (Proctor and Reeve, 1990). This is not due to callosal transmission delay, which is much shorter in humans, ~3–4 ms (Iacoboni *et al.*, 1994; Iacoboni and Zaidel, 1995). In fact, responses contralateral to lateralized flashes are slower than ipsilateral ones even when subjects respond with hands in the crossed position, with each hand in its heteronymous hemispace, i.e. left hand in right hemispace and right hand in left hemispace (Anzola *et al.*, 1977). The crossed-hands position produces overall longer reaction times, compared with the uncrossed-hands position in which each hand is in its homonymous hemispace (Anzola *et al.*, 1977; Berlucchi *et al.*, 1977; Nicoletti *et al.*, 1982). This is not produced by an ‘awkward’ hand position, since in tasks that do not require the spatial coding of sensory stimuli and motor responses, there is no difference in reaction times between crossed and uncrossed-hands (Nicoletti *et al.*, 1984). Longer reaction times in the crossed-hands position seem to originate from the incongruent mapping between oculomotor and somatomotor space (Riggio *et al.*, 1986; Umiltà and Nicoletti, 1990). Thus, the localization of blood-flow changes with the hands in the crossed position, relative to those with the hands uncrossed, should indicate

the brain area where oculomotor and somatomotor space coding merge. The data presented here suggest that the right precentral gyrus is the region where oculomotor and somatomotor space coding merge. Preliminary analyses of these data have been previously presented in abstract form (Iacoboni *et al.*, 1996a).

Methods

Subjects

Eight right-handed males (mean age \pm SD = 21.4 \pm 2.26 years) participated in this study. All subjects gave their informed consent according to the guidelines of UCLA Human Subjects Protection Committee. Subjects were right handed as assessed by a handedness questionnaire, modified from the Edinburgh inventory (Oldfield, 1971) and were found to have normal general medical histories and normal results in physical and neurological examinations.

Activation paradigm

Subjects held a microswitch in each hand to be used for motor responses. A Macintosh computer monitor was positioned 57 cm from their eyes. The software program MacProbe was used to present lateralized flashes and to record reaction times and accuracy of responses. Software characteristics are described elsewhere (Zaidel and Iacoboni, 1996). A central fixation cross subtending 1° of visual angle was displayed throughout the entire task. Stimuli subtended 1° of visual angle and consisted of lateralized square-shaped light flashes on a black background. Retinal eccentricity was 8° from the vertical meridian. Stimuli were flashed either in the right or in the left visual field in a random, counterbalanced fashion. Stimulus duration was 50 ms.

Subjects had four response conditions, according to a 2×2 design. The two axes of the design were compatible versus incompatible condition, and the crossed-hands versus uncrossed-hands position. In the compatible condition subjects had to respond with the hand in the hemispace ipsilateral to the lateralized flash, whereas in the incompatible condition subjects had to respond with the hand in the hemispace contralateral to the light flash. In the uncrossed position, subjects kept their left hand in left hemispace and their right hand in right hemispace, whereas in the crossed position, subjects crossed their arms, having their left hand in right hemispace and their right hand in left hemispace. Before the imaging session, subjects were trained with four blocks (one per response condition) of 72 trials each. To have a counterbalanced number of lateralized flashes and motor responses in each scan, stimuli were presented every 1.25 s, regardless of the response time of the previous trial. As we have noted elsewhere (Iacoboni *et al.*, 1996b), reaction times in this paradigm are consistently observed between 250 and 500 ms, allowing sufficient time from the end of the execution of the motor response to the presentation of

the next stimulus. Subjects began the task 30 s before each 60-s scan. In the pre-scan time, 24 lateralized flashes (12 left and 12 right) were presented. During the scan, 48 stimuli (24 left and 24 right) were presented in random order. The total number of trials during the scan time was 48×12 , i.e. 576 trials per subject.

Imaging

To reduce head movements we used a customized foam head holder (Smithers Corporation, Akron, OH). A 68e ring source was used for a transmission scan in each subject before the PET imaging session, in order to locate frontal and parietal cortex in the centre of the field of view, where 3D PET imaging sensitivity is optimized (Cherry *et al.*, 1993).

We performed twelve regional cerebral blood flow (rCBF) measurements in each subject, three per stimulus–response task. The order of the four stimulus–response tasks was counterbalanced across subjects. For each scan, a 10 mCi (370 MBq) bolus of $H_2^{15}O$ in 7 ml of normal saline via an intravenous line in the left or the right hand was used. For the crossed-hand position, four subjects were instructed to cross their arms with the right arm over the left one. In these subjects the intravenous line was placed in the right hand. The remaining four subjects were instructed to cross their arms with the left arm over the right one. In these subjects the intravenous line was placed in the left hand. Counts were collected from the time of the injection in a single 60-s frame. No arterial blood sampling was performed.

A Siemens/CTI 831–08 tomograph (Siemens Corporation, Hoffman Estates, IL), with eight data collection rings and axial field of view of 101.25 mm, was used for data acquisition. The scanner has been modified to allow removal of the septa for 3D PET data acquisition. Data were reconstructed using a 3D reconstruction algorithm (Cherry *et al.*, 1993). Attenuation correction was calculated (Siegel and Dahlbom, 1992), and no scatter correction was performed.

The 3D reconstruction algorithm produced images consisting of 15 planes of 128×128 pixels (interplane distance of 6.75 mm). In-plane smoothing of the images was applied using a two-dimensional 8 mm isotropic Gaussian filter. Images were registered using AIR (Woods *et al.*, 1992), which interpolated the original axial planes to 55 planes. The resulting images had cubic voxels of $1.75 \times 1.75 \times 1.75$ mm. Global normalization was used to remove differences in global activity across scans (Mazziotta *et al.*, 1985). The final image resolution was $10.12 \times 10.12 \times 10$ mm full-width at half-maximum.

Intersubject stereotaxis was performed using a 12 parameter affine registration model (Woods *et al.*, 1993). Statistical analyses were performed in the common space produced by the stereotaxis procedure. The activated areas were localized in Talairach space (Talairach and Tournoux, 1988).

Data analysis

For the behavioural data, repeated measures analyses of variance (ANOVAs) were performed, using accuracy of

responses and median reaction times for correct responses as the dependent variables, and with spatial stimulus–response compatibility condition (compatible, incompatible), position of the responding hand (crossed, uncrossed), task replication (from one to three) and visual field (left, right) or responding hand (left, right) as within-subject variables. Only trials performed during actual image acquisition were analysed. Reaction times ≤ 150 ms were considered anticipatory errors, whereas reaction times ≥ 600 ms were considered attentional errors. Anticipatory and attentional errors were both removed from the analysis.

For the rCBF data, a four-way ANOVA was performed using normalized counts in each voxel as the dependent variable and with spatial stimulus–response compatibility, position of the responding hand, task replication and subjects as between-voxel effects. We have discussed elsewhere the validity of this approach (Woods *et al.*, 1996). Since voxel-by-voxel ANOVAs entail multiple spatial comparisons, the significance thresholds were corrected in all analyses according to the volume of the cerebral search regions of interest and the final image resolution (Worsley *et al.*, 1996). In a previous experiment, we observed that spatial stimulus–response compatibility produced bilateral activation of the superior parietal lobule, whereas practice effects in this task produced activation of the left prefrontal, premotor and motor cortex (Iacoboni *et al.*, 1996b). Thus, we considered the two superior parietal lobules as search regions of interest for the spatial stimulus–response compatibility effect, which resulted in a statistical threshold of $t(14) = 3.41$ ($P < 0.05$), and the left prefrontal, premotor and motor cortex as search regions of interest for practice effects, which resulted in a statistical threshold of $t(14) = 3.59$ ($P < 0.05$). For the crossed-hands effect and for all the higher-order interactions, given that oculomotor and somatomotor space coding are subserved by parieto-frontal circuits in the lateral wall of the two hemispheres, we broadly defined the lateral wall of parietal and frontal lobe as search regions of interest, resulting in a statistical threshold of $t(14) = 4.54$ ($P < 0.05$). We also performed focused analyses for the crossed-hands effect, using unsmoothed images (full-width at half-maximum = 6.2 mm), with the right precentral gyrus and the postcentral gyrus as search regions of interest, which resulted in a statistical threshold of $t(14) = 3.64$ ($P < 0.05$).

Results

Crossed-hands effect

Incorrect responses, anticipatory and attentional errors were rare (~3%) and not significantly different between the crossed and uncrossed-hands position. In reaction times, responses were faster [$F(1, 7) = 24.857$, $P < 0.002$] in the uncrossed (294 ms) than in the crossed-hands position (320 ms). There was also a position-by-hand interaction [$F(1, 7) = 29.159$, $P < 0.001$]; in the uncrossed position of the responding hand, right hand responses (287 ms) were faster [$F(1, 7) =$

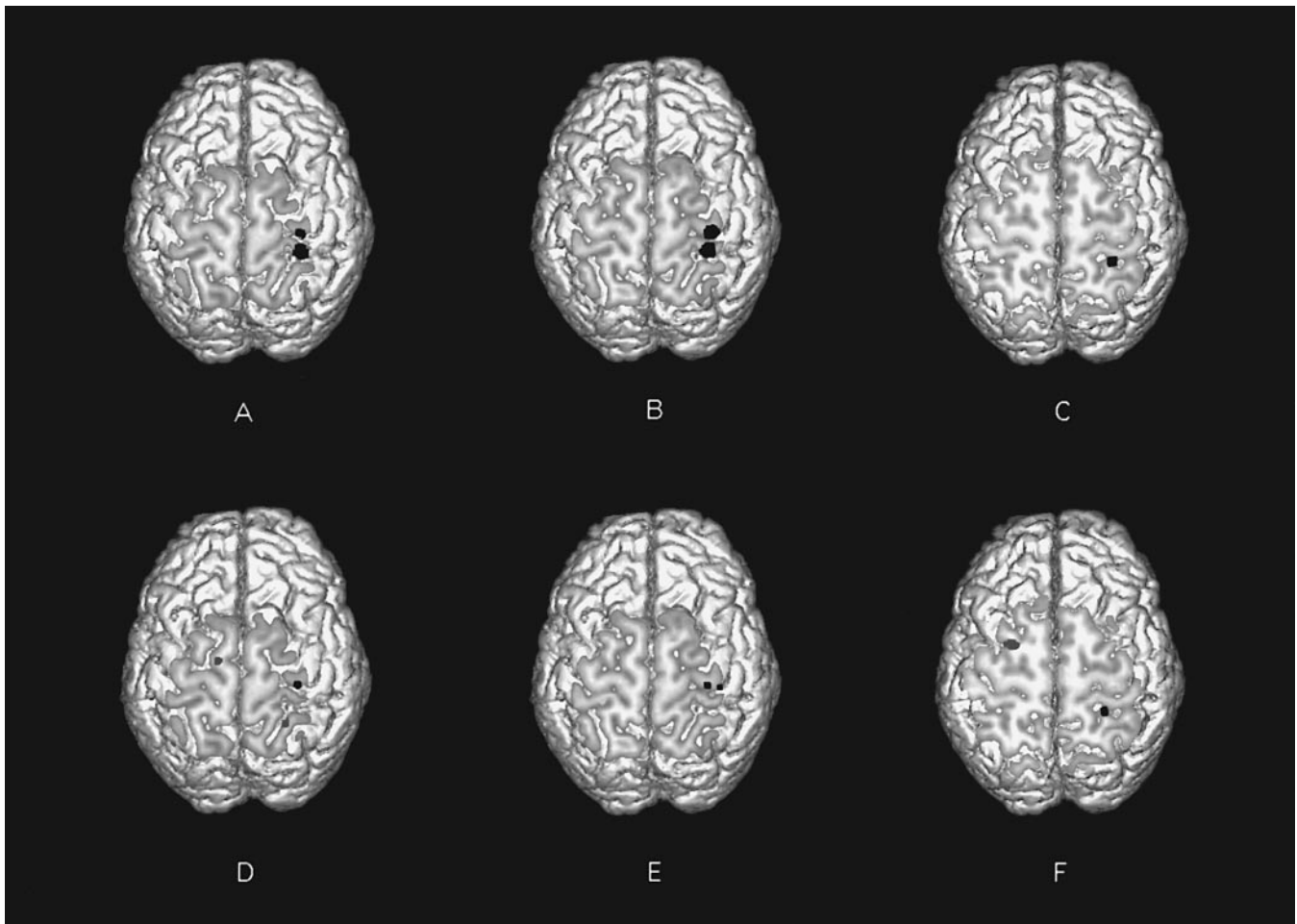


Fig. 1 Transverse views of the significant increases in rCBF (black) in the crossed-hand responses, compared with the uncrossed ones. *Top row*: the analysis with smoothed images shows significant increases in rCBF in the caudal half of the precentral gyrus (**A** and **B**) [stereotaxic coordinates, Talairach and Tournoux (1988), $x = 40, y = -9, z = 52$] and the postcentral gyrus (**A, B** and **C**) [stereotaxic coordinates, $x = 39, y = -27, z = 52$]. *Bottom row*: analysis of the same data, but with unsmoothed images, again shows voxels of significant increases in rCBF (black) in the caudal half of the precentral gyrus (**D** and **E**) [stereotaxic coordinates, $x = 39, y = -9, z = 52$] and the postcentral gyrus (**F**) [stereotaxic coordinates, $x = 38, y = -31, z = 48$]. Voxels in grey are located outside the defined region of interest for the analysis with unsmoothed images. MRI of a single subject is used for display purpose in these renderings. Volume renderings were made by using the software package Sunvision (Sun Microsystems, Mountain View, Calif., USA).

19.496, $P < 0.004$] than left hand responses (302 ms), whereas, in the crossed position of the responding hand, right hand responses (326 ms) were slower [$F(1, 7) = 10.376, P < 0.02$] than left hand responses (315 ms).

Significant increases in rCBF in the crossed-hands position of the responding hand, compared with the uncrossed one [$t(14) = 4.54, P < 0.05$], were located in the caudal regions of the precentral and postcentral gyri (Fig. 1A–C). No significant rCBF decreases were observed. No higher order interactions involving the (crossed or uncrossed) position of the responding hand were observed in blood flow.

Given the final image resolution after smoothing (*see* Methods section), the caudal voxels of activated area in the precentral gyrus and the rostral voxels of activated area in the postcentral gyrus are not completely independent. Hence, a correlation between the rCBF changes in these two areas, and differences in reaction times from the uncrossed to the

crossed-hands position of the responding hand (*see* below) would be difficult to interpret. Thus, we subsequently used unsmoothed images (full-width at half-maximum = 6.2 mm) to re-analyse increases in rCBF in the right precentral and postcentral gyri. Significant rCBF increases, in the crossed position of the responding hand compared with the uncrossed one [$t(14) = 3.64, P < 0.05$], were again observed in the caudal regions of the right precentral and postcentral gyri (Fig. 1D–F). We also tested the simple effect of crossed versus uncrossed position of the responding hand for the compatible and the incompatible condition separately. Significant rCBF increases, in the crossed position of the responding hand compared with the uncrossed one [$t(14) = 3.64, P < 0.05$], were again observed in the caudal region of the right precentral and postcentral gyri for compatible and incompatible conditions, when tested separately. Given the image resolution of the unsmoothed images, the activated

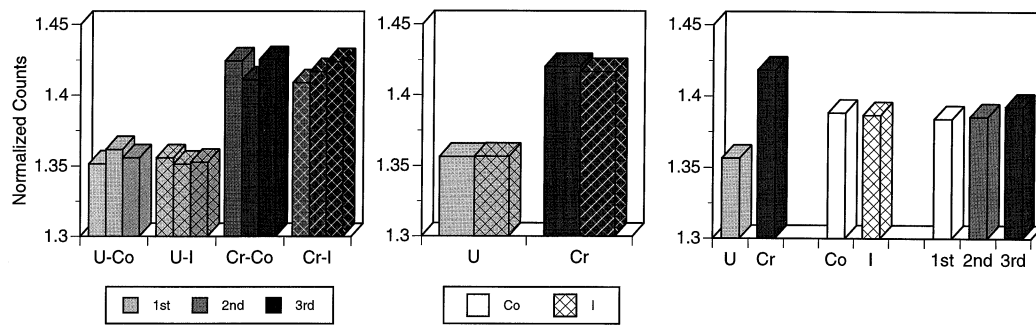


Fig. 2 Activity, as expressed by normalized counts, in the activated voxels shown in Fig. 1D and E. *Left*: average counts in each scan. U-Co = uncrossed-hands position, compatible condition; U-I = uncrossed-hands position, incompatible condition; Cr-Co = crossed-hands position, compatible condition; Cr-I = crossed-hands position, incompatible condition. Replication scans are coded from light to dark. Crossed-hands scans show more activity than uncrossed-hands scans. *Centre*: average counts for the four response tasks. U = uncrossed; Cr = crossed; Co = compatible; I = incompatible. No difference between compatible and incompatible scans is discernible in these voxels, whereas there is evidently a crossed-hands effect. *Right*: average counts for position of the responding hand (U = uncrossed; Cr = crossed), response condition (Co = compatible; I = incompatible) and for replication (1st, 2nd, 3rd). Only the crossed-hands effect is visibly affecting the activity of these voxels.

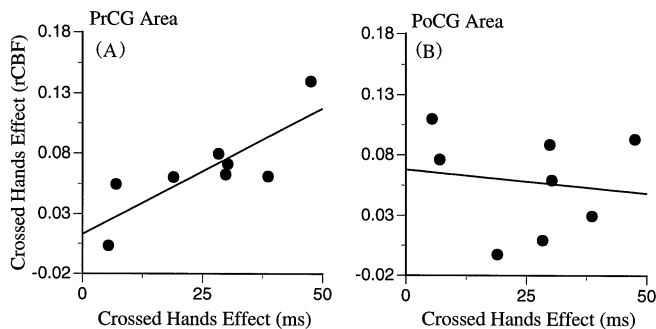


Fig. 3 The increases in reaction times and normalized rCBF counts from uncrossed to crossed position (crossed-hands effect) were highly correlated ($r = 0.815$, $P < 0.02$) in the right precentral gyrus (A), whereas they were not correlated ($r = -0.137$, not significant) in the right postcentral gyrus (B).

voxels in the right precentral and postcentral gyri can be considered independent. Figure 2 shows the activity of these voxels.

We then correlated the increases in rCBF in these voxels with the differences in reaction times between uncrossed and crossed-hands position of the responding hands. The increases in rCBF in the precentral gyrus were significantly correlated ($r = 0.815$, $P < 0.02$) with an increase in reaction time from the uncrossed to the crossed-hands position of the responding hand (Fig. 3A). In contrast, the increases in rCBF in the postcentral gyrus were not correlated with the increase in reaction times from uncrossed to crossed hand position ($r = -0.137$) (Fig. 3B).

Spatial compatibility effect

Incorrect responses, and anticipatory and attentional errors were rare (~3%) and not significantly different between the compatible and incompatible response conditions. A main effect of spatial stimulus–response compatibility was observed in reaction times [$F(1, 7) = 56.166$, $P < 0.0001$],

with faster reaction times for the compatible (285 ms) than the incompatible condition (330 ms).

Increases in blood flow were observed in left and right superior parietal lobule [$t(14) = 3.41$, $P < 0.05$] in the incompatible condition compared with the compatible one. The left dorsal premotor and primary motor areas produced similar t values (Fig. 4A). Given that they are located outside our *a priori* regions of interest, they should not be regarded as significant on the basis of this experiment alone. In a previous experiment on spatial stimulus–response compatibility, however, we observed activation of the dorsal premotor cortex during incompatible responses compared with compatible ones ($P < 0.001$, uncorrected for multiple spatial comparisons). At that time we did not have an *a priori* anatomical hypothesis. Thus, we reported only the areas that were significant after correction for multiple spatial comparisons using the whole brain as the region of interest (Iacoboni *et al.*, 1996b). In a third experiment on spatial compatibility, recently performed with another group of subjects (M.I., R.P.W. and J.C.M., unpublished observations), we have observed fully significant dorsal premotor cortex and superior parietal lobule activation during incompatible responses compared with compatible ones, when these regions were considered as search regions of interest. The interpretation of this anatomical consistency in three different experiments, in activations that might not reach a full statistical significance in a single experiment, after correction for multiple comparisons, is addressed in the Discussion. No blood-flow decreases were observed. No higher order interactions involving spatial compatibility were observed in blood flow.

Learning effect

Incorrect responses, anticipatory and attentional errors were rare (~3%) and not significantly different between replications. In reaction times, a main effect of replication

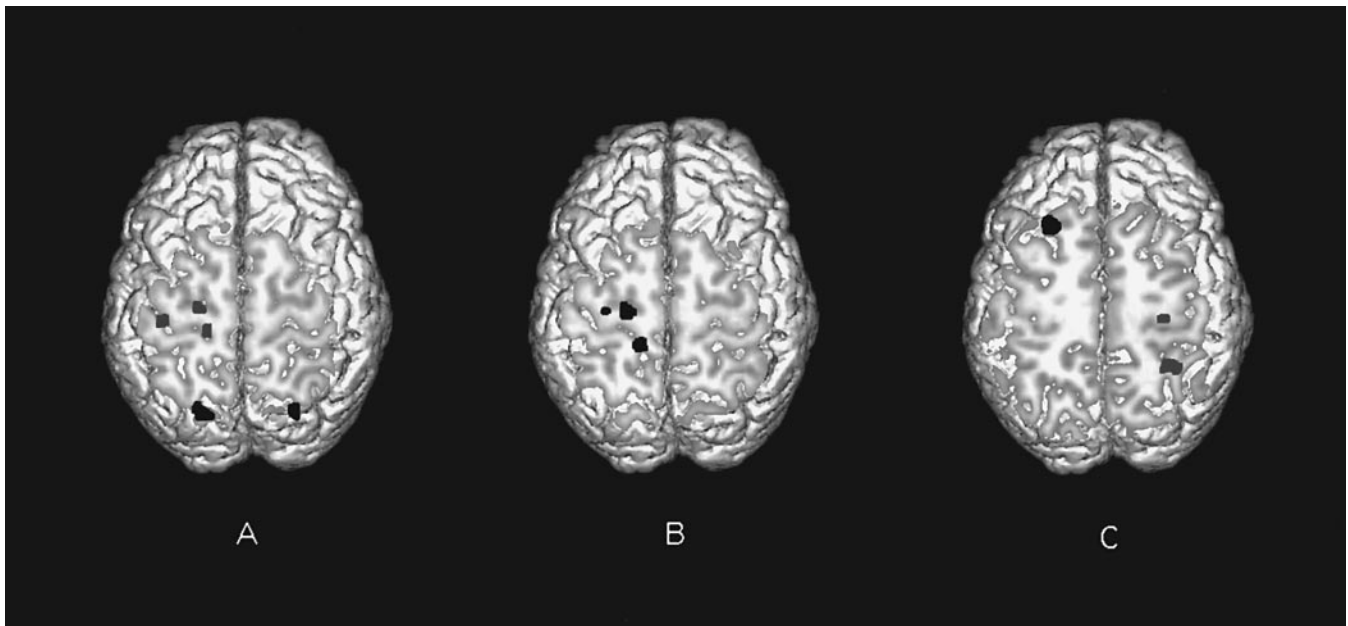


Fig. 4 (A) Increases in rCBF (black) in the left superior parietal lobule [stereotaxic coordinates: $x = -28$, $y = 38$, $z = 46$] and right superior parietal lobule [stereotaxic coordinates: $x = 28$, $y = -12$, $z = 47$], due to spatial stimulus–response compatibility. In grey, voxels in dorsal premotor cortex and the primary motor cortex, located outside the region of interest, and showing increases in rCBF reaching the same t -value as the superior parietal lobule voxels. (B) Left hemisphere learning-related increases in rCBF (black) in left premotor cortex and motor cortex. The two foci in premotor cortex have stereotaxic coordinates ($x = -36$, $y = -4$, $z = 50$) and ($x = -30$, $y = -4$, $z = 50$), and activation in the primary motor cortex has stereotaxic coordinates ($x = -25$, $y = -24$, $z = 50$). (C) Left hemisphere learning-related increases in rCBF (black) in prefrontal cortex [stereotaxic coordinates, $x = -30$, $y = 48$, $z = 28$]. In grey, voxels reaching the same statistical threshold but located outside the region of interest.

was observed [$F(2, 7) = 9.883$, $P < 0.003$]. The overall reaction times of the first scan in all conditions was 317 ms, of the second scan in all conditions was 311 ms, and of the last scan in all conditions was 294 ms. When tested for a linear trend, this effect was significant [$F = 18.291$, $P < 0.001$]. No higher order interactions involving learning were observed in reaction times.

Linear increases in rCBF [$t(14) = 3.59$, $P < 0.05$] with replication were observed in the left dorsal premotor cortex, the rostral sector of the precentral gyrus, in the anterior bank of the left central sulcus, the primary motor area (Fig. 4B) and in the left prefrontal cortex (Fig. 4C). Figure 5 shows the activity in the learning-dependent areas in the left dorsal premotor cortex and left primary motor area. This learning effect is in line with other imaging data (Grafton *et al.*, 1992, 1994) and with evidence from nonhuman primates (Mitz *et al.*, 1991). We have independently observed, reported and discussed this effect elsewhere (Iacoboni *et al.*, 1996a). No significant rCBF decreases due to replication were observed. No higher order interactions involving learning were observed in blood flow.

Discussion

The main results of our study can be summarized as follows. The crossed-hands position produced longer reaction times than the uncrossed position, and also increases in rCBF in the right precentral and postcentral gyri. Incompatible

responses produced longer reaction times than compatible responses, and also increases in rCBF in the superior parietal lobule and left dorsal premotor cortex (this latter activation was outside our region of interest, but has been consistently observed in three different spatial-compatibility experiments that we have performed so far). Practice effects produced linear decreases in reaction times and linear increases in rCBF in left prefrontal, the dorsal premotor cortex and primary motor area. No higher order interactions in reaction times or blood flow were observed. We will discuss the crossed-hands effect, the spatial-compatibility effect and the learning effect in three separate sections.

Crossed-hands effect

Taken together, the rCBF findings and their correlation with reaction times suggest that neurons in the caudal region of the right precentral gyrus merge oculomotor and somatomotor space coding. According to the localization of the activated voxels in Talairach space and corresponding Brodmann cytoarchitectonic maps, the activated neurons in the caudal portion of the precentral gyrus should be located in Brodmann area 4, i.e. in the primary motor cortex. However, recent anatomical evidence has challenged the traditional notion that the primary motor cortex encompasses the caudal portion of the precentral gyrus and has alternatively proposed that the primary motor cortex is buried in the anterior bank of the central sulcus, and that the caudal portion of the precentral

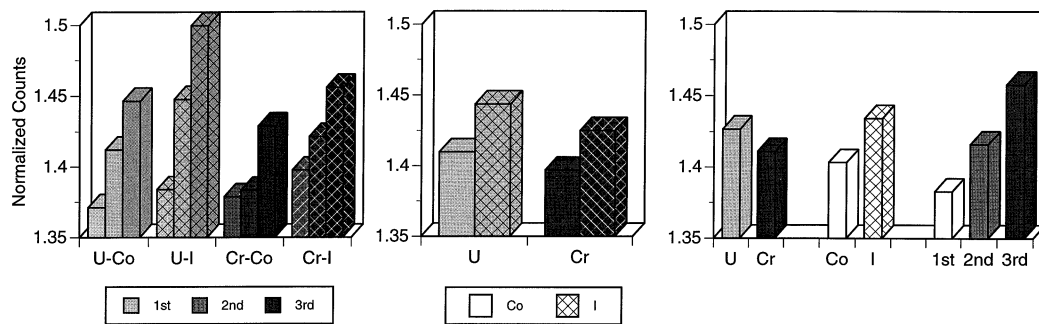


Fig. 5 Activity, as expressed by normalized counts, in the learning-related voxels shown in Fig. 4B (see Fig. 2 legend for details of abbreviations and coding of histograms). *Left*: average counts in each scan. A clear pattern of linear increases in rCBF due to replication is visible in each response task. *Centre*: average counts for the four response tasks. A difference, albeit not significant, between compatible and incompatible scans is discernible in these voxels, with greater rCBF activity during incompatible scans. *Right*: average counts for position of the responding hand, response condition, and replication. There is a clearcut linear trend with replication (~7% increase from the first to last replication) and a mild, if not significant, spatial-compatibility effect (~3%).

gyrus corresponds to caudal premotor cortex (Preuss *et al.*, 1996; Roland and Zilles, 1996). Moreover, given that the caudal precentral gyrus and anterior bank of the central sulcus are contiguous structures, and that the anatomical variability in the region around the central sulcus is not negligible, the localization of the activated voxels, whether in the caudal sector of the precentral gyrus or in the anterior bank of the central sulcus, is uncertain. Thus, according to our data, what we can conclude is that neurons in either the caudal precentral gyrus or the anterior bank of the central sulcus in the right hemisphere merge oculomotor and somatomotor space coding, and that different anatomical models would assign this activation to the right caudal premotor cortex or the right primary motor cortex.

Neurophysiological evidence suggests that merging of oculomotor and somatomotor space coding is more likely to occur in the premotor cortex than in the primary motor cortex; indeed, the dorsal premotor cortex is considered a critical structure in nonstandard mapping mechanisms in sensorimotor integration (Wise *et al.*, 1996), and the incongruent mapping of oculomotor and somatomotor space during crossed-hands position fits well the definition of nonstandard mapping. Further, it has been recently proposed that, in humans, the upper limb representation in premotor cortex would be located in the portion of the precentral gyrus immediately caudal to the middle frontal gyrus (Preuss *et al.*, 1996). In the experiment reported here, it is the upper limb that is placed in the 'wrong' hemisphere during crossed-hands response, and the activated voxels for crossed-hands position are actually located in the portion of the precentral gyrus that is caudal to the middle frontal gyrus.

In macaques, the caudal sector of the ventral premotor cortex is mainly composed of bimodal neurons, with visual and tactile receptive fields that are gaze-independent (Fogassi *et al.*, 1992, 1996). These neurons code space in somatocentric coordinates (Graziano *et al.*, 1994; Fogassi *et al.*, 1996). Caudal ventral premotor cortex is heavily interconnected with the caudal dorsal premotor cortex (Matelli *et al.*, 1986, 1991), which is probably involved in oculomotor space

coding. Indeed, intracortical stimulation of the dorsal premotor cortex in nonhuman primates elicits eye movements in both rostral and caudal sectors (Preuss *et al.*, 1996), and gaze angle modulates the neuronal activity in the dorsal premotor cortex preceding arm movements (Boussaoud, 1995; note that, although no attempt was made by Boussaoud to differentiate rostral from caudal dorsal premotor cortex, in Fig. 2 of his paper, he provides the electrode entry points, which clearly encompass the caudalmost sector of the dorsal premotor cortex). These data in nonhuman primates are in line with neuroimaging data in humans showing frontal eye field activity in a variety of locations in premotor areas of the lateral wall of the frontal lobe (Paus, 1996; for a discussion on the cortical localization of human frontal eye fields, see also Preuss *et al.*, 1996). Further, in caudal sectors of the ventral premotor cortex, neurons with gaze-dependent visual receptive fields (Boussaoud *et al.*, 1993), but also having tactile receptive fields (Fogassi *et al.*, 1996), have been reported. This neuronal population would be intermediate between the classic oculocentric neurons and the somatocentric ones (Fogassi *et al.*, 1996). Thus, the premotor cortex, in its caudal sector, contains three different populations of neurons that cover the whole spectrum of space coding, from oculocentric to somatocentric computations, via an intermediate coding. This suggests that the caudal premotor cortex is in a position to combine oculomotor and somatomotor space coding.

The possibility remains, however, that the activation observed in our experiments is actually located in the primary motor cortex. First of all, anatomically, the primary motor cortex is just one synapse away from the three neuronal populations in caudal premotor cortex that code space in an oculomotor, somatomotor and/or intermediate fashion, as described above. Thus, it is plausible that the primary motor cortex integrates the signals from these three neuronal populations just before motor response is delivered, when oculomotor and somatomotor space are incongruent, as in our crossed-hands position. Secondly, when Boussaoud *et al.* (1993) investigated ventral premotor neurons with gaze-

dependent neuronal activity, they actually found neurons with the same properties in the primary motor cortex (Boussaoud *et al.*, 1993). These neurons might participate in integrating a retinocentric signal in the primary motor cortex with a somatocentred signal coming from bimodal ventral premotor neurons (Graziano *et al.*, 1994; Fogassi *et al.*, 1996).

The empirical evidence in favour of the hypothesis that the activated voxels in the precentral gyrus might actually be located in the primary motor cortex is the activation in the caudal postcentral gyrus, because it may represent a corollary discharge. Given that the increases in rCBF in the postcentral gyrus do not correlate with increases in reaction time from the uncrossed to crossed-hands position, it is unlikely that the postcentral gyrus activation is due to the merging of oculomotor and somatomotor space coding. It is also unlikely that the activation in the postcentral gyrus is simply a sensorial artifact. Our subjects, when responding with crossed hands, held their forearms in direct contact with one another. Thus, an unbalancing of pure somatosensory inputs to the postcentral gyrus of the left and right hemispheres cannot be completely excluded. However, we counterbalanced the forearm positions across subjects (left or right forearms uppermost in the crossed-hands position with the intravenous line was counterbalanced accordingly, *see* Methods section). Activation asymmetries in functional neuroimaging are typically difficult to detect when sensory inputs are roughly equivalent. In contrast, we observed a striking asymmetry in the left and right postcentral gyri due to crossed-hands position. In fact, increases in rCBF in the right postcentral gyrus (+0.058 in normalized counts) were six times greater than in the left postcentral gyrus (+0.009 in normalized counts), and no voxel was activated in the left postcentral gyrus even at statistical thresholds of $P = 0.05$, uncorrected for multiple comparisons, which is the most liberal statistical approach we can adopt. Hence, the large asymmetry in increases in rCBF observed in the right and left postcentral gyri during crossed-hands position compared with uncrossed hands, is unlikely to be due to unbalancing of somatosensory inputs to the two hemispheres.

The activation of the right postcentral gyrus may actually reflect a motor-to-sensory corollary discharge from the primary motor cortex (Sperry, 1950; Nelson, 1996; Paus *et al.*, 1996). Indeed, the right postcentral gyrus activation is located in Brodmann area 2, according to the standardized reference atlas (Talairach and Tournoux, 1988). Area 2 is heavily interconnected with the primary motor cortex, especially with its rostral sector (Stepniewska *et al.*, 1993). The activation in area 2 could reflect corollary discharge from the rostral sector of the primary motor cortex, via feedback connections that have been documented, at least in monkeys (Stepniewska *et al.*, 1993). Note that the premotor cortex is not directly connected with area 2, and a corollary discharge in the postcentral gyrus originating from premotor areas cannot be hypothesized.

To summarize, our data clearly identify the right precentral gyrus as the region in which oculomotor and somatomotor

space coding are merged. Whether this merging process occurs in premotor cortex or in primary motor cortex remains to be established. Our results are in line with evidence from neurological patients. Some neglect patients with a right hemisphere lesion do not move the hand ipsilateral to the lesion in the contralateral hemispace (Bisiach *et al.*, 1995), a condition similar to our crossed position. These patients frequently have right pre-rolandic lesions, often encompassing premotor and primary motor areas (Bisiach *et al.*, 1990).

Spatial compatibility effect

In a previous experiment on spatial compatibility (Iacoboni *et al.*, 1996b), we reported the activation of the superior parietal lobule bilaterally, in the incompatible condition compared with the compatible one. At that time, we did not have any *a priori* anatomical region of interest and we corrected our statistical thresholds for the whole brain in the field of view, which resulted in a quite conservative t threshold. In that experiment, however, we observed (but did not report) that the dorsal premotor cortex was activated bilaterally at $P < 0.001$, uncorrected for multiple comparisons. In this study, we observed the bilateral activation of the superior parietal lobule within our region of interest, and a left dorsal premotor cortex activation outside the boundaries of our region of interest. In a third experiment on spatial compatibility, in which we used auditory stimuli on a separate sample of subjects, we have also observed the fully significant activation of the dorsal premotor cortex and the superior parietal lobule in the left hemisphere, when premotor and posterior parietal cortex are considered as search regions of interest (M.I., R.P.W. and J.C.M., unpublished observations). Taken together, the findings of this study and of the two other experiments on spatial compatibility suggest that the superior parietal lobule and dorsal premotor cortex are activated during incompatible responses, compared with compatible responses. Indeed, we have also co-registered the images of all three experiments on spatial compatibility in the same common anatomical space (21 subjects in total) and, if the three experiments are analysed together and statistical power is gained, incompatible responses, compared with compatible ones, entail the bilateral activation of both the dorsal premotor cortex and the superior parietal lobule, even when the whole brain in the field of view is used as the region of interest.

These findings reaffirm the critical role of the dorsal premotor cortex in nonstandard mapping, as required by incompatible responses, in sensorimotor integration tasks (Wise *et al.*, 1996). Also, the parallel activation of the dorsal premotor cortex and superior parietal lobule is in line with the emerging concept that these regions are involved in solving complex computational demands originating from sensorimotor integration tasks (Caminiti *et al.*, 1996; Grafton *et al.*, 1996b; Johnson *et al.*, 1996; Wise *et al.*, 1997). Several computational models have been proposed for premotor–

parietal circuits (briefly reviewed in Wise *et al.*, 1997). Unfortunately, our experimental design does not allow us to disentangle the specific contribution of the dorsal premotor cortex and superior parietal lobule in the spatial-compatibility computation. Analyses of functional connectivity of the dorsal premotor cortex and superior parietal lobule areas might help delineating specific computational roles in each region and we are currently performing them. The results of these analyses, however, are beyond the scope of the present paper.

Learning effect

Learning-dependent increases in blood flow were observed in the prefrontal cortex, dorsal premotor cortex and primary motor cortex in the left hemisphere. The learning-dependent areas in the dorsal premotor cortex are located caudally to the spatial compatibility-dependent dorsal premotor area described above. We have observed this same pattern in all three experiments on spatial compatibility performed so far. This functional dissociation in rostral and caudal human dorsal premotor cortex resembles the one observed in nonhuman primates, in which cytoarchitecture, connectivity and physiological properties differ between rostral and caudal dorsal premotor cortex (Matelli *et al.*, 1991; Fujii *et al.*, 1996). As Fig. 5 shows, the learning-dependent areas show some spatial-compatibility activity, albeit not significant. This might be due to two concomitant factors affecting the activity of the more rostral voxels during learning-dependent activation. These voxels, being anatomically close to the rostral dorsal premotor area coding spatial compatibility, may show mixed learning and spatial-compatibility activity. Part of this effect might be due to the smoothing of the data (we used unsmoothed data only for the focused analysis on the precentral and postcentral gyri foci of activation; at any rate, even unsmoothed data have a spatial resolution that can mix, in principle, the blood-flow response secondary to the activity of different neuronal populations). Part of this effect, however, might be due to an intermediate population of dorsal premotor neurons located between the pure spatial-compatibility population and the pure learning population. In keeping with this, detailed neurophysiological studies of premotor cortex show that the rostral and caudal dorsal premotor cortex present a gradual, gradient-like distribution of different neuronal properties rather than an abrupt change of neuronal characteristics from one sector to another (Boussaoud and Wise, 1993a, b; Johnson *et al.*, 1996).

Finally, our data show, in the same task, a strong functional lateralization of the precentral gyrus areas. Activation related to merging oculomotor and somatomotor space is located in the right precentral gyrus and, as shown by Fig. 2, the activity of these voxels do not show any learning effect, not even a trend. Activations related to learning, in contrast, are located in the left precentral gyrus and, as shown by Fig. 5, the activity of these voxels do not show any effect of crossed-hands position, not even a trend. This functional lateralization

in premotor and motor areas, reflected also by the absence of interaction in both reaction times and blood-flow changes between the position of the responding hand and learning, is strikingly different from the generally symmetrical activity in premotor and motor areas of the two hemispheres, observed in functional neuroimaging studies of simpler motor tasks (Passingham, 1993; Roland, 1993). This suggests that areas of motor significance in the two cerebral hemispheres may be roughly equivalent in controlling standard sensorimotor mapping but radically different when nonstandard sensorimotor mapping is required.

Conclusion

The main thrust of the present study is represented by the evidence that the right precentral gyrus is activated during incongruent, nonstandard mapping of oculomotor and somatomotor space and that the rCBF changes in these activated precentral gyrus voxels correlate with reaction-time costs produced by the crossed-hands position. Whether this activation is localized in caudal dorsal premotor cortex and/or in the primary motor cortex is still unclear. Future studies will be able to address this issue in both nonhuman primates and humans. In nonhuman primates, the neurons computing the integration of oculomotor and somatomotor space coding can be precisely defined by using tasks similar to ours, single unit recordings and cytoarchitectonic maps of the electrode entry points. In humans, fMRI (functional MRI) can conceivably be used first to map the right primary motor areas in each individual subject, and then to map the activation produced by the crossed-hand responses. This would enable estimation of the relative contributions of the primary motor cortex and caudal dorsal premotor cortex in the merging of oculomotor and somatomotor space coding.

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