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Bimodal (auditory and visual) left frontoparietal circuitry for sensorimotor integration and sensorimotor learning

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Summary

We used PET to test whether human premotor and posterior parietal areas can subserve basic sensorimotor integration and sensorimotor learning equivalently in response to auditory and visual stimuli, as has been shown in frontoparietal neurons in non-human primates. Normal subjects were studied while they performed a spatial compatibility task. They were instructed to respond to lateralized auditory and visual stimuli with the ipsilateral hand (compatible condition) or with the contralateral hand (incompatible condition). Reaction times were faster in the compatible than in the incompatible condition, for both auditory and visual stimuli. Left rostral dorsal premotor and posterior parietal blood-flow increases were observed in the incompatible condition, compared with the compatible condition, for both auditory and visual modalities. Blood-flow increases, which were correlated with the reaction-time learning curves, were observed in both auditory and visual modalities in the left caudal dorsal premotor cortex. These data suggest that, as in non-human primates, human frontoparietal areas can subserve basic sensorimotor transformations equivalently in the auditory and visual modality. Further, they reveal a functional rostrocaudal fractionation of human dorsal premotor cortex that resembles the rostrocaudal anatomical and physiological fractionation observed in non-human primates.

Keywords: human brain mapping; dorsal premotor cortex; posterior parietal cortex; sensorimotor learning; stimulus–response compatibility

Abbreviation: rCBF = regional cerebral blood flow

Introduction

In the primate brain, posterior parietal and premotor cortical areas are critical structures for sensorimotor integration (Critchley, 1953; Hyvarinen, 1982; Passingham, 1993). Generally, the role of these regions in sensorimotor integration is investigated in tasks that require the integration of visual stimuli with motor responses (Wise *et al*., 1997). Nonetheless, in the non-human primate, evidence suggests the existence of premotor (Vaadia *et al*., 1986; Vaadia, 1989) and posterior parietal neurons (Mazzoni *et al*., 1996; Stricanne *et al*., 1996) that respond equivalently to visual and auditory stimuli having the same significance for motor behaviour. It has been suggested that some neurons with these characteristics may code the motor significance of external sensory stimuli (Andersen, 1995; Andersen *et al*., 1997; Snyder *et al*., 1997). Some of these neurons, however, seem to have a prevalent stimulus-related activity (Vaadia *et al*., 1986). Thus, these frontoparietal neuronal populations may be more precisely defined as subserving bimodal (auditory and visual) basic sensorimotor transformations.

Studies in neurological patients with premotor and parietal lesions are consistent with the notion that these cortical regions are important in subserving sensorimotor transformations (Halsband and Freund, 1990; Rushworth *et al*., 1997). However, when neurological patients with naturally occurring lesions are studied, precise anatomical localization is difficult. In two previous PET experiments (Iacoboni *et al*., 1996*b*, 1997*a*), we measured reaction times and regional cerebral blood flow (rCBF) while normal subjects were performing spatial stimulus–response compatibility tasks. In these tasks, subjects were required to respond to lateralized light flashes with the ipsilateral (compatible condition) or the contralateral (incompatible condition) hand.

Thus, in both conditions the same stimuli and responses were used; only the mapping between stimuli and responses was changed. This type of paradigm allows a good control of sensory and motor activity in different experimental conditions when using a technique, such as PET, that cannot afford the temporal precision of single-unit recordings to disentangle sensory and motor aspects of basic sensorimotor transformations.

In both PET studies (Iacoboni *et al*., 1996*b*, 1997*a*), contralateral motor responses produced longer reaction times (~40–60 ms) than ipsilateral responses. This cannot be attributed to callosal transmission delay, which is known to be ~3–4 ms in humans (Iacoboni *et al*., 1994; Iacoboni and Zaidel, 1995). Indeed, contralateral responses were slower than ipsilateral ones even when subjects responded with crossed hands, the left hand in right hemispace and the right hand in left hemispace (Iacoboni *et al*., 1997*a*). The longer reaction times for contralateral responses may be produced by the more complex sensorimotor mapping required by the incompatible condition (Umiltá and Nicoletti, 1990), which may also lead to increased executive control. This is also suggested by rCBF increases in dorsal premotor cortex and superior parietal lobule in the incompatible condition, compared with the compatible one (Iacoboni *et al*., 1996*b*, 1997*a*). Indeed, these two areas are known to be involved in spatial behaviour and spatial working memory (Courtney *et al*., 1996, 1998; Jeannerod, 1997).

In those two studies, we also observed learning-dependent, left dorsal premotor rCBF changes that follow the reaction-time learning curves of the subjects. The learning dependent dorsal premotor area was consistently located caudally to the dorsal premotor area responding to spatial compatibility, suggesting a regional fractionation in the human dorsal premotor cortex that resembles the fractionation of non-human primate dorsal premotor cortex described by previous studies (Matelli *et al*., 1985, 1991).

To test whether human dorsal premotor and posterior parietal areas can be similarly activated by identical sensorimotor transformations for auditory and visual stimuli, we studied a group of normal subjects performing a spatial compatibility task in which lateralized auditory stimuli were used. We co-registered the PET images of the subjects participating in this auditory experiment with those of the subjects participating in the previous visual experiment on spatial compatibility (Iacoboni *et al*., 1996*b*), to enable comparison of the anatomical locations of the activated areas in these two groups of subjects. The second previously reported experiment on spatial compatibility in which we used visual stimuli (Iacoboni *et al*., 1997*a*) was not used for comparison with the novel auditory experiment presented here because of experimental design differences. Preliminary analyses of these data have been previously reported in abstract form (Iacoboni *et al*., 1996*a*, 1997*b*).

Methods

Subjects

In accord with UCLA Human Subject Protection Committee guidelines, informed consent was obtained from all subjects. Eight subjects participated in the auditory experiment. Due to large head movements, one subject was excluded from the analysis. The remaining seven subjects, six males and one female, all right-handers, had a mean age (± SD) of 24.9 ± 3.63 years. Six right-handers, four males and two females, with a mean age of 25.6 ± 2.06 years, participated in the visual experiment (Iacoboni *et al*., 1996*b*). Handedness was assessed by means of a handedness questionnaire, modified from the Edinburgh inventory (Oldfield, 1971). Subjects were normal in terms of their history and general medical and neurological examinations.

Sensorimotor task

A Macintosh computer monitor was positioned 57 cm away from the subject's eyes in both the auditory and the visual experiment. A central fixation cross was presented throughout both experiments. The software package MacProbe was used for stimulus presentation and response recording. Software characteristics have been described elsewhere (Zaidel and Iacoboni, 1996). In the auditory task, subjects listened through earphones to auditory tones of 1000 Hz that were presented for 100 ms to the left or the right ear. In the visual task, subjects were presented with light flashes lasting 50 ms and subtending 1° of visual angle at 8° from the midsagittal plane and on the same horizontal plane as visual fixation.

In both experiments, subjects used hand-held microswitches for motor responses. Stimuli were presented in both experiments every 1.25 s, regardless of the response time on the previous trial. This kept the number of sensory stimuli and motor responses constant for each scan in each subject. Subjects began the task 30 s before the scan. Twenty-four sensory stimuli (12 left and 12 right) were presented before the scan and 48 stimuli (24 left and 24 right) during the 60-s PET scan.

Repeated measures ANOVAs (analyses of variance) were performed using the accuracy of responses and median reaction times for correct responses as the dependent variables. The experiment (auditory and visual) was treated as a between-subject factor, and response condition (compatible and incompatible), replication scan (scans 1–6) and response hand (left and right) were treated as within-subject factors. Only trials performed during rCBF data acquisition were analysed. Reaction times of $<$150 ms were considered anticipatory errors, and reaction times of $>$600 ms were considered attentional errors. Both were removed from the ANOVA.

Brain imaging

We used a customized foam head holder (Smithers Corporation, Akron, Ohio, USA) to minimize head movements. A transmission scan, using a ^{68}Ge ring source, was performed in each subject before the PET imaging session, in order to locate premotor and posterior parietal areas in the centre of the field of view, where 3D PET imaging has the highest sensitivity (Cherry *et al*., 1993). Twelve PET scans, six per response condition, were performed in each subject. Response conditions were alternated during the imaging session, and were counterbalanced across subjects. For each PET scan, a 10-mCi (370 MBq) bolus of $H_2{}^{15}O$ in 7 ml of normal saline was injected via an intravenous line in the left hand. Counts were collected in a single 60-s frame, starting at the time of the injection.

The PET scanner used in both experiments was a Siemens/CTI 831–08 tomograph (Siemens Corporation, Hoffman Estates, Ill., USA), modified for 3D data acquisition and reconstruction (Cherry *et al*., 1993) and with axial field of view of 101.25 mm. PET images were reconstructed to obtain 15 planes of 128 × 128 pixels and an inter-plane distance of 6.75 mm. We applied in-plane Gaussian filtering to produce a final image resolution of 10.12 × 10.12 × 10 mm full-width at half-maximum. Image registration was performed with automated image registration (Woods *et al*., 1998*a*). The original axial planes were interpolated to create 55 planes, and global normalization was applied (Mazziotta *et al*., 1985). Inter-subject stereotaxis was performed using a 12-parameter affine registration model (Woods *et al*., 1998*b*).

Three-way ANOVAs were performed using normalized counts in each voxel as the dependent variable and with response condition (compatible and incompatible), replication scan (scans 1–6) and subjects as between-voxel effects (Woods *et al*., 1996). In these ANOVAs, the two experiments were always analysed separately, and a common anatomical space was used only for anatomical comparisons. With dorsal premotor cortex and the lateral wall of posterior parietal cortex already well established (Iacoboni *et al*., 1996*b*, 1997*a*) as the general regions associated with visuomotor integration, we restricted our primary search for potentially similar auditory-motor integrative areas to these anatomically defined regions. Statistical thresholds, estimating variance separately for each voxel, were adjusted for multiple spatial comparisons accordingly (Worsley *et al*., 1996). We then used the significantly activated areas in the auditory task as hypothesis driven search regions to test whether these specific areas were also activated in the visual task. This hypothesis driven search differs from our original analysis of the visual data in which the entire brain was used as an anatomically defined search region (Iacoboni *et al*., 1996*b*).

Results

Behavioural data

The very small number of incorrect responses (~2%) did not differ between the auditory and visual tasks or between response conditions (compatible and incompatible). The accuracy of responses also showed no task × response-condition interaction. For reaction times, no overall differences between the auditory and visual task were observed [$F(1,11) = 0.328$, $P > 0.5$]. Ipsilateral responses were 52 ms faster than contralateral responses, for both the auditory [$F(1,6) = 99.378$, $P < 0.0001$] and the visual [$F(1, 5) = 66.200$, $P < 0.0005$] task (Fig. 1).

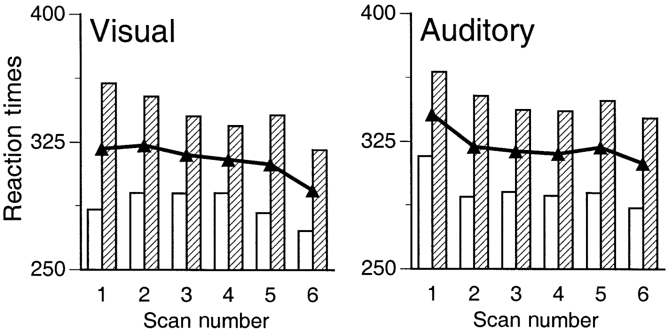

Fig. 1 Reaction times in auditory and visual spatial stimulus–response compatibility. The overall spatial compatibility effect is identical in both tasks (52 ms). The learning curves are similar in both tasks and for both spatial compatibility conditions (not statistically different, $P = 0.78$). Open bars represent the compatible response condition, hatched bars the incompatible response condition and closed triangles mean reaction times.

Reaction times decreased in parallel from the first to the last scan in both response conditions and for both auditory and visual tasks. The reaction-time learning-curve slope was significant for a linear trend for both the auditory ($P < 0.05$) and the visual tasks ($P < 0.05$). The reaction-time learning curve also fits the 'power law of practice' for both auditory ($r = -0.847$, $P < 0.05$) and visual tasks ($r = -0.816$, $P < 0.05$). The 'power law of practice' is a ubiquitous learning pattern in sensorimotor tasks that indicates a linear relationship between the logarithm of the performance and the logarithm of the amount of practice (Newell and Rosenbloom, 1981).

No interactions were observed between task and spatial compatibility [$F(1,11) = 0.002$, $P = 0.96$], between task and learning [$F(1,11) = 0.497$, $P = 0.78$] or between task, spatial compatibility and learning [$F(1,11) = 0.335$, $P = 0.89$].

Imaging data

In subjects participating in the auditory experiment, the incompatible response condition, compared with the compatible one, produced rCBF increases [$t(30) = 5.15$, $P < 0.05$, corrected for the anatomically defined search region] in voxels located in a left dorsal premotor area, in the superior frontal sulcus, anterior to the precentral sulcus [stereotaxic coordinates (Talairach and Tournoux, 1988), $x = -24$, $y = 5$, $z = 52$]. The same voxels had a similar stimulus–response activity in subjects participating in the visual experiment, [$t(25) = 2.68$, $P < 0.05$, corrected for the hypothesis driven search region] (Fig. 2). In subjects participating in the auditory experiment, the incompatible response condition, compared with the compatible one, also produced rCBF

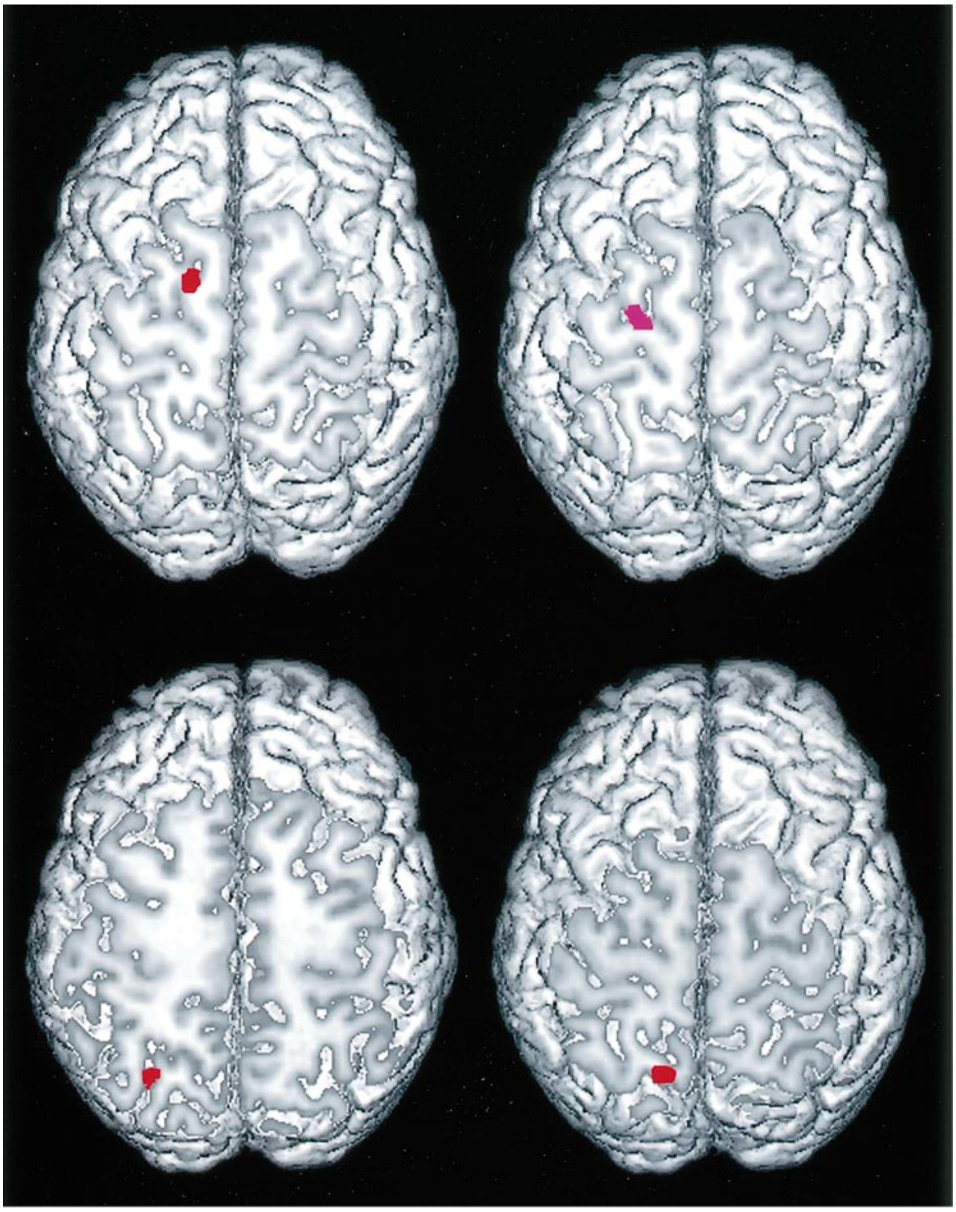

Fig. 2 *Top left*: rostral dorsal premotor area showing stimulus–response activity in auditory and visual spatial stimulus–response compatibility (red). These voxels, as explained in detail in the Methods section, were first found significant for stimulus–response tasks in the auditory experiment. Subsequently, the same voxels were formally tested for stimulus–response activity in the visual task, and their normalized counts were also found significant for stimulus–response tasks. The same approach applies to the other three areas shown in this figure. Normalized counts in each scan in the auditory and visual tasks for this area and the other areas shown in this figure are presented in graphical form in Fig. 3. *Top right*: caudal premotor area showing learning-dependent activity in auditory and visual spatial stimulus–response compatibility (purple). *Bottom left*: intraparietal sulcus area showing significant stimulus–response activity in auditory and visual spatial compatibility (red). *Bottom right*: area in the transverse parietal sulcus showing stimulus–response activity in auditory and visual spatial compatibility (red). The MRI of a single subject participating in the visual experiment is used for display purposes in these renderings; it was made using the software package Sunvision (Sun Microsystems, Mountain View, Calif., USA). The left side of each image shows the subject's left hemisphere.

increases [$t(30) = 5.15$, $P < 0.05$, corrected for the anatomically defined search region] in voxels located in two posterior parietal areas of the left hemisphere (Fig. 2). One of the two areas was located in the anterior bank of the transverse parietal sulcus, in the superior parietal lobule (stereotaxic coordinates, x = –15, y = –52, z = 50). The other posterior parietal area was located more laterally, in the intraparietal sulcus (stereotaxic coordinates, x = –29, y = –54, z = 45).

In subjects participating in the visual experiment, the same voxels located in the two posterior parietal areas described above also showed significant rCBF increases [$t(25) = 2.41$ and $t(25) = 2.28$, $P < 0.05$, corrected for the hypothesis driven search region)] during incompatible responses, compared with compatible responses.

With regard to learning-dependent activity, subjects participating in the auditory experiment showed serial rCBF increases that followed the subjects' reaction-time learning curves [$t(30) = 5.15$, $P < 0.05$, corrected for the anatomically defined search region] in voxels located in a left dorsal premotor area, in the precentral sulcus [$x = -28$, $y = -9$, $z = 54$], posterior to the dorsal premotor area significant for spatial compatibility described above. These same voxels showed similar learning-dependent rCBF increases in the visual task [$t(25) = 2.66$, $P < 0.05$, corrected for the hypothesis driven search region], and these increases followed the reaction-time learning curves of subjects participating in the visual task (Fig. 2). The activity in these voxels was also significant for time effects without prespecified curve fitting in both the auditory [$F(5,30) = 9.65$, $P < 0.05$, corrected for the anatomically defined search region] and visual task [$F(5,25) = 4.25$, $P < 0.05$, corrected for the hypothesis driven search region].

No stimulus–response or learning-dependent rCBF decreases were observed in either experiment. No higher order interactions were observed. Figure 3 summarizes the activity of all the activated areas in both auditory and visual task.

Discussion

In two different samples of subjects, one performing a spatial compatibility task with auditory stimuli, and another performing the same task with visual stimuli, we observed four distinct cortical areas of activation that were common to both groups of subjects. Three areas were related to the explicit sensorimotor mapping required by the task, and were located in the superior frontal sulcus, in rostral dorsal premotor cortex, and in the transverse parietal and intraparietal sulci, in posterior parietal cortex. The fourth area was related to the implicit sensorimotor learning that made subjects' reaction times progressively shorter in both response conditions and for both sensory modalities. This area was located in the precentral sulcus, in caudal dorsal premotor cortex. All four areas were lateralized to the left hemisphere.

Behavioural performance, as expressed by reaction times, and cortical activity, as measured by blood flow changes, will each be discussed in separate sections. First, however, we comment on a methodological issue. Ideally, one would perform the auditory and visual experiment in the same set of subjects to circumvent inter-subject anatomical differences. However, radiation exposure limits preclude a full experimental design comprising six replication scans per response condition per stimulus modality that allows a more powerful approach for studying sensorimotor learning. Note, however, that inter-subject anatomical differences may produce apparently different activated areas between groups or may simply prevent the observation of commonly activated areas, but it is unlikely that they would produce spurious common activations in two different sets of subjects.

Behaviour

Three main aspects of the performance, as expressed by reaction times, are of interest here. First, overall reaction times in the auditory and visual task are largely similar. This is not often observed when reaction times to auditory and visual stimuli are compared. Generally, reaction times to auditory stimuli are shorter than reaction times to visual stimuli, although this is more frequently observed in simple (detection) reaction-time studies than in choice reaction-time studies as in our case [see, for example, classic studies such as Todd (1912) and, more recently, Miller (1982, 1986)]. One can invoke individual differences between the subjects enrolled in the auditory and visual study to explain our unusual finding, but the frequent replicability of shorter reaction times to auditory stimuli across several studies makes this explanation unlikely. It is possible that the lack of an overall reaction-time difference between the two modalities is due to a peculiar aspect of our study. To maximize cortical activation during scan time, stimuli were presented at a very fast pace, i.e. 1.25 s per trial. This is a much faster pace than for canonical behavioural studies, in which each trial generally lasts 3–5 s. This may have made the task slightly more difficult, and may have equated reaction times in the two modalities. In keeping with the hypothesis that the tasks were more difficult at a very fast pace of stimulus presentation, learning in our subjects is slower than in published studies on learning in spatial stimulus–response compatibility (Dutta and Proctor, 1992; Proctor and Dutta, 1993).

Alternatively, one might hypothesize that the processing in posterior parietal areas (that may be specifically required by spatial compatibility tasks) may have equalized the overall reaction times. In fact, when latencies in single-unit studies are considered, lateral intraparietal neurons in non-human primates that respond to auditory stimuli have the same median latency as lateral intraparietal neurons that respond to visual stimuli (Mazzoni *et al.*, 1996), even though it is well known that primary visual neurons have longer latencies than primary auditory neurons (Maunsell and Gibson, 1992; Recanzone *et al.*, 1993). Faster responses to auditory stimuli, compared with visual stimuli, have also been observed in premotor neurons in the monkey (Vaadia *et al.*, 1986). Thus, one could speculate that the posterior parietal involvement in the information processing steps required by the spatial compatibility task may have equalized the overall reaction times in the two modalities, in that both auditory and visual stimuli are processed in posterior parietal regions relevant to sensorimotor transformations at approximately the same latency in the information processing sequence.

With regard to spatial compatibility, similar effects have

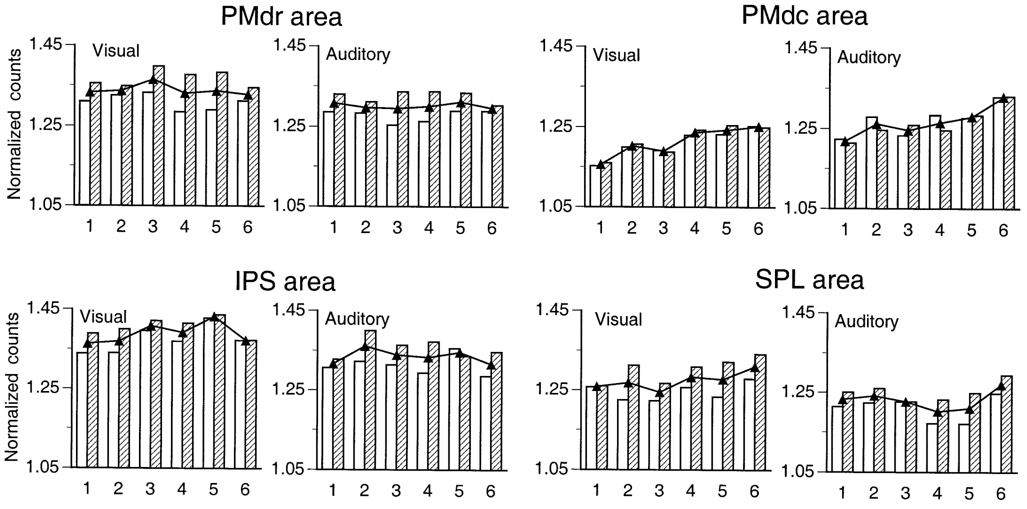

Fig. 3 Normalized counts in the four areas activated in both visual and auditory task. The rostral dorsal premotor area (PMdr), located in the superior frontal sulcus, shows an increase in normalized counts during incompatible response condition (hatched bars) compared with the compatible one (open bars), of 4.5% in the visual experiment and 3.8% in the auditory experiment. The closed triangles represent the average counts of the two response conditions in each scan. No learning effects are observed in the rostral area. The caudal dorsal premotor area (PMdc), located in the precentral sulcus, shows an increase in normalized counts, from the first to the last scan, of 8.3% in the visual experiment and 9% in the auditory experiment. This area shows no stimulus–response activity; the difference between the two response conditions was 0.5% in the visual experiment and 0.6% in the auditory experiment. The intraparietal sulcus area (IPS) shows rCBF increases from the compatible to incompatible response condition, of 2.9% in the visual experiment and 3.0% in auditory experiment. Learning effects are not significant in this area. The superior parietal lobule area (SPL), located in the transverse parietal sulcus, shows an rCBF increase of 3.9% from the compatible to incompatible response condition in the visual experiment; in auditory experiment the increase was 4.0% in the transverse parietal sulcus area. Learning effects are not significant in this area.

previously been observed in the auditory and visual modality (for an overview of several studies, see Proctor and Reeve, 1990). Thus, our finding of an identical spatial compatibility effect (52 ms) in both auditory and visual modalities is not surprising. Finally, the learning curves in both auditory and visual modalities are also largely similar. To the best of our knowledge, this is the first study in which learning in spatial compatibility in the auditory modality has been investigated, the two previous studies on learning in spatial compatibility being confined to visual stimuli (Dutta and Proctor, 1992; Proctor and Dutta, 1993). Although largely similar learning in the two modalities cannot be considered conclusive evidence in favour of shared neural substrates for learning spatial stimulus–response associations in the auditory and visual domain, the reaction-time data are consistent with the observation of a dorsal premotor area with similar learning-dependent activity in both auditory and visual tasks.

Blood flow

In non-human primates, a variety of corticocortical circuits connecting dorsal premotor and posterior parietal cortices have been described recently, which are involved in sensorimotor integration and sensorimotor learning (Passingham, 1989, 1993; Wise *et al.*, 1996, 1997). A series of recent functional neuroimaging studies largely confirms this role in human frontoparietal areas (Deiber *et al.*, 1997; Winstein *et al.*, 1997; Grafton *et al.*, 1998). In humans, however, few data are available with regard to the integration of auditory stimuli with motor responses, and they are restricted to brain-damaged patients (Halsband and Freund, 1990). Our data suggest that dorsal premotor and posterior parietal cortex can subserve the integration of auditory stimuli and motor responses, and that there exists some frontoparietal areas that are involved in sensorimotor integration for both auditory and visual modalities. This would be in line with neurophysiological evidence in the non-human primate showing premotor and posterior parietal neurons equally responsive to both auditory and visual stimuli (Vaadia *et al.*, 1986; Vaadia, 1989; Mazzoni *et al.*, 1996; Stricanne *et al.*, 1996).

The two left posterior parietal areas observed here may be related to processing the significance of external stimuli for spatial motor behaviour, which is invariant across the two experiments. In monkeys, the removal of the superior parietal lobule produces the inability to select a given action to an arbitrarily associated external stimulus (Halsband and Passingham, 1982). In humans, neurological patients with stroke lesions encompassing the posterior parietal cortex show more persistent motor deficits in the long-term (Pantano *et al.*, 1996). If the significance of sensory stimuli for action is abolished, motor rehabilitation and spontaneous motor recovery are limited. Further, in optic ataxia patients with lesions in the upper part of the posterior parietal cortex, left-sided lesions were associated with sensorimotor integration disorders in which motor deficits were more evident, whereas right-sided lesions were associated with sensorimotor integration disorders in which spatial deficits were more evident (Perenin and Vighetto, 1988). This suggests a functional specialization of the upper part of the human posterior parietal cortex, with the left superior parietal lobule more specialized for motor control or, as recently proposed, for motor attention, as distinguished from orienting (or spatial) attention (Rushworth *et al.*, 1997). Finally, the rostral dorsal premotor area showing stimulus–response activity in both modalities supports the role of dorsal premotor cortex in response selection, and in control of motor behaviour guided by external sensory stimuli and sensorimotor mapping, especially in non-standard situations (Wise *et al.*, 1996), as in our incompatible response condition.

An alternative explanation is that the stimulus–response compatibility activations seen in frontal and parietal areas in our study may be accounted for by the increased executive control required by the more difficult incompatible task. There is evidence that frontoparietal areas are involved in working memory tasks (Courtney *et al.*, 1996); in particular, an area in dorsal premotor cortex has been recently described that seems specialized in spatial working memory (Courtney *et al.*, 1998).

If the rostral dorsal premotor area described here responds to the increased executive control demands required by the incompatible response condition, the caudal dorsal premotor area showing learning-dependent activity is definitely not affected by different task demands between compatible and incompatible response conditions. In fact, the two dorsal premotor areas described here show a functional double dissociation. The functional fractionation of human dorsal premotor cortex suggested by our data closely resembles the pattern of rostrocaudal fractionation observed in non-human primate dorsal premotor cortex (Matelli *et al.*, 1985, 1991). This suggests that a modular organization of dorsal premotor areas may be largely invariant in primates, as is the case in medial premotor areas (Picard and Strick, 1996). In medial premotor areas, when one looks at activation maps in a variety of functional neuroimaging studies, there appears to be a pattern such that anterior areas (the so-called 'pre'-supplementary motor area) are activated by 'cognitive' tasks, whereas posterior areas (supplementary motor area 'proper') are activated by 'motor' tasks [see Picard and Strick (1996) and references therein]. Our data, if one interprets a differential activation between compatible and incompatible tasks as reflecting attentional demands, fit this pattern. If this is a correct interpretation, then the learning that occurs in the caudal dorsal premotor area may be interpreted more as 'motor' than 'cognitive'.

The involvement of dorsal premotor cortex in sensorimotor learning in both non-human primates and humans is well known (Mitz *et al.*, 1991; Germain and Lamarre, 1993; Passingham, 1993; Roland, 1993; Iacoboni *et al.*, 1996*b*). However, most of the human empirical evidence is restricted to sensorimotor learning in tasks in which visual stimuli were used. The learning-dependent dorsal premotor area described here showed rCBF increases that fitted the reaction-time learning curve for both auditory and visual stimuli. To the best of our knowledge, this is the first time that a human dorsal premotor cortex area with these characteristics has been described. Future studies may determine how the activity in this area can be modulated. For instance, it is well known that the simultaneous presentation of auditory and visual stimuli produces a shortening of reaction times (Todd, 1912; Miller, 1982, 1986) and may also reduce the learning component in this task. Future studies may determine whether tasks in which auditory and visual stimuli are presented simultaneously are associated with less blood flow changes over time in this region.

Increased learning-dependent neuronal firing, which follows the behavioural learning curve, as the rCBF time–activity profile in the learning-dependent dorsal premotor area did in our study, has been reported in non-human primates (Mitz *et al.*, 1991). Interestingly, the increased learning-dependent neuronal firing in dorsal premotor cortex has been reported to lag behind the behavioural learning curve in monkeys (Mitz *et al.*, 1991). This suggests that a stimulus–response association must have been already established by other neurons subserving the retrieval mechanism of correct motor responses to sensory stimuli more than learning *per se*. This is in line with our findings showing separate dorsal premotor areas for spatial compatibility and for sensorimotor learning.

In monkeys, anterior and posterior dorsal premotor areas are reciprocally connected by robust corticocortical connections (Matelli *et al.*, 1991). Assuming similar connections in the human, one might hypothesize that the functional segregation observed in our study between the two dorsal premotor areas can be modified in an efficient interaction, when needed, and according to task demands. This would follow the general organizing principles of segregation and integration in the brain (Tononi *et al.*, 1994, 1996), subserving a flexible and adaptive behaviour that can be modified on a case-by-case basis.

Finally, all the activated areas observed in this study were lateralized to the left hemisphere. Chronometric investigations, comparing reaction times in the same right-handed subjects, have shown much shorter reaction times with the right hand than with the left hand in spatial compatibility tasks compared with simple (detection) reaction-time tasks with lateralized flashes (Anzola *et al.*, 1977). This suggests that the human left hemisphere may be superior in tasks, such as spatial compatibility, in which stimulus–response associations and response selection are required.

With regard to sensorimotor learning, some evidence for hemispheric asymmetry has recently been provided in humans (Thut *et al.*, 1996, 1997). This lateralization may not be specific to the human brain, since lateralized left frontal, learning-dependent activity has recently been reported in a non-human primate during sensorimotor learning (Gemba *et al*., 1995).

One must keep in mind, however, that functional maps in activation studies only show voxels where activity is beyond a statistical threshold. In other words the maps 'binarize' (active or not active), brain activity that is, in fact, continuous. Thus, lateralized activation patterns in functional neuroimaging must always be considered as relative, rather than absolute. In keeping with this, when we analysed the data of three different experiments on spatial compatibility, encompassing 21 subjects, we gained enough statistical power to be able to observe bilateral activations in both dorsal premotor and superior parietal cortex (Iacoboni, 1998).

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