Interhemispheric Transmission of Visuomotor Information in Humans: fMRI Evidence

Tettamanti, M., E. Paulesu, P. Scifo, A. Maravita, F. Fazio, D. Perani, and C. A. Marzi. Interhemispheric transmission of visuomotor information in humans: fMRI evidence. J Neurophysiol 88: 1051–1058, 2002; 10.1152/jn.00417.2001. Normal human subjects underwent functional magnetic resonance imaging (fMRI) while performing a simple visual manual reaction-time (RT) task with lateralized brief stimuli, the so-called Poffenberger’s paradigm. This paradigm was employed to measure interhemispheric transmission (IT) time by subtracting mean RT for the uncrossed hemifield-hand conditions, that is, those conditions not requiring an IT, from the crossed hemifield-hand conditions, that is, those conditions requiring an IT to relay visual information from the hemisphere of entry to the hemisphere subserving the response. The obtained difference is widely believed to reflect callosal conduction time, but so far there is no direct physiological evidence in humans. The aim of our experiment was twofold: first, to test the hypothesis that IT of visuomotor information requires the corpus callosum and to identify the cortical areas specifically activated during IT. Second, we sought to discover whether IT occurs mainly at premotor or perceptual stages of information processing. We found significant activations in a number of frontal, parietal, and temporal cortical areas and in the genu of the corpus callosum. These activations were present only in the crossed conditions and therefore were specifically related to IT. No selective activation was present in the uncrossed conditions. The location of the activated callosal and cortical areas suggests that IT occurs mainly, but not exclusively, at premotor level. These results provide clear cut evidence in favor of the hypothesis that the crossed-uncrossed difference in the Poffenberger paradigm depends on IT rather than on a differential hemispheric activation.

INTRODUCTION

There is abundant evidence that interhemispheric transfer (IT) of visuomotor information can be assessed by a simple behavioral method, the so-called Poffenberger paradigm (Marzi 1999; Poffenberger 1912). The rationale is straightforward: in a simple unimanual reaction-time (RT) paradigm with lateralized visual stimuli, the crossed hemifield-hand combinations typically yield longer RTs than the uncrossed combinations. This crossed-uncrossed difference (CUD) is widely interpreted as reflecting IT time because in the crossed conditions, the hemisphere of stimulus entry is different from the hemisphere controlling the motor response and an IT is necessary. In contrast, in the uncrossed conditions, the hemisphere of stimulus entry and that subserving the response coincide and an IT is unnecessary. Therefore by subtracting the mean RT of the two uncrossed combinations (right hemifield/right hand and left hemifield/left hand) from the mean RT of the two crossed combinations (right hemifield/left hand and left hemifield/right hand), one can infer IT time from the CUD. The typical estimate obtained in normal individuals is about 4 ms (Marzi et al. 1991). The CUD has been shown to be very stable over the entire distributions of RTs, that is, it is fairly consistent across fast and slow RTs (Iacoboni and Zaidel 2000). That the corpus callosum is involved in IT has been convincingly shown by the marked lengthening of the CUD in patients with either a surgical section (CUD 14 times longer than in normals) or a genetic absence (CUD 5 times longer than in normals) of the corpus callosum (see Marzi et al. 1991 for a review). However, direct physiological evidence is lacking.

This “structural” hypothesis that the callosal transmission is responsible of the CUD has been challenged by a hypothesis that considers the CUD as related to a differential hemispheric activation. According to such a “dynamic” hypothesis, the hemisphere directly accessed by the visual input is more strongly activated than the indirectly accessed one and therefore responds more quickly to visual stimuli (Kinsbourne 2002; Ledlow et al. 1978). According to this view, the CUD does not reflect callosal conduction time but rather the difference between the response speed of the directly versus the indirectly activated hemisphere. Recently, in a PET study of normal subjects performing a Poffenberger paradigm, Marzi et al. (1999) found that different areas are selectively activated in the crossed versus the uncrossed conditions. This evidence is not in keeping with the differential hemispheric activation hypothesis of Kinsbourne that predicts that in the uncrossed conditions, there should be a higher degree of hemispheric activation in the crossed conditions as a result of the direct versus callosal input to either hemisphere. In Marzi et al.’s study (1999), different areas were activated in the crossed and un-
crossed conditions, and therefore it is difficult to decide whether the overall pattern of activation was greater or not in one or the other condition.

In the present study, we used functional magnetic resonance imaging (fMRI) to assess the involvement of specific brain structures in the IT of visuomotor information. A positive answer would support the IT hypothesis of the CUD in the Poffenberger paradigm. We used fMRI because its temporal resolution is higher than that of PET and makes it possible to acquire a high number of scans in each subject (Joliot et al. 1999; Paulesu et al. 1995). In particular, we wanted to test directly the possibility of an activation of the corpus callosum. Of course, activation of the white matter in an fMRI experiment is typically considered as problematic. The literature on metabolic and perfusion imaging of the corpus callosum is scanty, although white-matter glucose metabolism seems to be correlated with the degree of gray-matter activity as pointed out by Sokoloff (1979) in his pioneering description of the deoxyglucose method. He noted that the metabolism of the corpus callosum was about 30% higher in unanesthetized than anesthetized rats. Recently, Weber et al. (2002) have measured glucose metabolism in the rat’s corpus callosum during intracortical electrostimulation of the motor cortex. Using [18F] fluorodeoxyglucose (FDG) autoradiography, they found a tight positive correlation between rate of stimulation and callosal cerebral metabolic rate for glucose. It is important to point out that the direct injection of FDG in the electrically stimulated cortical area produced no increase in callosal uptake, and this rules out the possibility that the observed FDG uptake in the corpus callosum might be ascribed to axonal diffusion. Changes of callosal glucose metabolism have been recently measured in vivo in humans by Karbe et al. (1998): they analyzed with PET the regional glucose metabolism of the corpus callosum and of speech-relevant cortical areas in 10 individuals during word repetition and found task-induced metabolic changes of the callosal midbody and isthmus. In our previous perfusion PET study (Marzi et al. 1999), we did not find direct evidence of a callosal activation during IT, but we found cortical areas that were selectively activated during the crossed rather than the uncrossed conditions and therefore were likely to be involved in IT. Studies showing a hemodynamic response in the hemispheric white matter are scanty: Brandt et al. (2000) found a negative signal change in the occipital white matter containing the optic radiations contralateral to the visually stimulated hemisphere, and Mosier and Bereznyaya (2001) found a direct activation of the corpus callosum during swallowing.

To our knowledge, evidence against the possibility of measuring activations in the corpus callosum has never been provided. Moreover, an increase in perfusion in the white matter, though less strong than in the gray matter, has been demonstrated in various studies (Preibisch and Haase 2001; Rostrup et al. 2000).

The design of our study involved subtraction of the faster uncrossed responses from the crossed responses. This procedure enabled us to find out what areas are selectively activated during the conditions requiring an IT. A second aim of the present experiment was to find out whether IT of visuomotor information transfers at visual or at premotor callosal and cortical sites, or at both, a question that has been long debated (Berlucchi et al. 1995).

METHODS

Subjects

Eight normal right-handed subjects (age range, 21–28 yr) participated in the study. Informed consent was obtained from all subjects after explanation of the purpose and the nature of the study. The experiment was approved by the Ethical Committee of the Milan San Raffaele Hospital.

Behavioral paradigm

The visual stimuli consisted of a square patch of light of about 1° size and 25 ms duration appearing at a retinal eccentricity of about 7° along the horizontal meridian of one or the other visual hemifield. They were tachistoscopically projected through the Faraday cage onto a nonmagnetic opaque screen placed outside the magnet bore by means of a projector connected to a personal computer. Subjects viewed the stimuli through a mirror, placed above their eyes, on the head-coil. They were supposed to press a key as quickly as possible with the index finger following stimulus presentation. RT was measured to the nearest millisecond by means of a response-box connected to the computer. One control and four experimental conditions were included in the task design. In the control condition, no stimuli were presented, and no responses were required; subjects were only supposed to maintain the gaze on the central fixation (rest condition). The experimental conditions were the following: stimuli to the right visual field (RVF) and response with right hand (RH) (uncrossed); stimuli to the left visual field (LVF) and response with left hand (LH) (uncrossed); stimuli to the RVF and response with the LH (crossed); and stimuli to the LVF and response with the RH (crossed). Both the control and the experimental conditions consisted of four blocks of 25 trials. Each block lasted about 30 s. Immediately before the start of each block written information on the hemifield of stimulus appearance and the hand to be used for response appeared on the screen for 12 s.

Functional data

fMRI data were acquired using a 1.5 Tesla GE (General Electric, Milwaukee, WI) scanner with a standard head coil. After the scout scan, for the visualization of the anterior commissure-posterior commissure (AC-PC) line, an anatomical image (SE, TR = 600 ms, TE = 50 ms, 256 × 256 × 24, 280 × 280 mm, slice thickness = 4 mm) in the same location of the fMRI data was acquired to facilitate the subsequent image processing (i.e., the normalization to the Talairach space). The functional images were acquired using a gradient echo EPI pulse sequence (TR = 2400 ms, TE = 60 ms, 64 × 64, 280 × 280 mm). The slices were 4 mm thick and positioned to cover the Talairach space from −24 to +68 mm with respect to the AC-PC plane. Each sequence consisted of 126 TRs (volumes). Data analysis was performed in MATLAB 4.2 (Math Works, Natick, MA) using statistical parametric mapping software (SPM-97, Wellcome Department of Cognitive Neurology, London, UK). First, fMRI scans were realigned within sessions; scans were subsequently normalized into the standard stereotaxic space implemented within the software to allow inter-subject data averaging and comparison across tasks. The stereotaxically normalized scans were smoothed through a Gaussian filter of 10 × 10 × 10 mm. Statistical analyses were performed according to the implementation of the general linear model for fMRI data devised by Friston et al. (1995) for SPM-96. Global differences in fMRI signal were compensated for by proportional scaling for all voxels. Average scans were obtained for each experimental condition and baseline, for each subject, to perform a random-effects analysis as implemented in SPM97 (Frisson and Pocock 1992). Comparisons between experimental conditions were performed as main effects according to a subtractive design: The main effect of right visual field was calculated according to the following formula: (RVF/RH +
FIG. 1. Mean reaction time for the 4 conditions of hemifield of visual presentation and hand used for response. LVF, left visual hemifield; RVF, right visual hemifield; LH, left hand; RH, right hand. Notice that for either hemifield the responses using the ipsilateral hand are faster than those using the contralateral hand.

RVF/LH – (LVF/LH + LVF/RH). The main effect of left visual field was given by (LVF/LH + LVF/RH) – (RVF/RH + RVF/LH). By the same logic, the main effect of right hand was given by (RVF/RH + LVF/RH) – (LVF/LH + RVF/LH); finally the main effect of left hand was given by (LVF/LH + RVF/LH) – (RVF/RH + LVF/RH).

The crucial effects of crossing condition were calculated by the subtractions: crossed conditions minus uncrossed conditions (RVF/LH: 262 ms; LH/LVF: 264 ms) yielded longer RTs than the two uncrossed conditions (RH/RVF: 257 ms; LH/LVF: 260 ms). The mean CUD was 5 ms, a value very close to that reported in Marzi et al.’s (1991) meta-analysis (4 ms). Further, in keeping with the above-mentioned meta-analysis, the longest RTs were those of the crossed condition RVF/LH confirming evidence for a slower IT from left to right hemisphere than vice versa; that is, IT was slower when the visual stimulus was initially channeled to the left hemisphere, and the motor response was subserved by the right hemisphere rather than in the reverse condition (Marzi et al. 1991). Six of seven subjects showed a positive CUD. The behavioral data of one subject were lost due to a technical failure. The fMRI data were instead available for all eight subjects.

Functional imaging

Table 1 and Fig. 2 show the main effects of field (A and B) and hand (C and D). Following right hemifield (A) stimulation there was a clear activation of the left temporo-occipital junction corresponding to Brodmann area (BA) 37 and 19 and of the left cuneus (BA 18). A corresponding contralateral activation was observed following left hemifield stimulation (B) with an activation of the right temporo-occipital junction (BA 37 and 19).

Following right-hand responses there was an activation of the left precentral gyrus (BA 4 and 6), whereas following

TABLE 1. Main effects of field and hand

<table>
<thead>
<tr>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of right visual field stimulation (RVF/RH + RVF/LH) – (LVF/LH + LVF/RH)</td>
<td>-42</td>
<td>-68</td>
<td>8</td>
</tr>
<tr>
<td>L temporo-occipital junction (BA 37 and 19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L cuneus (BA 18)</td>
<td>-12</td>
<td>-80</td>
<td>12</td>
</tr>
<tr>
<td>Effect of left visual field stimulation (LVF/LH + LVF/RH) – (RVF/RH + RVF/LH)</td>
<td>-56</td>
<td>-62</td>
<td>4</td>
</tr>
<tr>
<td>R temporo-occipital junction (BA 37 and 19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of responding with the right hand (RVF/RH + RVF/LH) – (LVF/LH + RVF/LH)</td>
<td>-32</td>
<td>-18</td>
<td>60</td>
</tr>
<tr>
<td>L precentral gyrus (BA 4 and 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of responding with the left hand (LVF/LH + RVF/LH) – (RVF/RH + LVF/RH)</td>
<td>-42</td>
<td>-18</td>
<td>60</td>
</tr>
<tr>
<td>R precentral gyrus (BA 4 and 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R parietal operculum (BA 40 and 43)</td>
<td>-44</td>
<td>-16</td>
<td>20</td>
</tr>
</tbody>
</table>

RVF and LVF, right and left visual field, respectively; RH and LH, right and left hand, respectively; BA, Brodmann area.
left-hand responses there was an activation of the right precentral gyrus (BA 4 and 6) and parietal operculum (BA 40 and 43), see C and D. This pattern of activation is clearly reassuring as to the efficacy of the lateralization of both the visual input and the motor output.

The crucial comparison was the overall crossed minus uncrossed subtraction (averaged across hemispheres), see Table 2 and Fig. 3. There were significant activation foci, notably in the premotor area (BA 6), the insula, the cingulate gyrus (BA 24 and 32), the mesial frontal cortex (BA 9), and the paracentral lobule (BA 5), bilaterally. The inferior frontal gyrus (BA 47), the superior and middle temporal gyri (BA 21 and 22) on the left, and the precuneus (BA 7), the retrosplenial cortex (BA 23 and 31) and the corpus callosum on the right showed unilateral activations.

The main thrust of this pattern of activation is that there were areas that were selectively activated in the crossed conditions, i.e., those requiring an IT, while no areas were selectively activated in the uncrossed conditions, i.e., those not requiring an IT. The consistency across subjects of this pattern of activated areas is shown in Fig. 4.

Overall, these results are in keeping with an IT explanation of the CUD.

An intriguing result was the selective activation of the corpus callosum, which was localized in the genu as shown in Fig. 3. As pointed out in the introduction, activation of the white matter has been rarely reported in the human functional imaging literature. To rule out a contribution of the nearby gray matter on the observed callosal activation, we performed two additional analyses. First, a statistical analysis was performed on unsmoothed data and without global signal normalization, to detect genuine white-matter blood-oxygenation-level-dependent (BOLD) signal changes induced by the experimental manipulation. This enabled us to observe an independent peak of activation in the corpus callosum (x = 10, y = 20, z = 16; Z score = 2.52) specific for the crossed minus uncrossed subtraction, which was not spatially contiguous with the activation foci in the cingulate cortex. Second, the structural MRI of each subject was segmented (Ashburner and Friston 1997) to identify voxels belonging only to the white matter. These white-matter images were used to mask out from the functional images all voxels belonging to gray matter. A statistical analysis was then performed on the segmented functional images.

This further analysis confirmed activation in the corpus callosum (x = 16, y = 38, z = 12; Z score = 2.8) specific for the crossed minus uncrossed subtraction.

**DISCUSSION**

Our results have implications for the understanding of the neurophysiological foundations of IT in the Poffenberger paradigm, supporting only one of the two hypotheses mentioned in the introduction. The theory that postulates an overall greater activation when the visual stimulus is directly conveyed to the hemisphere controlling the motor response in comparison to the condition when an IT is required (Kinsbourne 2002; Ledlow et al. 1978) is not borne out by the present data. The direct comparisons of crossed versus uncrossed conditions showed a well-defined set of cortical areas, as well as the genu of the corpus callosum, that were selectively activated in the IT condition. In contrast, there were no specific activations related to the condition not requiring an IT. Therefore this evidence is not in keeping with the idea that the faster RT observed in the uncrossed conditions is related to a higher degree of activation of the directly accessed hemisphere. At variance with our previous PET data, we did not observe relative activations in the uncrossed conditions. This discrepancy can be explained by the fact that BOLD signal decreases are not detected with fMRI in normal conditions. A decrease of the BOLD signal would require increase of oxygen extraction ratio (OER). Previous PET studies (see Frackowiak 1985 for a review) have shown that the OER raises only for a substantial decrease of the ratio between regional cerebral blood flow (rCBF) and regional cerebral blood volume, as during ischemia. This is very unlikely to occur for the rCBF decrease ranges observed during activation studies. Hence, the present fMRI data suggest that the previous activations observed with PET in the subtraction uncrossed minus crossed conditions can be interpreted as relative rCBF decreases in the crossed conditions.

Compared with the uncrossed conditions, the crossed conditions activated an extended network involving mainly visuomotor and premotor components (see Table 2). Temporo-frontal connections conveying visual information to motor areas have been recently revealed with fMRI and transcranial magnetic stimulation (Brandt et al. 2001). This study showed that the intermediate nodes of such connections are located in

**TABLE 2. Effect of crossing condition averaged across hemispheres**

<table>
<thead>
<tr>
<th>Crossed minus uncrossed conditions</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>R precentral gyrus, ventral premotor area (BA 6)</td>
<td>44</td>
<td>−10</td>
<td>20</td>
<td>5.2</td>
</tr>
<tr>
<td>R precuneus (BA 7)</td>
<td>20</td>
<td>−52</td>
<td>28</td>
<td>4.1</td>
</tr>
<tr>
<td>R retrosplenial cortex (BA 23 and 31)</td>
<td>28</td>
<td>−56</td>
<td>12</td>
<td>3.6</td>
</tr>
<tr>
<td>R insula</td>
<td>30</td>
<td>20</td>
<td>12</td>
<td>3.8</td>
</tr>
<tr>
<td>R corpus callosum</td>
<td>14</td>
<td>28</td>
<td>16</td>
<td>4.3</td>
</tr>
<tr>
<td>R/L cingulate gyrus (BA 24 and 32)</td>
<td>2</td>
<td>30</td>
<td>20</td>
<td>3.2</td>
</tr>
<tr>
<td>R/L mesial frontal cortex (BA 9)</td>
<td>0</td>
<td>42</td>
<td>16</td>
<td>3.7</td>
</tr>
<tr>
<td>R/L paracentral lobule (BA 5)</td>
<td>2</td>
<td>−32</td>
<td>68</td>
<td>4.4</td>
</tr>
<tr>
<td>L inferior frontal gyrus (BA 47)</td>
<td>−24</td>
<td>16</td>
<td>−16</td>
<td>4.5</td>
</tr>
<tr>
<td>L precentral gyrus, ventral premotor area (BA 6)</td>
<td>−42</td>
<td>−6</td>
<td>20</td>
<td>3.4</td>
</tr>
<tr>
<td>L superior temporal sulcus (BA 22)</td>
<td>−52</td>
<td>−36</td>
<td>12</td>
<td>3.8</td>
</tr>
<tr>
<td>L middle temporal gyrus (BA 21)</td>
<td>−46</td>
<td>−36</td>
<td>0</td>
<td>3.4</td>
</tr>
<tr>
<td>L insula</td>
<td>−30</td>
<td>0</td>
<td>16</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Uncrossed minus crossed conditions
No voxels above threshold of significance
the superior temporal sulcus and insular and parainsular cortex. In the present study, posterior temporo-occipital (BA 37 and 19) and dorsal premotor frontal (BA 4 and 6) areas were activated by both crossed and uncrossed conditions (see Table 1) as a main effect of visual field and hand, respectively, whereas the superior temporal sulcus and the insular cortex were specifically activated by the crossed conditions (see Table 2). Posterior parietal areas, including the precuneus (BA 7), which was also selectively activated by the crossed as compared with the uncrossed conditions, have been extensively shown to convey to dorsal premotor areas visual and attentional information necessary for selection, preparation, and execution of movements (Desmurget et al. 1999; Gitelman et al. 1999). In addition, the ventral premotor area (BA 6) has been shown in primates to be directly connected to the motor cortex (Barbas and Pandya 1987). Overall, it seems that the crossed conditions engaged more than the uncrossed conditions the intermediate nodes connecting visual with motor areas. This might be a consequence of the additional processing, compared with the uncrossed conditions related to the transfer of part of the information through the corpus callosum to contralateral areas.

A novel finding is represented by the direct evidence of the involvement of the corpus callosum in IT. A crucial question is of course: why should the corpus callosum show BOLD effects? Activation of the white matter has been reported with some caution in the neuroimaging literature despite that glucose-metabolism studies have clearly shown measurable metabolic changes in the white matter, which has Ranvier’s nodes where Na+/K+ dependent ATPase operates to restore ionic balance.

**FIG. 3.** Areas of activation (in red-yellow color scale) for the crossed minus uncrossed comparison are shown superimposed on axial and sagittal views of the mean anatomical image of the 8 participants. The main activation foci (see also Table 2 for stereotaxic coordinates) are indicated by → the corresponding Brodmann areas (BA) or, if absent, the anatomical names, are given in boxes. The corresponding stereotaxic levels along the z axis are indicated below each slice in mm. L, left hemisphere; R, right hemisphere; CC, corpus callosum; INS, insula. **Bottom:** the callosal activation which is clearly localized to the genu.
FIG. 4. Histograms for the significant activations foci reported in Table 2. Outlined white bars indicate mean adjusted blood-oxygenation-level-dependent (BOLD) responses per condition, averaged over all adjusted mean summary images (AMSI) of all the 8 participants (32 AMSI × condition). Superimposed onto average effects are the mean responses of each individual subject (averaged over all 4 AMSI × condition × subject) in the different conditions. Data of each single subject were connected by color lines [see legend box at bottom right for color codes associated to Subject 1 (S1) to 8 (S8)] to illustrate differences in BOLD responses among the 2 crossed, the 2 uncrossed, and the rest condition (central fixation).
gradients perturbed by the spreading of the action potential. Previous studies demonstrated that the working of the Na\(^+/K^+\)-dependent ATPase is a primus mover of increased metabolic demands of brain tissue (Mata et al. 1980). However, white matter is not a prime site for getting a BOLD effect, and as pointed out in the INTRODUCTION, there are only few studies showing white matter activation (e.g., Mosier and Bereznaya 2001). It seems that the BOLD signal reflects local field potentials rather than spiking (Logothetis et al. 2001) and is likely to reflect activity around synapses. Some other possibilities of explaining BOLD effects, in addition to rCBF increases consequent to the metabolic demands of the Na\(^+/K^+\)-dependent ATPase in white matter, include reverse transport of glutamate in axons, and axo-axonal coupling. As to the former, it is known that neurotransmitter-mediated signaling is not restricted to synaptic regions but also takes places along fiber tracts and is responsible for signaling between axons and glial cells (Chiu and Kriegler 1994). In one postulated mechanism, glutamate is released from axons via the reversal of a transporter and induces intracellular calcium spiking in glial cells via metabotropic glutamate receptors. As to the latter possibility, recently, Schmitz et al. (2001) have provided evidence suggesting that hippocampal neurons are coupled by axo-axonal junctions, providing a novel mechanism for very fast electrical communication.

Despite these putative mechanisms, we would like to point out that the reported callosal activation should be taken with caution in view of its implications with respect to models of the BOLD signal main sources (Rostrup et al. 2000). Differences in perfusion and, as a consequence, in BOLD signal between rest and activation state are normally much smaller in the white than in the gray matter (Preibisch and Haase 2001) and, as stated in the INTRODUCTION, very few studies have reported activations in the white matter. However, it may be that for certain tasks, such as the Poffenberger paradigm, the increased demand for axonal communication through the corpus callosum is sufficient to induce enough local increases in metabolism through the preceding mechanisms (and perfusion to match) such that BOLD activity can be identified. Of course, further studies will be needed to substantiate our findings, for example, by taking advantage of a higher magnetic field that could reveal activations at the single subject level and, due to a better spatial resolution, provide more details on the exact localization of such activations.

One important question is what part of the corpus callosum is involved in IT of visuomotor information. Our results have shown an activation of the genu. So far there is no consistent behavioral evidence indicating that the selective lesion of this portion of the corpus callosum impairs visuomotor IT. Tassinari et al. (1994) tested seven patients with an anterior callosal section in the Poffenberger paradigm and found no effect on the CUD. In contrast, recently, Tomaiuolo et al. (2001) have reported a considerable lengthening of the CUD in a patient with an extensive lesion of the corpus callosum sparing the splenium and the rostrum but certainly including the genu. Finally, Iacoboni et al. (1994) found a CUD lengthening in a patient following a section of the corpus callosum that spared the splenium. This effect, however, was limited to stimuli presented at 8° eccentricity, while stimuli presented at 4° did not yield a CUD effect. On the whole, therefore the evidence on the effects of lesions including the genu is not conclusive.

In keeping with a possibly important role of the genu in IT is recent evidence provided by Stancak et al. (2000) that there is a positive correlation between the size of the genu (and of the anterior part of the truncus) of the corpus callosum and the amplitude of the premovement electroencephalographic potential recorded on the hemisphere ipsilateral to the performing hand. This would suggest that the genu transmits interhemispheric information to prepare the ipsilateral hemisphere to perform hand movements triggered by the contralateral hemisphere. Another, not mutually exclusive, possibility is that visuomotor IT occurs in different callosal zones but could be revealed in the present study only in the genu because this part of the callosum has the highest density of small fibers, a substantial proportion of which is unmyelinated (Aboitiz et al. 1992). This anatomical fact might be responsible for the observed activation of the genu and not of other callosal areas. Unmyelinated fibers are expected to show an overall higher degree of metabolic demands due to the extensive activity of membrane Na\(^+/K^+\)-dependent ATPase which in myelinated fibers are restricted to the Ranvier node. This possibility, however, requires a note of caution because the energy demands at the nodes of Ranvier are presumably very high (Aiello and Bach-y-Rita 2000).

All in all, the present results are in keeping with a neural model of the Poffenberger paradigm in which the corpus callosum and related cortical areas transmit a premotor preparatory signal from the hemisphere of stimulus entry to that producing the motor response. Further studies are needed to confirm a direct fMRI activation of the callosal white matter.

We thank K. Mosier for suggesting the possible mechanisms underlying BOLD effects in white matter. We also thank B. Weber for sending a preliminary version of a paper on glucose metabolism in the rat corpus callosum and for suggesting other possible mechanisms of BOLD effects in white matter.

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