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Interhemispheric visuo-motor integration in humans: the role of the superior parietal cortex

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Abstract

We used event-related functional magnetic resonance imaging (fMRI) to investigate the neural correlates of basic interhemispheric visuo-motor integration. In a simple reaction time task, subjects responded to lateralized left and right light flashes with unimanual left and right hand responses. Typically, reaction times are faster for uncrossed responses (that is, visual stimulus and response hand on the same side) than for crossed responses (that is, visual stimulus and response hand on opposite sides). The chronometric difference between crossed and uncrossed responses is called crossed–uncrossed difference (CUD) and it is typically taken to represent a behavioral estimate of interhemispheric transfer time. The fMRI results obtained in normal right-handers show that the crossed conditions yielded greater activity, compared to the uncrossed conditions, in bilateral prefrontal, bilateral dorsal premotor, and right superior parietal areas. These results suggest that multiple transfers between the hemispheres occur in parallel at the functional levels of sensory–motor integration (posterior parietal), decision-making (prefrontal) and preparation of motor response (premotor). To test the behavioral significance of these multiple transfers, we correlated the individual CUDs with the difference in signal intensity between crossed and uncrossed responses in the prefrontal, dorsal premotor, and right superior parietal activated areas. The analyses demonstrated a strong correlation between the CUD and signal intensity difference between crossed and uncrossed responses in the right superior parietal cortex. These data suggest a critical role of the superior parietal cortex in interhemispheric visuo-motor integration.

Keywords: Corpus Callosum; Functional magnetic resonance imaging; Crossed–uncrossed difference; Poffenberger paradigm

1. Introduction

Almost a century ago, a simple behavioral paradigm was proposed to measure the time it takes to transfer visuo-motor information from one hemisphere to the opposite one in humans (Poffenberger, 1912). Subjects are required to perform a simple reaction time task to lateralized light flashes. In some blocks of trials, subjects respond with the left hand as soon as they see the stimulus, and in other blocks of trials they use the right hand. Lateralized light flashes are presented to subjects so that four combinations of visual hemifield–response hand occur. When the light stimulus and the response hand are on the same side (for instance, left visual hemifield and left hand), there is in principle no need to transfer information from one hemisphere to the other, because the same hemisphere receives the visual stimulus and controls the motor response. In keeping with this simple concept, visual hemifield–response hand conditions of this sort are called the "uncrossed" conditions. When the light stimulus and the response hand are on opposite sides (for instance, left visual hemifield and right hand), it is necessary to transfer information from one hemisphere to the opposite, because one hemisphere receives the visual stimulus and the contralateral hemisphere controls the motor response. Thus, visual hemifield–response hand conditions of this sort are called the "crossed" conditions. When one subtracts the reaction times (RTs) of the uncrossed conditions from the RTs of the crossed conditions and divides this difference by two, one obtains an estimate of the time it takes to transfer visuo-motor information from one hemisphere to the contralateral one. This estimate is called the CUD, which stands for crossed–uncrossed difference. A meta-analysis of several studies encompassing more than 300 normal volunteers has returned a CUD value in normal subjects of about 4 ms (Marzi, Bisiacchi, & Nicoletti, 1991). The same meta-analysis has also returned CUD values of about 15 ms for callosal agenesis patients

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and 30–60 ms for split-brain patients. At first sight, these data seem to suggest that the CUD is a measure of callosal relay of visuo-motor information through relatively fast callosal fibers which are missing in callosal agenesis and split-brain patients. The functional and anatomical loci of the CUD, however, have been under scrutiny for decades now and alternative explanations have been proposed.

Early behavioral studies converged on suggesting two major aspects of the CUD. First, the CUD seems to reflect an axonal delay, and second, the information transferred is not likely to be visual. The evidence supporting these conclusions is as follows. When subjects cross their hands, such that they respond with the left hand in the right hemispace and the right hand in the left hemispace, responses are still faster with the hand *anatomically* ipsilateral to the visual stimulus (Anzola, Bertoloni, Buchtel, & Rizzolatti, 1977). This is in contrast with the pattern observed in choice response times tasks. In these tasks, when subjects cross their hands, they respond faster when the hand is *spatially* ipsilateral to the visual stimulus (Wallace, 1971). Thus, some early studies (Anzola et al., 1977; Berlucchi, Crea, DiStefano, & Tassinari, 1977) concluded that the CUD, rather than reflecting the formation of a stimulus–response spatial compatibility code, reflects an axonal conduction delay. Moreover, the experimental manipulation of visual parameters seems not to affect the CUD in normal subjects, thus suggesting that the transfer does not involve a purely visual functional and anatomical locus (Berlucchi, Heron, Hyman, Rizzolatti, & Umiltá, 1971).

Two more recent studies, however, when taken together, suggest that the lack of an effect on the CUD by manipulation of visual parameter may simply reflect the ‘masking’ of the behavioral effect due to a fast motor transfer, rather than the absence of visual transfer. In normal subjects, the manipulation of motor parameters affected the CUD, whereas the manipulation of visual parameters did not (Iacoboni & Zaidel, 1995). However, in a patient who underwent partial callosotomy preserving the splenium of the corpus callosum, where visual fibers are typically grouped (Zaidel & Iacoboni, 2003), the experimental manipulation of visual parameters affected the CUD only after callosotomy, when motor fibers, typically grouped in the mid-body of the corpus callosum, were likely removed by the surgery (Iacoboni, Fried, & Zaidel, 1994). Taken together, these data suggest that multiple transfers may actually occur at different speeds, with the ‘motor’ transfer faster than the ‘visual’ one (Clarke & Zaidel, 1989).

Both theoretical and empirical challenges to this simple view of serial information processing have been posed in the literature. The theoretical challenge comes from the hypothesis that the difference in RT expressed by the CUD is not due to axonal conduction delay but rather to differences in hemispheric priming. The hemispheric priming hypothesis suggests that RT are faster in the uncrossed conditions because the hemisphere that receives the visual stimulus is primed, activated by the light flashes, and when this same hemisphere also controls the motor response, as in the uncrossed conditions, then faster responses occur (Kinsbourne, 2003; Ledlow, Swanson, & Kinsbourne, 1978). The empirical challenges mostly derive from electrical scalp recordings that have yielded two findings that are inconsistent with the serial model and the RT data. First, estimates of callosal relay tend to be longer when electrical scalp recordings are considered. Second, complex patterns of recursive activations have suggested that the serial model of information processing through the corpus callosum may not be valid even when simple visuo-motor integration tasks are considered (Saron, Foxe, Simpson, & Vaughan, 2003).

It is still possible, however, that in addition to multiple interhemispheric transfers that are affected by multiple variables (among them the state of activation of relevant cortical areas at any given point during the task, giving rise, perhaps, to the widely known variability of RT in simple reaction time tasks), the CUD represents an axonal conduction delay through callosal fibers. Recent RT data on a large data set comprising 40,000 trials, in which the CUD has been shown to be very stable across fast and slow RT, support the interpretation of the CUD as reflecting, all the other factors being equal, a simple axonal conduction delay through the corpus callosum (Iacoboni & Zaidel, 2000).

Two recent imaging studies have investigated the neural underpinnings of the Poffenberger paradigm. In a study using positron emission tomography (PET), increases in signal were observed in anterior regions for the uncrossed conditions and in posterior regions for the crossed conditions (Marzi et al., 1999). A later study from the same group, using functional magnetic resonance imaging (fMRI), yielded somewhat different results. Activations in frontal, parietal, and temporal areas were observed when the uncrossed conditions were subtracted from the crossed conditions, but no differences in signal were observed when the crossed conditions were subtracted from the uncrossed ones (Tettamanti et al., 2002). Further, this later study also reports signal increases in the genu of the corpus callosum during the crossed conditions compared to the uncrossed ones that is interpreted as reflecting axonal conduction events.

A problem common to both of these two imaging studies is that subjects were performing the task in a completely blocked fashion. That is, in one block of trials they were responding with, say, the left hand to left light flashes only, and in the next block of trials they were responding with, say, the left hand to right light flashes only. Typically, behavioral studies are performed intermixing left- and right-sided light flashes, to avoid anchoring visual attention to a specific location of the visual field. Thus, to further investigate interhemispheric visuo-motor integration with imaging techniques that allow paradigm designs more similar to the ones performed in behavioral laboratories, we adopted the approach of event-related fMRl that allowed to interleave left-sided and right-sided light flashes while normal volunteers were imaged during task performance. This approach has also the advantage of allowing the correlation of chronometric performance with signal intensity changes, thus allowing the analysis of more precise brain–behavior relationships.

2. Materials and methods

2.1. Subjects

We studied five normal volunteers, three males and two females. They were all right-handers, as assessed by a modified version of the Edinburgh Handedness Inventory (Oldfield, 1971), and with a mean age of 23.6 ± 2.5 years. All subjects were screened to rule out medication use, a history of neurological or psychiatric disorders, head trauma, substance abuse, or other serious medical conditions. No neurological abnormalities were identified by neurological examination performed just before the scanning session. Participants gave informed consent according to the guidelines of the Institutional Review Board at UCLA, which follows the principles of the Declaration of Helsinki.

2.2. Imaging

We used a GE 3.0T MRI scanner with an upgrade for echo-planar imaging (EPI) (Advanced NMR Systems Inc.). A two-dimensional spin-echo image (TR = 4000 ms; TE = 40 ms, 256 × 256, 4 mm thick, 1 mm spacing) was acquired in the sagittal plane to screen for structural abnormalities in the brain and to allow slice prescription of the EPI sequences. A high resolution structural T2-weighted EPI brain volume (spin-echo, TR = 4000 ms, TE = 54 ms, 128 × 128, 26 slices, 4 mm thick, 1 mm spacing) was initially acquired. This brain volume was coplanar with the functional images subsequently acquired. For each subject, two functional EPI scans (gradient-echo, TR = 3000 ms, TE = 70 ms, 64 × 64, 21 slices, 4 mm thick, 1 mm spacing) were acquired, each for a duration of 3 min and 36 s. Each scan consisted of 18 trials of left and right light flashes (9 left-sided, 9 right-sided), randomly presented. Each trial lasted 12 s, to allow for the return of the BOLD response to baseline (Aguirre, Zarahn, & D'Esposito, 1998). Four initial dummy scans were used to allow for the stabilization of the MR signal.

The functional images were aligned with the T2-weighted structural image for each subject using a rigid-body linear registration algorithm (Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998). The images were then registered to a Talairach-compatible (Talairach & Tournoux, 1988) MR atlas (Woods, Dapretto, Sicotte, Toga, & Mazziotta, 1999) with fifth-order polynomial nonlinear warping (Woods, Grafton, Watson, Sicotte, & Mazziotta, 1998). Data were smoothed using an in-plane, Gaussian filter for a final image resolution of 8.7 mm × 8.7 mm × 8.6 mm.

2.3. Behavioral task

The software MacProbe was used for stimulus presentation and response recording (Hunt, 1994; Zaidel & Iacoboni, 1996). The fMRI unit was equipped with a stimulation and response recording environment controlled by a Macintosh computer system. Visual stimuli were provided with a magnet-compatible resonance technology three-dimensional visual stimulation device. To record reaction times we used a magnet-compatible electrostatic pointing device. This device is based upon an ALPS (Alps Electronics, San Jose, CA) "Glide Point" with multiple response buttons connected to a remote stimulus display and response computers via a twisted pair differential line driver that passes through the MR scanner filter panel and then to the Macintosh ADB port.

Subjects had a fixation cross in the middle of the screen and were presented with stimuli consisting of black flashes on a light gray background. The stimuli subtended 1° of visual angle at 8° of retinal eccentricity to the left or to the right of the vertical meridian and on the horizontal meridian. Stimuli were presented for 50 ms. In each trial there was a random time window of 2000 ms for stimulus presentation. This was done to avoid anticipation of responses in this simple reaction time task in which no response selection is required. The random time windows and the variable RT at each trial were compensated by the computer to obtain a fixed total trial time of 12 s. A total of 18 trials (9 left-sided stimuli, 9 right-sided stimuli, randomly presented) composed a whole fMRI run. Subjects were instructed to fixate the fixation cross and to respond with a finger key press as soon as they detected the stimulus. Subjects performed two fMRI runs, one responding with the left index finger, and the other one responding with the right index finger. The order of left and right hand responses was counterbalanced across subjects.

2.4. Image statistics

Image statistics was performed with analyses of variance (ANOVAs), allowing to factor out trial-to-trial variability within run as well as inter-subject signal variability (Aguirre et al., 1998; Iacoboni, Ptito, Weekes, & Zaidel, 2000; Iacoboni, Woods, Lenzi, & Mazziotta, 1997; Iacoboni, Woods, & Mazziotta, 1996, 1998; Iacoboni et al., 1999, 2001; Koski et al., 2002; Woods, Iacoboni, Grafton, & Mazziotta, 1996) while modeling the typical hemodynamic response of BOLD fMRI (Aguirre et al., 1998). Factors included in the ANOVAs were subjects ($n = 5$), trial repeats ($n = 9$), visual field (left, right), and response hand (left, right). Significance level was set at $P = 0.001$ uncorrected at each voxel. To avoid false positives, only clusters bigger than 10 significantly activated voxels were considered (Forman et al., 1995).

3. Results

First, median RTs were computed for each subject and for each of the four visual hemifield–response hand conditions. Then, the mean of the two uncrossed conditions (left visual hemifield–left hand and right visual hemifield–right hand) were subtracted from the mean of the two crossed conditions (left visual hemifield–right hand and right visual hemifield–left hand) and this difference was divided by two to obtain the CUD. The CUD obtained while subjects were imaged in the scanner was 8.04 ms. This value is twice as long as the one yielded by the meta-analysis of the Poffenberger paradigm (Marzi et al., 1991), but still well within the range of CUDs obtained from the studies included in the meta-analysis. In fact, the CUDs of those studies ranged from 1 to 10 ms (Marzi et al., 1991).

When a contrast between the crossed minus the uncrossed conditions was performed, reliable (d.f. $= 96$, $t = 3.18$, $P = 0.001$ at each voxel) BOLD fMRI signal changes were observed bilaterally in prefrontal (one area was located in dorsolateral prefrontal cortex and the other one in the anterior sector of the rostral cingulate area, RCZa), dorsal premotor cortex, and in the right superior parietal cortex (Fig. 1 and Table 1). When the opposite contrast was performed, that is, uncrossed minus crossed conditions, no reliable BOLD fMRI changes were observed.

We subsequently correlated the individual CUDs with the difference in signal intensity between crossed and uncrossed

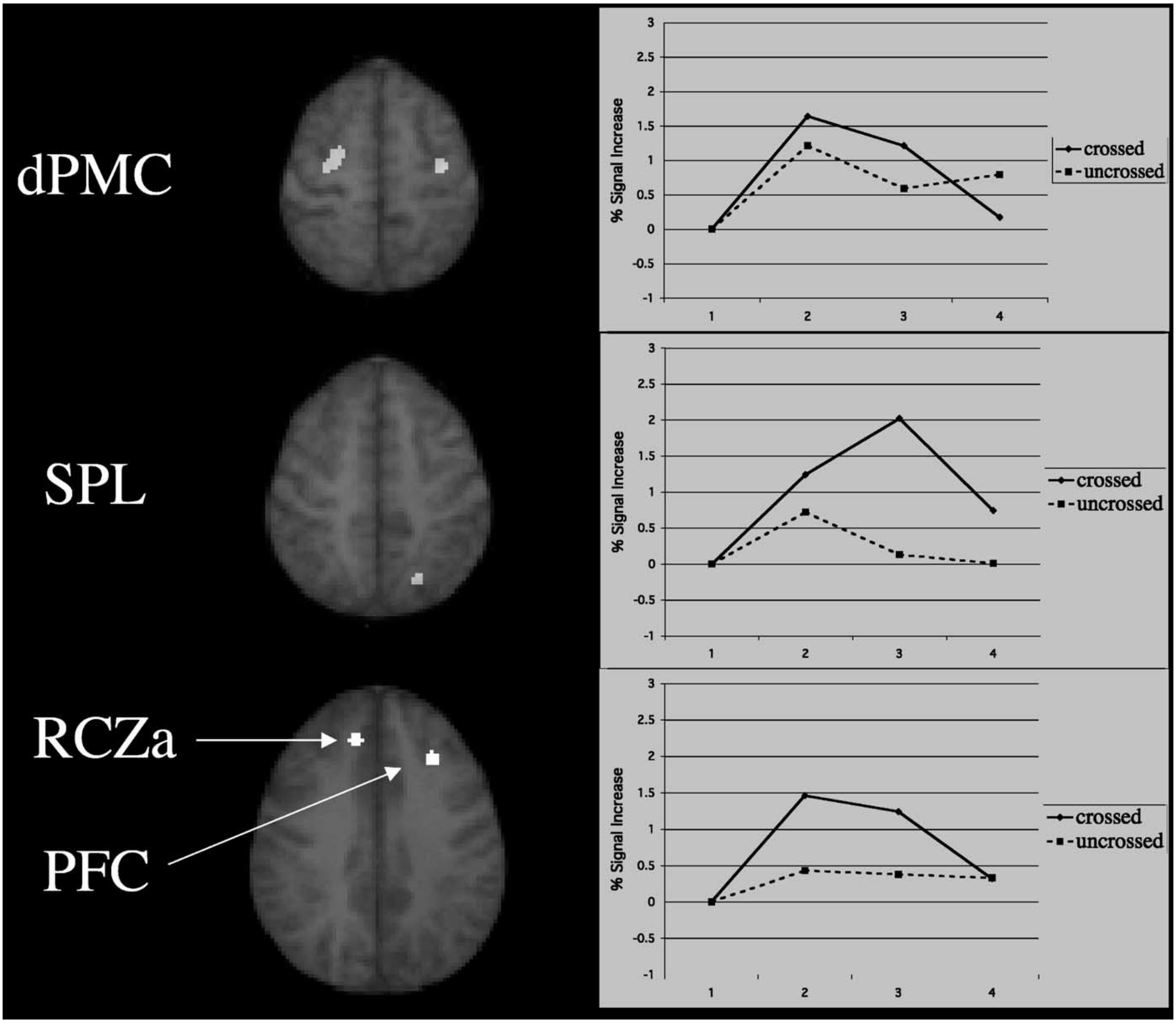

Fig. 1. Areas (dPMC = dorsal premotor cortex; SPL = superior parietal lobule; RCZa = anterior sector of the rostral cingulate zone; PFC = prefrontal cortex) of differential BOLD responses for crossed minus uncrossed responses. The four data points in each graph correspond to the four brain volumes (TR = 3000 ms) encompassing the 12 s trials. BOLD activity is expressed as percent change from the first volume of the trial.

Table 1
Activation peaks

Hemisphere	Region	Putative BA	Talairach-coordinates		
			x	*y*	*z*
L	dPMC	BA6	−23	−13	56
R	dPMC	BA6	32	−15	56
R	SPL	BA7	20	−66	52
L	RCZa	BA32/8	−11	33	36
R	PFC	BA9/8	28	24	36

BA = Brodmann Area.

responses in the bilateral prefrontal, dorsal premotor, and right parietal areas shown in Fig. 1. Given the time course of the BOLD signal (Aguirre et al., 1998), it is reasonable to assume, as we did, that most of the signal correlated with the behavioral performance on the Poffenberger paradigm is found in the second of the four time-points forming the BOLD response for each trial in our experimental design, corresponding to 3–6 s post-stimulus. There was a strong correlation between CUD and signal intensity in the right superior parietal area ($r = 0.906$, $P = 0.034$). The prefrontal ($r = 0.438$, n.s.) and dorsal premotor ($r = 0.522$, n.s.) were not correlated. The right parietal area demonstrated a strong delayed response in its time series (see Fig. 1). This delayed response (6–9 s post-stimulus) is likely due to a re-entrant signal from other areas, rather than to a signal directly related to the task. At any rate, we also correlated this delayed response to the CUD, and found a weaker correlation ($r = 0.5$, n.s.).

4. Discussion

To the best of our knowledge, this is the first time that event-related fMRI is used to investigate the neural underpinnings of interhemispheric visuo-motor integration required by the Poffenberger paradigm. We found that crossed responses yielded significantly greater signal intensity than uncrossed responses in prefrontal, dorsal premotor, and right superior parietal cortex. We also found that the CUD in our subjects correlated strongly with the signal intensity changes in the right superior parietal cortex, thus suggesting a key role of right superior parietal cortex in the type of interhemispheric visuo-motor integration required by the Poffenberger paradigm.The localization of activation in our study is in line with concepts that emerged from the chronometric literature in normals and split-brain patients. Experimental manipulations of visual parameters have failed to have any effect on the CUD in normal subjects (Berlucchi et al., 1971). In contrast, the manipulations of motor parameters have effectively altered the CUD in normal subjects (Iacoboni & Zaidel, 1995). These findings suggest that the fastest transfer of information through the corpus callosum occurs through fibers of motor “significance”, including premotor and parietal fibers, which are typically grouped in the mid-body and anterior regions of the corpus callosum (Zaidel & Iacoboni, 2003). In fact, as mentioned earlier, in a patient who underwent partial callosotomy sparing the splenium of the corpus callosum, where visual fibers are grouped, the manipulation of visual parameters was ineffective before the surgery, when motor fibers were intact, but became effective in altering the CUD after the callosotomy, that is, when motor fibers were likely transected and visual transfer likely dominated (Iacoboni et al., 1994). More recent evidence from partial callosal lesions seems to converge on the role of intermediate callosal regions for an efficient interhemispheric visuo-motor transfer (Peru, Beltramello, Moro, Sattibaldi, & Berlucchi, 2003; Tomaiuolo, Nocentini, Grammaldo, & Caltagirone, 2001). Even though the complexity of callosal topography (Zaidel & Iacoboni, 2003) makes it difficult to map with certainty cortical activations onto specific sectors of the corpus callosum, the dorsal premotor and superior parietal activations are compatible with a critical role of the mid-body of the corpus callosum in visuo-motor interhemispheric transfer.

The areas activated in our study have in common being involved in some aspects of motor behavior. The superior parietal activation shows activity strongly correlated with the CUD. A role of the right posterior parietal cortex in interhemispheric visuo-motor integration is also suggested by a lengthening of the CUD in patients with unilateral right parietal lesions (Marzi, Bongiovanni, Miniussi, & Smania, 2003). The activation of the superior parietal lobule, in an area close to the medial bank of the intraparietal sulcus, may be interpreted as reflecting aspects of sensory–motor integration and motor intention, as suggested by neurophysiological evidence (Andersen, Snyder, Bradley, & Xing, 1997; Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975). In particular, a recent study combining anatomical and electrophysiological mapping of the posterior parietal cortex of the ferret (Manger, Masiello, & Innocenti, 2002) has shown that parietal callosal connections do not follow the ‘midline rule’ of visual areas (Berlucchi, Gazzaniga, & Rizzolatti, 1967; Hubel & Wiesel, 1967). that is. a preferential distribution of callosal connections in cortical visual areas representing the central portions of the visual field. These data suggest that callosal parietal connections process information beyond relatively ‘low level’ visual features. Moreover, the existence of ‘motor command’ neurons in the superior parietal lobule (Mountcastle et al., 1975) is in line with the behavioral evidence, summarized earlier, supporting the idea that transfer occurs at ‘premotor stage’. Finally, the reliable correlation between the CUD and right superior parietal cortex reported here seems to provide a link between behavioral evidence in humans and single-cell recordings in macaques. In a recent study intermixing stop-trials (where subjects are supposed to refrain from responding) with ‘go’ trials, it has been shown that subjects are more likely to refrain from responding during crossed responses, thus suggesting that the transfer occurs at pre-ballistic, controlled stage (Cavina-Pratesi, Bricolo, Pellegrini, & Marzi, 2003). Single-cell recordings in ‘go–no-go’ paradigms have shown that superior parietal neurons in macaques code the ‘intention-to-move’ during ‘no-go’ trials (Kalaska & Crammond, 1995). Taken together, this suggests that our findings of a strong correlation between the CUD and signal intensity in the right superior parietal cortex indicates that what is transferred is a ‘motor intention’.

An alternative interpretation of the role of the superior parietal activation, however, cannot he ruled out. Intriguingly, imaging data on the neural correlates of spatial compatibility suggested a strong role of the posterior parietal cortex in the compatibility effect (Iacoboni et al., 1996, 1997, 1998), showing even a correlation between spatial compatibility and blood flow changes in the superior parietal cortex (Iacoboni et al., 1996). Well-controlled early behavioral studies seemed to rule out the role of spatial compatibility in the CUD (Anzola et al., 1977; Berlucchi et al., 1977). It has been pointed out, however, that when the number of trials is limited and the subjects not experienced in the task, stimulus–response compatibility may occur even in the Poffenberger paradigm (Brysbaert, 1994). The early studies (Anzola et al., 1977; Berlucchi et al., 1977) involved hundreds and hundreds of trials and experienced subjects. Our study, in contrast, required inexperienced subjects to perform a limited number of trials. Thus, it is possible that the prominent role of the superior parietal cortex in the present study is due to the constraints of the experimental design we adopted and reflects automatic stimulus–response spatial codes that would disappear with practice in the Poffenberger paradigm.

The superior parietal cortex is heavily interconnected, both anatomically and functionally, with the dorsal premotor cortex (Wise, Boussaud, Johnson, & Caminiti, 1997). The late increased activity in the superior parietal area that can be observed in Fig. 1 may indeed represent re-entrant signals from premotor cortices. High density scalp recordings in humans performing the Poffenberger paradigm have revealed activity patterns that are also consistent with this idea (Saron et al., 2003). The dorsal premotor areas are well known for their importance in response selection and stimulus–response associations (Passingham, 1993). These areas, however, are also important for response preparation (Passingham, 1993) and this is probably why they are engaged by the simple detection task we used. The premotor cortices are connected by robust callosal projections (Zaidel & Iacoboni, 2003). This anatomical pattern of connectivity, together with the chronometric findings cited earlier suggesting a fast motor transfer of information in the normal brain, explain the involvement of dorsal premotor areas in the Poffenberger paradigm.

The rostral cingulate zone is often found activated conjointly with the prefrontal cortex (Picard & Strick, 1996). Within this zone, two well identified sectors, an anterior one (RCZa) and a posterior one (RCZp) have been proposed to be associated with two identified cingulate motor areas in the monkey (CMAr and CMAv). Neurons in CMAr have been associated with higher order motor plans. In keeping with this, RCZa activations are generally observed in imaging studies during complex motor tasks involving finger or mouth movements (Picard & Strick, 1996). It is quite surprising to observe the activation of this area, and of the prefrontal one, in our task, given that this task is one of the simplest, if not the simplest, visuo-motor task one can possibly perform. A possible explanation for this finding may be that in our experiment we spaced the experimental trials several seconds apart, in order to allow the BOLD signal to go back to baseline. Thus, the attentional requirements of the task and the prolonged motor readiness required by its spaced trials may have engaged higher order motor areas. This may also explain the somewhat longer than usual CUD.

Taken together, our data suggest that multiple types of information are transferred through the corpus callosum in simple reaction times to lateralized flashes, but also that all of them are likely related to some aspects of motor behavior, from sensory–motor integration and motor intention (superior parietal cortex) to decision-making (higher order prefrontal and cingulate areas) and to response preparation (dorsal premotor cortex). Moreover, our data suggest that the right superior parietal cortex seems to play a key role in interhemispheric visuo-motor integration and that the nature of the information transferred that best correlates with the CUD is a ‘motor intention’.

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