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RESEARCH ARTICLE

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Visuo-motor pathways in humans revealed by event-related fMRI

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Abstract Whether different brain networks are involved in generating unimanual responses to a simple visual stimulus presented in the ipsilateral versus contralateral hemifield remains a controversial issue. Visuo-motor routing was investigated with event-related functional magnetic resonance imaging (fMRI) using the Poffenberger reaction time task. A 2 hemifield × 2 response hand design generated the "crossed" and "uncrossed" conditions, describing the spatial relation between these factors. Both conditions, with responses executed by the left or right hand, showed a similar spatial pattern of activated areas, including striate and extrastriate areas bilaterally, SMA, and M1 contralateral to the responding hand. These results demonstrated that visual information is processed bilaterally in striate and extrastriate visual areas, even in the "uncrossed" condition. Additional analyses based on sorting data according to subjects' reaction times revealed differential crossed versus uncrossed activity only for the slowest trials, with response strength in infero-temporal cortices significantly correlating with crossed–uncrossed differences (CUD) in reaction times. Collectively, the data favor a parallel, distributed model of brain activation. The presence of interhemispheric interactions and its consequent bilateral activity is not determined by the crossed anatomic projections of the primary visual and motor pathways. Distinct visuo-motor networks need not be engaged to mediate behavioral responses for the crossed visual field/response hand condition. While anatomical connectivity heavily influences the spatial pattern of activated visuo-motor pathways, behavioral and functional parameters appear to also affect the strength and dynamics of responses within these pathways.

Keywords Event-related fMRI · Poffenberger paradigm · BOLD time course · Visuo-motor routing · Interhemispheric transfer

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Introduction

Anatomical studies of the visual system have demonstrated how cortical areas are highly interconnected and organized in parallel, distributed networks both in animals (e.g. Ungerleider and Mishkin 1982; Felleman and Van Essen 1991; Zeki 1993) as well as humans (e.g. Burkhalter and Bernardo 1989; Clarke and Miklossy 1990; Clarke 1994; Di Virgilio and Clarke 1997; Zilles and Clarke 1997). Moreover, neurophysiological evidence indicates that responses to sensory stimuli can rapidly propagate through these networks and that several regions can be simultaneously active (e.g. Nowak and Bullier 1997; Schroeder et al. 1998; Schmolesky et al. 1998; Blanke et al. 1999; Martinez et al. 1999; Thut et al. 1999, 2000a, b; Morand et al. 2000; Murray et al. 2001, 2004; Foxe and Simpson 2002; Saron et al. 2001, 2003a, b; Michel et al. 2004). Of increasing interests, therefore, are the questions of both how and when information is routed through such interconnected networks, as well as which pathways play a critical role in mediating behavior.

One particular case is that of visuo-motor routing, as in a simple reaction time paradigm wherein the subject performs a motor response to the detection of a visual stimulus. The initially divided representations of the

visual fields as well as the lateralized motor representations make it possible to generate experimental conditions that, in principle, would result in distinct routes of visuo-motor interaction. Specifically, visual stimuli presented laterally to either the same or opposite side of space as the hand mediating the motor response produce the so-called ''uncrossed'' and ''crossed'' conditions, respectively. Poffenberger (1912) used these conditions as a putative means of measuring interhemispheric transmission time. The underlying premise is that the ''uncrossed'' condition does not require visuo-motor information transfer to the other hemisphere, since the hemisphere mediating the motor response is the same as that initially receiving the sensory input. By contrast, in the ''crossed'' condition information must be transferred between the hemispheres. The typical behavioral consequence with this paradigm is that reaction times are slower for the crossed versus uncrossed condition (the so-called crossed–uncrossed difference or CUD). Relatively consistent CUD estimates on the order of ~4 ms have been obtained from healthy individuals (Marzi et al. 1991; Iacoboni and Zaidel 2000), which have been interpreted as reflecting the engagement of a longer/slower visuo-motor pathway in the crossed condition than in its uncrossed counterpart. That is, these conditions would either (1) utilize distinct brain networks for visuo-motor routing and/or (2) engage the same networks but with different temporal/functional dynamics.

The robustness of this behavioral measure raises the question of its neurophysiological basis. The predominant hypothesis is that the CUD reflects transmission time across the corpus callosum, or at least the additional collective transmission time in the case of the crossed conditions. A critical role of callosal fibers is supported by the repeated observation of substantially larger CUD measures in acallosal and callosotomized patients than in healthy subjects (reviewed in Marzi et al. 1991). Despite this clear demonstration of the importance of the corpus callosum in normal brain functions and behavior, direct generalization is problematic due to likely plasticity in these patients (e.g. Brysbaert 1994). In fact, recent functional imaging studies of such patients would indicate that these individuals might use an altogether different brain network than healthy controls (Marzi et al. 1999). While such data provide important insights on the possibility of multiple interhemispheric anatomic channels, it cannot be concluded from the study of such patients whether these channels are regularly used in the intact brain or rather become functionally relevant only after injury and/or agenesis. Thus, the precise functional importance of the corpus callosum and other, subcortical interhemispheric pathways requires investigations of the intact brain.

Recently, several groups have used hemodynamic brain imaging methods in healthy individuals to determine the neurophysiological basis of the CUD. Three such functional magnetic resonance imaging (fMRI) studies provide evidence for increased activity in the white matter tracks of the corpus callosum (Tettamanti et al. 2002; Omura et al. 2004; Weber et al. 2005). However, the neurophysiologic credibility of blood oxygenation level dependent (BOLD) activation within the white matter remains debated, leading many authors, who do observe activations within the corpus callosum, to suggest caution in over-interpreting their findings (e.g. Tettamanti et al. 2002). Two other groups provide evidence for a predominant role of parietal areas in mediating the CUD (Marzi et al. 1999; Iacoboni and Zaidel 2004). In addition to different spatial patterns of activations, methodological variations hinder consensus across these studies. For example, some applied a blocked design, increasing the likelihood of attentional biases (Marzi et al. 1999; Tettamanti et al. 2002; Weber et al. 2005). Others observed CUD in BOLD activity only after applying a relaxed statistical criterion (Omura et al. 2004), or had tested a limited number of participants with very few trials per condition (Iacoboni and Zaidel 2004). Consequently, the results of each of these studies await replication, and the identification of regions differentially activated under crossed and uncrossed conditions remains largely unresolved.

There are additional difficulties in interpreting the CUD behavioral measure. One source stems from the fact that some groups have either failed to observe such reaction time differences or have observed differences opposite to anatomical predictions—i.e. the crossed condition resulted in faster reaction times than the uncrossed condition (see e.g. Ledlow et al. 1978; Saron and Davidson 1989; Braun 1992; Thut et al. 1999; Saron et al. 2003a, b). By contrast, others have observed stable CUD measures across a wide distribution of reaction times (Iacoboni and Zaidel 2000). Likewise, and as mentioned above, there is abundant anatomical data concerning the interconnectivity of the cerebral hemispheres as well as functional data concerning neural response propagation. Anatomical tracing studies indicate that even lower levels of the visual anatomical hierarchy are interconnected with the opposite hemisphere (e.g. Clarke and Miklossy 1990; DiVirgillio and Clarke 1997; Clarke 2003; see also Catani et al. 2003 for recent diffusion tensor tractography results). fMRI has extended upon these anatomical results to show activity within the occipital and parietal cortices of the ipsilateral hemisphere in response to passively viewed unilateral stimuli (Tootell et al. 1998; see also Brandt et al. 2000; ffytche et al. 2000). This activation pattern further varied as a function of the stimuli's physical properties, with moving gratings yielding both a dorsal and ventral extension within the ipsilateral hemisphere and naturalistic images yielding predominantly the latter (Tootell et al. 1998). Corroborating results are also available from electroencephalographic studies that observed early ipsilateral responses over posterior as well as frontal scalp sites (e.g. Rugg et al. 1985; Clark et al. 1995; Murray et al. 2001; Saron et al. 2001, 2003a, b; see also Blanke et al. 1999 for human intracranial evidence). Other studies using hemodynamic methods and blocked designs, however, report little or no evidence of such

bilateral responses to unilaterally presented stimuli (e.g. Marzi et al. 1999; Tettamanti et al. 2002). Thus, the extent to which unilateral stimuli lead to bilateral responses remains unresolved. However they were critical for determining whether the CUD comparison might be better interpreted as reflecting a relative functional difference in visuo-motor pathways, rather than an absolute measure of interhemispheric versus intrahemispheric transmission (see also Saron et al. 2003a).

A similarly controversial aspect of visuo-motor routing is concerned with the functional level at which interhemispheric interactions occur (e.g. Cavina-Pratesi et al. 2004). The application of electrophysiological and hemodynamic measures to the Poffenberger paradigm has yielded conflicting interpretations. Interhemispheric transfer of visuo-motor information in the "crossed" condition has been proposed to occur first at a pre-motor/motor level (e.g. Thut et al. 1999; Tettamanti et al. 2002; Iacoboni and Zaidel 2003, 2004), or already at a visual level (e.g. Brown et al. 1994; Ipata et al. 1997; Murray et al. 2001; see also Corballis et al. 2003 for supporting evidence from patients with partial callosal lesions/sections). Others, applying a case-study approach to the analysis of electrophysiological data, report how visuo-motor routing varies both between individuals and also as a function of reaction time (Saron et al. 2003a, b). One possibility, for which these authors provide preliminary data, is that trials leading to fast reaction times within a subject's own reaction time distribution may rely on a predominantly motor-level of interhemispheric interaction, whereas trials leading to slow reaction times might rely on a predominantly visual-level transfer (Saron et al. 2003a, b; see also Clarke and Zaidel 1989). This proposition would appear to run counter to that put forward by Iacoboni and Zaidel (2000), which suggests that the CUD across the reaction time distribution reflects hard-wired, functionally invariant mechanisms. The question whether there are distinct and behaviorally defined networks of visuo-motor routing for the crossed and uncrossed conditions as a function of subjects' reaction times, therefore, remains unresolved.

To examine the pathways of visuo-motor routing fMRI was used. Specifically, to determine whether the so-called "crossed" and "uncrossed" conditions rely on distinct brain networks for visuo-motor integration, an event-related fMRI paradigm was used as subjects completed a simple RT task with a 2 hemifield $\times$ 2 hand of response design. Recent developments in the analysis of event-related fMRI data indicate that latency analyses can be performed on the directly measured hemodynamic response function (HRF) by means of rapid sampling of the BOLD signal (e.g. Menon et al. 1998; Henson et al. 2002; Bellgowan et al. 2003; Formisano and Goebel 2003; Ritzl et al. 2003; Saad et al. 2003). As such, both the spatial as well as the temporal pattern of responses during visuo-motor integration were analyzed.

Materials and methods

Subjects

Ten subjects (aged 25–51 years, mean ± SD = 33.1 ± 8.8 years; four male and six female) participated after providing written informed consent. All subjects were right-handed (Oldfield 1971), had no history of neurological or psychiatric disease, and had normal or corrected-to-normal vision. The Ethical Committee of the Centre Hospitalier Universitaire Vaudois approved all procedures. This research was in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Magnetic resonance imaging

Functional MRI data were acquired using an event-related design on a 1.5 T Siemens Magnetom Vision system equipped for echoplanar imaging. To reduce head motion, subjects' heads were fixed in the coil by a vacuum beanbag. The BOLD signals were obtained with a single shot gradient-echo EPI sequence (TR = 2 s, TE = 60 ms, FoV = 240 mm, flip angle = 90°, matrix size 64×64). Each volume was comprised of 16 slices (slice thickness 5 mm, gap 1 mm) parallel to the bicommissural plane and covering the entire cerebral hemispheres. Slices were acquired in descending order (i.e. first slice at the top of the head). To provide precise structural and anatomical localization of brain activity, a sagittal T1-weighted 3D gradient-echo sequence (MPRAGE) was acquired for each subject (128 contiguous sagittal slices, slice thickness 1.25 mm, matrix size 256×256, TR = 9.7 ms, TE = 4 ms, FoV = 256 mm, flip angle = 12°).

Experimental procedure

Subjects performed a simple reaction time task to laterally presented black-and-white checkerboard stimuli (3° wide × 4° high; the middle of which appeared 9.5° from central fixation; see Fig. 1 for a schematic representation of the stimulus) projected onto a screen affixed to the end of the head coil. Subjects viewed this screen from an inclined mirror positioned above their eyes, as they lay supine within the magnet's bore. Approximately every 16 s (see below for precise intervals), a checkerboard appeared in either the right or left visual field (RVF or LVF, respectively) for a duration of 100 ms. The visual field stimulated was randomly intermixed across trials. Subjects were asked to respond to stimulus detection by pressing keys on a MRI-compatible device (Photon Control Inc., Burnaby, BC, Canada) in a manner similar to rolling keys on a piano (i.e. by pressing four keys, one per finger, in one swift and continuous movement like tapping one's finger's on a table). Reaction times were recorded as the latency at

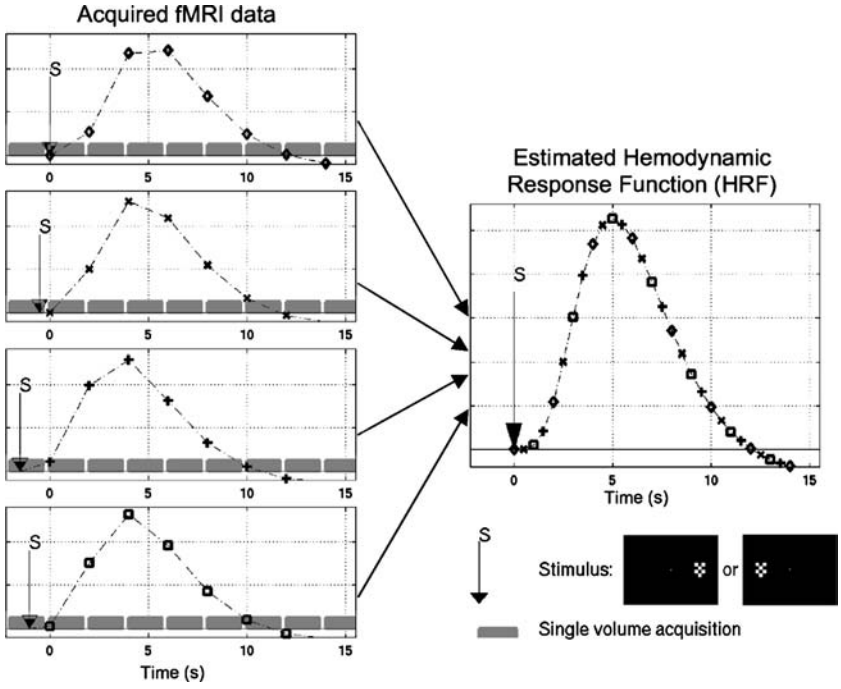

Fig. 1 Schematic representation of stimulus presentation and fMRI signal acquisition. The delay between stimulus presentation (represented by the *black arrows*, 100 ms duration) and BOLD signal acquisition throughout the entire volume (*small rectangles*, 1.7 s duration) varied across the experiment in steps of 125 ms. The merging of the acquisitions allows for a sampling of the hemodynamic response with a temporal resolution finer than the TR

which the first of the keys was pressed. This type of response was selected to optimize motor activations in fMRI images. Response hand was maintained throughout a block of trials, and subjects completed two blocks—the first with the right hand (RH) and the second with the left (LH). This 2 (response hand) × 2 (visual field) design yielded the following four experimental conditions for each subject: RH-RVF, RH-LVF, LH-RVF, and LH-LVF.

The inter-stimulus interval (ISI) varied pseudo-randomly from 14.125 to 17.875 s in steps of 125 ms. This range of long ISIs was chosen to allow the BOLD signal to return to baseline between stimulus presentations. There was a pseudo-random, variable delay between stimulus onset time and volume acquisition of 0 to 1.875 s at steps of 125 ms, yielding a total of 16 different delays. By varying the temporal relationship between volume acquisition and stimulus presentation, the hemodynamic response was sampled at different time points during the experiment. Under the assumption that the hemodynamic responsiveness remains constant across trials throughout the whole experiment, this method, which is a variant of the method proposed by Josephs et al. (1997), effectively samples the BOLD signal with a temporal resolution of 125 ms (shown schematically in Fig. 1). Each of the four experimental conditions included 32 trials, allowing for two volume acquisitions at each of the 16 delays used. 514 volumes were acquired during each session, and the first two volumes were discarded to allow for T1 equilibration effects.

Data analyses

Two types of analyses were conducted in order to investigate whether the "crossed" and "uncrossed" combinations of visual field stimulated and response hand engage distinct networks for visuo-motor routing. The first determined whether distinct spatial patterns of activated brain regions were present. The second determined whether the temporal dynamics within activated brain regions varied across experimental conditions. This was done by measuring the peak latency of the estimated HRF (details are described below).

Spatial domain: activation maps

Activation maps were obtained using SPM99 software (Wellcome Department of Cognitive Neurology, London, UK) running on a Silicon Graphics Octane computer. Volumes were first spatially realigned to the first volume acquired in the session to reduce the effect of head movement during the acquisition. Each volume was then temporarily realigned to the first slice acquired (the one at the top) to correct the effect that slices in the same volume were acquired sequentially during a period of 1.7 s and therefore have a different delay relative to stimulus onset. Volumes were then normalized to a standard brain, based on the Montreal Neurological Institute (MNI) template, re-sampled to a voxel size of 3×3×3 mm^3 using a bilinear interpolation, and smoothed with an isotropic Gaussian kernel (FWHM = 9 mm).

For each subject, a high-pass filter was applied on the time series to minimize possible effects of baseline drift, and the statistical analysis was performed with the General Linear Model (GLM), using the canonical HRF and its temporal derivative as a basis function, as defined in SPM99. An *F*-test was then performed to obtain the statistical parametric maps, which were thresholded ($p < 1\times10^{-5}$ uncorrected) to identify active voxels in the

data of each individual subject. Structural and functional volumes were co-registered within the same coordinate system by normalizing structural images to the MNI template brain and re-sampling voxels to a $1\times1\times1$ mm^3 size. Inference on the population (group analysis) was obtained by means of a second level of statistics, according to the random effects theory (Holmes and Friston 1998).

Several spatial analyses were conducted. The first determined active regions in each condition (voxel-level threshold at $p<0.001$; 20 voxel spatial extent threshold). This addressed the question of whether or not each condition resulted in bilateral responses, even though functionally unnecessary in the uncrossed conditions. The second set of analyses tested for main effects of each visual field and each response hand, as well as of crossed versus uncrossed conditions (see Tettamanti et al. 2002 for a similar analysis). Effects of LVF were identified by contrasting conditions involving the LVF with those involving the RVF, independently of response hand [i.e. (LH-LVF + RH-LVF) versus (LH-RVF + RH-RVF)]. The inverse contrast tested for a main effect of RVF stimulation. The main effect of left response hand was assessed with the contrast of (LH-LVF + LH-RVF) versus (RH-LVF + RH-RVF), and the main effect of right response hand was assessed with the inverse contrast. Global crossed versus uncrossed differences in BOLD activation patterns were assessed with the contrast of (LH-RVF + RH-LVF) versus (LH-LVF + RH-RVF). More focused contrasts then examined the effect of stimulated visual field while holding response hand constant, as well as the effect of response hand while holding the stimulated visual field constant. In all cases, only those activations significant at $p<0.001$ (voxel-level) and with a spatial extent of at least 20 contiguous voxels were considered. A third set of analyses tested for differences in the BOLD activation patterns as a function of reaction time. Those trials yielding the fastest, the middle, and the slowest third of reaction times were analyzed separately ($N=11$ trials per condition and subject for the fastest and the slowest reaction time portion, $N=10$ for the middle portion). In both cases, crossed versus uncrossed conditions were compared [i.e. (RH-LVF + LH-RVF) versus (RH-RVF + LH-LVF)].

Temporal domain: estimated hemodynamic responses

Areas were selected according to the SPM activation maps obtained from the group study and from each individual subject, in the four conditions (i.e. the first spatial analysis described above). For each experimental condition, only those areas showing activity for all subjects were retained for temporal analysis. Anatomical localization was defined on cortical structural basis and MNI coordinates (see e.g. Yousry et al. 1997; Lancaster et al. 2000). Inside each of those regions, the hemodynamic time course was extracted at the location of the statistically most activated voxel. Analysis was restricted to only this most activated voxel (instead of a group of voxels) because the denoising effect provided by such a spatial averaging was already performed effectively by the Gaussian spatial filter, applied during the pre-processing steps described above (this filter itself is a spatial averager, since it weights the response at one voxel by its neighbors, thereby reducing the variability across space).

Given the rather long ISI used, it was reasonable to assume minimal interaction between responses to successive stimuli (Buckner et al. 1996; Menon and Kim 1999). Therefore, it was possible to reconstruct the hemodynamic response by simply averaging the two samples collected at each time point relative to stimulus onset. To do this, a customized toolbox for Matlab was developed (The Mathworks Inc., Natick, MA, USA). The signal obtained was then filtered (0.28 Hz low-pass) to remove high-frequency noise. To prevent phase distortion in the filtered signal, that would have compromised the time analysis, the filter was applied according to the *zero-phase forward and reverse filtering* technique (Matlab 2000). Baseline value was estimated as the mean value of the signal during the 2 s preceding the stimulus onset.

Delays in the hemodynamic signals were estimated as the latency of the peak of the reconstructed response. To better estimate this latency, the signal around the peak (±1.25 s, equal to ten data points before and after the peak) was fitted with a cubic curve and the latency was estimated as the peak of this cubic fit. Estimation of the delay in the hemodynamic signal based on the latency of the peak was preferred to analyses using HRF fitting because this simple method does not require a priori hypotheses on the shape of the response. Note that it was not feasible to perform this analysis as a function of reaction time, since there was no means of assuring that reaction times were evenly distributed throughout the ISI range of the study, which is necessary to estimate the hemodynamic signal. A further comment worth mentioning is that in the present study only two samples were collected at each time point relative to stimulus onset. While increasing this number would have the benefit of improving the estimation of the timecourse of the BOLD response, it would come at the cost of extending an already long experiment for the subject and therefore possibility introducing effects of arousal and fatigue.

Results

Behavioral results

In the four conditions, mean ($\pm$SD) reaction times were 473 ± 81 ms for RH-RVF, 472 ± 86 ms for RH-LVF, 496 ± 87 ms for LH-RVF, and 487 ± 85 ms for LH-LVF. These values were submitted to a 2×2 repeated measures

ANOVA with the within subjects factors of response hand and visual field stimulated. Neither main effect nor their interaction reached our significance criterion of $p \leq 0.05$, providing no *statistical* evidence of a robust CUD. However, comparison of the group mean reaction times from the "crossed" conditions (484 ms) with those from the "uncrossed" conditions (480 ms) yielded an *absolute* CUD of ~4 ms (note: this is not the result of a statistical test, but rather a quantification measure), consistent with the findings of previous research (e.g. Marzi et al. 1991; Iacoboni and Zaidel 2000; Tettamanti et al. 2002). A Page test (Hollander and Wolfe 1973) evaluated the relative reaction time speed across the four experimental conditions, and the following rank order was observed: RH-LVF < RH-RVF < LH-LVF < LH-RVF ($p = 0.031$). This pattern is largely consistent with that observed in a previous meta-analysis, where the LH-RVF condition consistently had the slowest reaction time (Marzi et al. 1991). This general consistency with previous studies provide one indication that our paradigm indeed emulates a prototypical Poffenberger experiment, despite the lengthy ISI used and the non-standard motor response required. We would also note at this point that other studies that obtained a similar pattern of behavioral results used a blocked design as well as more simple light flashes, suggesting that the Poffenberger paradigm withstands such variations (as already noted by Marzi et al. 1991). It likewise is worth mentioning that our RTs are substantially slower than what has been obtained in several prior fMRI/PET studies (e.g. Marzi et al. 1999; Tettamanti et al. 2002; Weber et al. 2005). One possibility is that this follows from the different motor response required of subjects.[1] Another is that such differences follow from blocked versus event-related paradigms and potential influences on attention/arousal. Further experiments will be required to fully resolve this issue.

In order to examine the stability/variability of the CUD across the reaction time distribution of individual subjects, the fastest third, middle third, and slowest third of the reaction times for each subject and experimental condition were separated (hereafter "fast", "middle", and "slow", respectively; $N = 11$, 10, and 11 trials for each subject and condition, respectively). For the fast trials, mean reaction times for the four conditions were 385 ± 72 ms for RH-RVF, 381 ± 71 ms for RH-LVF, 414 ± 79 ms for LH-RVF, and 409 ± 76 ms for LH-LVF. Comparison of the group mean reaction times from the crossed conditions (397 ms) with those from the uncrossed conditions (397 ms) yielded an *absolute* CUD of < 1 ms. For the middle trials, mean reaction times for the four conditions were 471 ± 83 ms for RH-RVF, 472 ± 93 ms for RH-LVF, 490 ± 91 ms for LH-RVF, and 486 ± 83 ms for LH-LVF. This comparison yielded an *absolute* CUD of ~2 ms (481 versus 479 ms). For the slow trials, mean reaction times for the four conditions were 568 ± 105 ms for RH-RVF, 569 ± 109 ms for RH-LVF, 593 ± 103 ms for LH-RVF, and 577 ± 98 ms for LH-LVF. This case yielded an *absolute* CUD of ~9 ms (581 versus 572 ms). Thus, the CUD appears to be essentially absent over the fastest and middle thirds of reaction times, but robust over the slowest third. We return to this point below in terms of variation in crossed versus uncrossed differential activation patterns as a function of reaction time. We further submitted mean reaction times to a 2×2×3 repeated measures ANOVA with the within subjects factors of response hand, visual field stimulated, and portion of reaction time distribution. Not surprisingly, there was a significant main effect of portion of the reaction time distribution ($F_{(2,8)} = 92{,}18$; $p < 0.001$). No other main effect or interaction reached the $p < 0.05$ significance criterion.

Spatial domain: activated areas versus 'rest'

Group results are shown in Fig. 2, which shows the activated areas in each of the four experimental conditions from a sample of slices with the left side of the figure corresponding to the left hemisphere, and listed in Table 1, which provides the anatomical location, MNI coordinates, and *Z* scores of the statistically most active voxels for those areas consistently activated across subjects. In general across the four conditions, we observed large activations of the medial and lateral occipital lobe contralateral to the hemifield stimulated, as well as a smaller activation of the medial and lateral occipital lobe ipsilateral to the hemifield stimulated. In the right hemisphere such activity often extended into the temporal lobe. Activations of the precentral gyrus were strongly lateralized to the hemisphere contralateral to the response hand with minimal ipsilateral activation. Similar frontal midline activations were observed in all four conditions. However, because of the spatial resolution and filtering of the fMRI data, we are hesitant to classify activity within this region as specifically originating in either the left or right hemisphere. Variable thalamic activations were also present in all conditions.

The coordinates of these regions, when transformed into Talairach space, correspond to the anatomical location of visual areas V1 and V5 in the occipital lobe and to areas M1 and SMA in the frontal lobe (Yousry et al. 1997; Lancaster et al. 2000). The mean distance between the most activated voxel in each area of each individual and the mean MNI coordinate was always smaller than 10 mm (maximal standard deviation < 5.3 mm, see Table 1). That is, this subset of regions was consistently and reliability activated in all subjects.

[1] We have partially addressed this issue in a separate pilot study examining simple reaction times to visual, auditory, or simultaneous auditory-visual multisensory pairs. The same subjects first responded with a single finger and several weeks later were re-tested using the piano roll movement used in the present study (both the experiments were conducted within the MR scanner environment). The same pattern of reaction times was observed for both types of motor response, except that the reaction time distribution was simply shifted later in the case of the piano roll

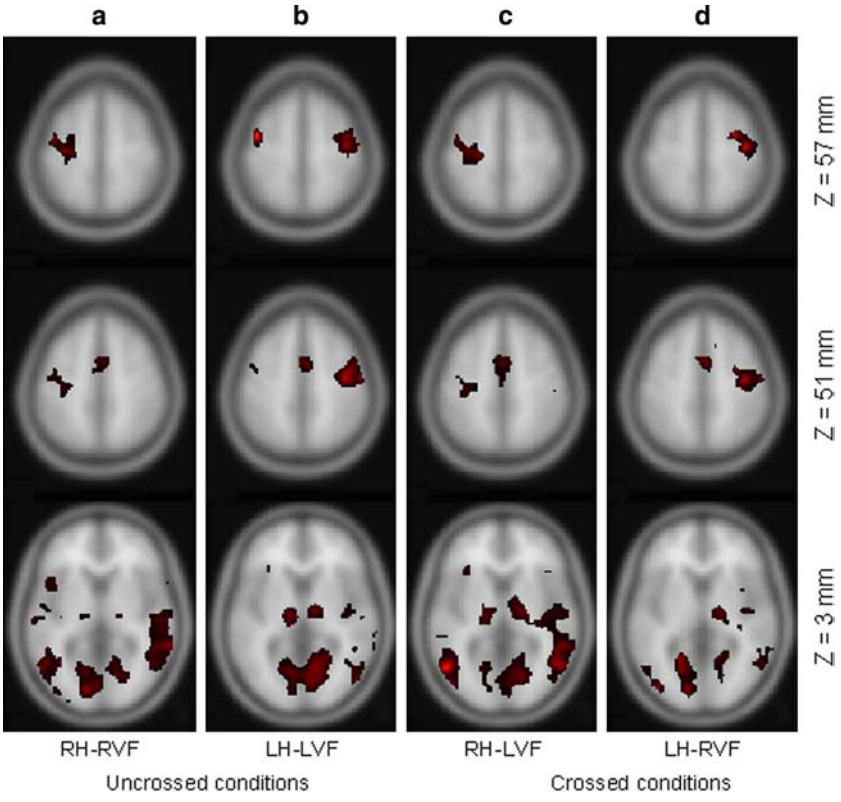

Fig. 2 Group results showing activated areas in each of the four experimental conditions. **a** RH response to RVF stimulation; **b** RH response to LVF stimulation; **c** LH response to RVF stimulation; **d** LH response to LVF stimulation. *Slices* are parallel to the bicommissural plane at levels $z = 3$, 51, and 57 mm and are displayed in neurological convention (*left hemisphere on left*)

Table 1 Anatomical location, corresponding functional area, mean MNI coordinates, and *Z* scores [a] of the statistically most active voxels across subjects and conditions

Anatomical location	Functional area	Mean MNI coordinates			Mean ± SD distance from mean coordinates (mm)	*Z*-score[a]			
		x	y	z		RH-RVF	RH-LVF	LH-RVF	LH-LVF
Right cuneus (BA 17)	V1 (right)	11	−79	5	6.5 ± 2.8	4.18	4.17	3.10	4.00
Left cuneus (BA 17)	V1 (left)	−10	−82	5	5.6 ± 3.3	4.25	3.42	4.16	3.78
Right posterior middle temporal gyrus (BA 37)	V5 (right)	50	−67	3	9.4 ± 5.6	3.77	4.28	3.70	3.74
Left posterior middle temporal gyrus (BA 37)	V5 (left)	−49	−69	2	8.5 ± 3.5	3.96	4.78	3.43	3.31
Medial frontal gyrus (BA 32)	SMA	0	4	50	8.1 ± 2.9	4.07	3.92	4.22	4.43
Right precentral gyrus (BA 4 and 6)	M1 (right)	41	−12	59	9.3 ± 3.3	3.45	3.63	4.64	4.45
Left precentral gyrus (BA 4 and 6)	M1 (left)	−39	−15	58	10.4 ± 3.9	4.07	4.13	N/A	4.78

[a] *Z*-score refers to the local maximum in the group statistics nearest to the mean point (listed here in the third column)

We return to these regions in our analysis of the time course of BOLD responses, below.

Specifically, the RH-RVF condition (Fig. 2a) activated in the left hemisphere (i.e. that contralateral to the stimulus) large regions of the medial and lateral occipital lobe that extended into the temporo-parieto-occipital junction, a large region of the precentral gyrus, and voxels within the posterior thalamus. In the right hemisphere (i.e. that ipsilateral to the stimulus), this condition activated smaller regions of the medial and lateral occipital lobe that extended into the temporo-parieto-occipital junction and superior temporal plane, voxels within the posterior thalamus, and sparse voxels in the precentral gyrus. In addition, there was a large region of the medial frontal gyrus activated.

The RH-LVF condition (Fig. 2b) activated in the right hemisphere (i.e. that contralateral to the stimulus) large regions of the medial and lateral occipital lobe that extended into the temporo-parieto-occipital junction, a small region of the precentral gyrus, as well as voxels within the posterior thalamus. In the left hemisphere (i.e. that ipsilateral to the stimulus), this condition activated smaller regions of the medial occipital lobe, a large region of the lateral occipital lobe, a large region of the

precentral gyrus, and voxels within the posterior thalamus. A large region within the medial frontal gyrus was also activated.

The LH-RVF condition (Fig. 2c) activated in the left hemisphere (i.e. that contralateral to the stimulus) large regions of the medial and lateral occipital lobe, and a large region of the medial frontal cortex. No activation was observed in the left precentral gyrus. In the right hemisphere (i.e. that ipsilateral to the stimulus) this condition activated smaller regions of the medial and lateral occipital lobe, voxels within the posterior thalamus and insula, as well as a large region of the precentral gyrus.

The LH-LVF condition (Fig. 2d) activated in the right hemisphere (i.e. that contralateral to the visual stimulus) large regions of the medial and lateral occipital lobe that included extension into the temporo-parieto-occipital junction, a large region of the precentral gyrus, voxels within the posterior thalamus and insula, and a large region of the medial frontal cortex. In the left hemisphere (i.e. that ipsilateral to the visual stimulus) this condition activated smaller regions of the medial occipital lobe and only a few voxels in the lateral occipital lobe and precentral gyrus.

Thus, robust bilateral responses were obtained for each of the four experimental conditions. A Page test evaluated the relative magnitude of global activity (i.e. the total number of active voxels irrespective of hemisphere and without the application of the 20-voxel spatial criterion) across the four experimental conditions, and the following rank order was observed: RH-LVF > RH-RVF > LH-LVF > LH-RVF ($p < 0.01$). This pattern mirrors that observed with reaction times, such that conditions leading to faster responses activated a larger number of voxels. Conditions involving the RVF or LVF consistently activated a larger number of voxels. To test whether the combination of response hand and stimulated visual field influenced the extent of bilateral activation, we calculated the total number of activated voxels for each condition and hemisphere (Table 2) and submitted these values to a three-way repeated measures ANOVA with the within subjects factors of response hand, visual field stimulated, and cerebral hemisphere. Only those effects yielding p-values ≤ 0.05 were considered statistically significant. There was a main effect of response hand ($F_{(1,9)} = 6.94$; $p = 0.027$), with conditions requiring right-hand responses yielding more activated voxels than conditions requiring left-hand responses. Both the main effect of visual field stimulated ($F_{(1,9)} = 3.35$; $p = 0.100$) and of hemisphere ($F_{(1,9)} = 3.94$; $p = 0.078$) approached our significance criterion. The interaction between these factors of visual field and hemisphere was significant ($F_{(1,9)} = 21.61$; $p = 0.001$), indicating that the number of activated voxels observed in each hemisphere varied with the visual field stimulated. Despite this interaction, we would emphasize that unilateral visual stimulation always led to a bilateral response. Moreover, follow-up comparisons revealed that LVF presentations led to a preponderance of activity within the right versus left hemisphere ($t_{(9)} = 3.75$; $p = 0.005$), and RVF presentations led to a statistically indistinguishable number of activated voxels in each hemisphere ($t_{(9)} = 0.02$; $p = 0.98$). All other interactions in the ANOVA failed to reach the 0.05 significance criterion.

To this point, these analyses indicate that brain responses to the ''uncrossed'' condition were bilateral and not restricted to a single cerebral hemisphere. Rather, the ''uncrossed'' conditions led to robust activity (predominantly) within the medial and lateral occipital lobe of the hemisphere ipsilateral to the visual stimulus. This constitutes demonstration of interhemispheric transfer under unilateral viewing conditions, in contrast to the conclusions of previous hemodynamic brain imaging studies reporting activity restricted to the contralateral hemisphere (Marzi et al. 1999). In addition, the present results run counter to the observation of a rostral versus caudal asymmetry between uncrossed and crossed conditions, respectively, in a PET study using a blocked design (Marzi et al. 1999). It is important to note, however, that this previous study (Marzi et al. 1999) as well as the subsequent fMRI study by this group (Tettamanti et al. 2002) never analyzed experimental conditions versus 'rest', which is necessary for determining the extent of bilateral activity elicited by unilateral stimuli. Another, non-exclusive possibility is that the blocked design of these studies (and the attentional set assumed by subjects) significantly contributed to the observed activation patterns. Instead, our data support the activity of a common spatial network across all conditions. We next address whether and how responses within this network differed with visual field, response hand, as well as crossed versus uncrossed conditions.

Spatial domain: main effects of visual field and response hand

Figure 3 and Table 3 show the main effects of visual field and response hand. The contrast of conditions involving stimulation of the RVF versus those involving

Table 2 Average number of active voxels (i.e. in the absence of spatial extent criterion) in each experimental condition

Experimental condition	Left hemisphere[a]	Right hemisphere[a]	Total
RH-RVF	3,577 (50.3%)	3,530 (49.7%)	7,107
RH-LVF	4,180 (48.4%)	4,462 (51.6%)	8,642
LH-RVF	2,350 (49.5%)	2,393 (50.5%)	4,743
LH-LVF	2,497 (43.0%)	3,305 (57.0%)	5,802

[a]the percentage of the total across hemispheres is given in parentheses

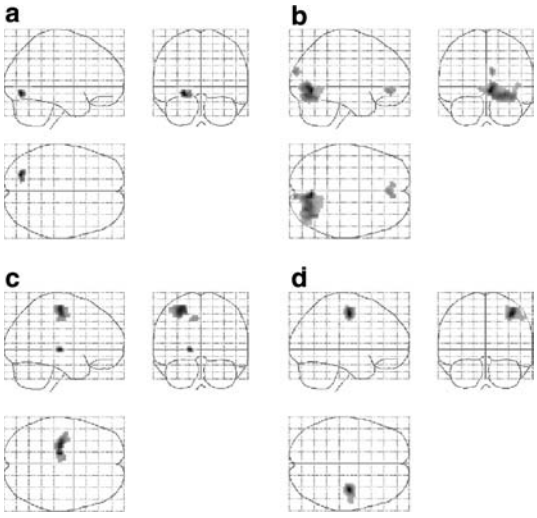

Fig. 3 Group results showing activated areas for the main effects of each visual field and each response hand. These activations are schematized on a glass brain. **a** Main effect of stimulation to the RVF; **b** main effect of stimulation to the LVF; **c** main effect of responding with the right hand; and **d** main effect of responding with the left hand. See Materials and methods for details on these contrasts

the LVF revealed activation within the left occipital lobe. The inverse contrast revealed a similar, though larger, activation in the right occipital lobe. The contrast of conditions involving manual responses with the right hand versus those involving the left hand revealed activation within the left precentral gyrus. The inverse contrast similarly revealed activation in the right precentral gyrus. This pattern largely replicated that observed by Tettamanti et al. (2002), who used a blocked design, indicating the sensitivity of the present event-related fMRI paradigm. Likewise, it provides one indication of subjects' adequate fixation and cooperation with the motor task.

Spatial domain: crossed versus uncrossed activation patterns

The global comparison of crossed versus uncrossed conditions failed to reveal any differentially active regions. To more focally test for differences in the activation patterns between the "crossed" and "uncrossed" conditions, we first contrasted RVF and LVF stimulus presentations when the same response hand was used (Fig. 4a). This contrast yielded activated voxels in the occipital lobe contralateral to the visual hemifield where the stimulus was presented, irrespective of whether or not the motor response was ipsilateral to the visual stimulation. Details on activated areas revealed by this contrast are provided in Table 4. We next contrasted RH and LH motor responses when the same visual field was stimulated (Fig. 4b). This contrast activated voxels in the motor representation contralateral to the hand mediating the response (see Table 4 for details). That is, our analyses provide no evidence of an alteration in the spatial activation pattern at either a global or focal level between the "crossed" and "uncrossed" conditions. No distinct regions were selectively observed for either the "crossed" or "uncrossed" conditions.

Given that our behavioral data would suggest that the CUD varies across different thirds of the reaction time distribution (<1, ~ 2, and 9 ms for the fastest, middle, and slowest thirds, respectively), we repeated the comparison of crossed versus uncrossed spatial patterns of BOLD activations separately for each of these portions of the reaction time distribution (Fig. 5 and Table 5). This comparison with fastest trials as well as the middle trials failed to reveal any statistically significant

Table 3 Anatomical location, MNI coordinates, and *Z* scores of the statistically most active voxels for main effects of visual field stimulated and response hand

	MNI coordinates			*Z* Score
	x	*y*	*z*	
Effect of RVF stimulation (RH-RVF + LH-RVF)-(RH-LVF + LH-LVF)				
Left lingual gyrus (BA 19)	−24	−75	−9	3.89
Effect of LVF stimulation (RH-LVF + LH-LVF)-(RH-RVF + LH-RVF)				
Right lingual gyrus (BA 18)	6	−69	−6	4.67
Right cuneus (BA 19)	9	−93	21	3.83
Right medial frontal gyrus (BA 10 and 11)	3	45	−9	3.74
Effect of right hand response (RH-RVF + RH-LVF)-(LH-RVF + LH-LVF)				
Left thalamus	−15	−18	0	4.43
Left precentral gyrus (BA 4)	−30	−18	57	4.29
Left cingulate gyrus (BA 24)	−12	−21	42	3.52
Effect of left hand response (LH-RVF + LH-LVF)-(RH-RVF + RH-LVF)				
Right precentral gyrus (BA 4 and 6)	39	−12	51	4.91

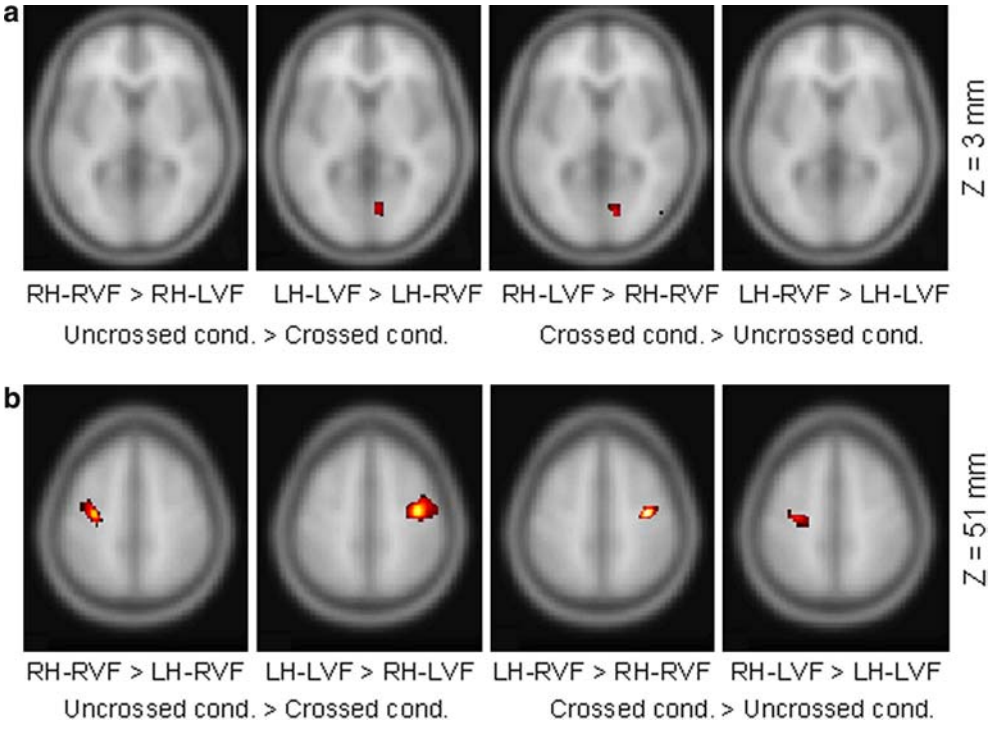

Fig. 4 Group results of focal contrasts to examine effects of visual field and response hand. **a** V1 and surrounding areas ($z = 3$ mm) that present higher activation during the stimulation of one visual field, keeping fixed the motor response and **b** SMA and M1 areas ($z = 3$ mm) that present higher activation during the response of one hand, keeping fixed the visual stimulation. *Slices* are in the same convention as in Fig. 2

activation. By contrast, this comparison with slow trials revealed several clusters of differential activation within the right occipital gyrus (BA19) and right fusiform gyrus, extending into the right middle temporal gyrus (BA37/39). These results suggest that the speed of reaction time may contribute to whether or not differential activation strengths are observed for the crossed versus uncrossed comparison. Likewise, visual cortical areas appear to play a critical role in interhemispheric interactions during slow trials. To further assess this possibility, we correlated CUD magnitude with the crossed versus uncrossed difference in BOLD responses for each of the three portions of the reaction time distribution, separately. Clusters where this correlation was conducted were defined by the above results for slow trials. A significant correlation between CUD magnitude and BOLD response difference was observed within BA37 for slow trials ($r = 0.764$; $p = 0.01$), but not for

Table 4 Anatomical location, MNI coordinates, and Z scores of the statistically most active voxels for focal contrasts of visual field stimulated and response hand

	MNI coordinates			Z Score
	x	y	z	
Effect of stimulated visual field (holding response hand constant)				
RH-RVF–RH-LVF				
No suprathreshold clusters				
LH-LVF–LH-RVF				
Right lingual gyrus (BA 18)	9	−75	3	3.76
Right lingual gyrus (BA 18)	21	−72	−15	3.68
RH-LVF–RH-RVF				
Right fusiform gyrus (BA 19)	39	−75	−15	4.72
Right lingual gyrus (BA 18)	12	−78	−3	4.29
LH-RVF–LH-LVF				
No suprathreshold clusters				
Effect of response hand (holding stimulated visual field constant)				
RH-RVF–LH-RVF				
Right precentral gyrus (BA 4 and 6)	−30	−18	57	4.55
LH-LVF–RH-LVF				
Left cingulate gyrus (BA 31)	−9	−24	42	4.72
Right thalamus	9	−3	9	4.03
Left precentral gyrus (BA 4 and 6)	−30	−18	51	3.98
LH-RVF–RH-RVF				
Left precentral gyrus (BA 4 and 6)	39	−15	60	5.12
RH-LVF–LH-LVF				
Left precentral gyrus (BA 4 and 6)	39	−12	51	4.61

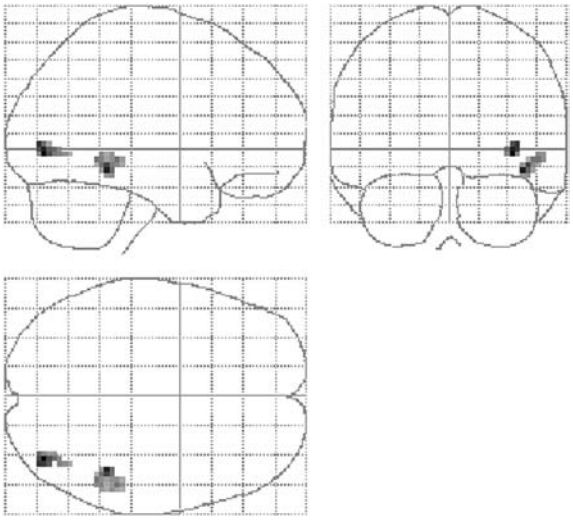

Fig. 5 Group results showing activated areas for the global crossed versus uncrossed conditions contrast for the slowest third of reaction times (see "Materials and methods" for details). These activations are schematized on a glass brain

middle trials ($r = -0.470$; $p = 0.17$), or fast trials ($r = 0.173$; $p = 0.63$). No significant correlations were observed in any of the other tested clusters. Lastly, the comparison of the uncrossed versus crossed spatial patterns of BOLD activations separately for each of these portions of the reaction time distribution failed to reveal any significant voxels.

Temporal domain: time course of bold responses

The estimated BOLD signal time courses (displayed as the percent signal change) and their mean peak latencies are shown in Fig. 6 and Table 6, as measured at the locations listed in Table 1. The BOLD responses for these voxels were averaged across subjects for each of the four experimental conditions, separately. Signal amplitudes are consistent with previous event-related fMRI experiments (e.g. Henson et al. 2002; Formisano and Goebel 2003). Time delays of the signals were measured as the latencies of the positive-going peaks in BOLD responses from stimulus onset (see "Materials and methods" for details). Since the signal from M1 ipsilateral to the responding hand consistently yielded a negative BOLD signal (see Fig. 6), this region was excluded from this temporal analysis.

Peak latencies as measured from each of the remaining brain regions were submitted to a 2×2 repeated measures ANOVA with within-subjects factors of visual field and response hand. This was done for each functional area separately. For area V1 of the right hemisphere, there was a significant main effect of stimulated visual field ($F_{(1,6)} = 8.773$; $p = 0.025$) with stimulation of the LVF yielding earlier peak latencies. For area V1 of the left hemisphere, the main effect of stimulated visual field approached our significance criterion ($F_{(1,6)} = 4.101$; $p = 0.089$), with stimulation of the RVF demonstrating earlier peak latencies. There was also a significant interaction between stimulated visual field and response hand ($F_{(1,6)} = 9.621$; $p = 0.021$) that followed from a larger LVF versus RVF difference for left-handed versus right-handed responses (mirroring the patterns of reaction times). This indicates that the responding hand plays a role in modulating the peak of the BOLD response in V1. This may reflect an effect of task set (responding hand was blocked) similar to effects of attention recently described by Weber et al. (2005). Lastly, neither main effect nor their interaction reached our significance criterion for area V5 of either hemisphere or SMA.

It is important to note that peak latency of the BOLD response need not correspond with neural response latencies. However, demonstration of a change in BOLD dynamics across stimulus conditions (all of which have the same presentation duration) does suggest that functional anatomy plays a role in peak BOLD response latencies within a given voxel. Whether or not these shifts in BOLD dynamics are directly related to the shifts in neural activity (as observed with other methods including event-related potentials) is beyond the scope of the present study and must instead await further experimentation and methodological advances that enable the precise localization of ERP sources.

Discussion

The main finding of the present study is that highly similar spatial patterns of brain activation were observed for all experimental conditions of a simple visual reaction time paradigm, wherein the visual field of stimula-

Table 5 Anatomical location, MNI coordinates, and *Z* scores of the statistically most active voxels in the global crossed versus uncrossed comparison for trials leading to the fastest third or slowest third of reaction times

	MNI coordinates			*Z* Score
	x	*y*	*z*	
Crossed versus uncrossed difference (RH-LVF + LH-RVF)–(RH-RVF + LH-LVF)				
Fast trials: no suprathreshold clusters				
Middle trials: no suprathreshold clusters				
Slow trials:				
Right inferior occipital gyrus (BA 19)	36	−78	−3	3.71
Right middle temporal gyrus (BA 37)	42	−42	−12	3.68

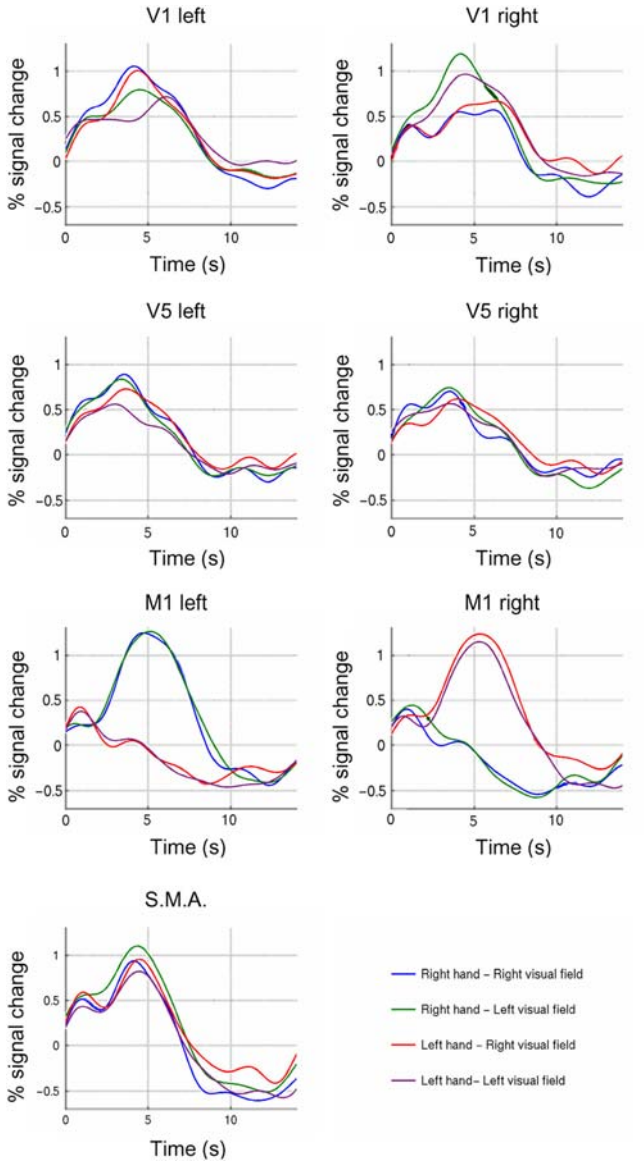

Fig. 6 Time course of the mean BOLD signal in the areas of interest, listed in Table 3, during the four experimental conditions

tion and/or hand of motor response were varied. Additional results indicate that the global comparison of crossed conditions against their uncrossed counterparts failed to reveal differentially activated areas. However, such differential activity was observed within visual cortical areas when distinct portions of the reaction time distribution were separately analyzed, indicating that visuo-motor pathways may vary with processing speed. This suggests that visuo-motor pathways can vary functionally. In support of this suggestion, we found a significant correlation between the strength of the CUD measured from the BOLD response and the magnitude of the CUD measured from reaction times within BA37 for the slowest third of the reaction time distribution. This was not observed for the middle or fastest thirds. These results have implications for our understanding of visuo-motor routing and response propagation. First, these results are consistent with the parallel and distributed responses observed using electrophysiological methods. Second, the collective data support the view that interhemispheric interactions occur in response to unilaterally presented visual stimuli irrespective of response hand, and that these interactions occur predominantly at the level of visual cortices. Finally, the results of this study indicate that simple models of visuo-motor pathways are insufficient. Rather, a common network of brain areas appears to be active under all conditions, varying instead in its strength as a function of reaction time and crossed and uncrossed conditions.

The present results provide functional evidence that the CUD is likely not the simple result of the selective activation of areas for the crossed conditions, but rather likely follows from a change in the strength and/or dynamics of responses in already active structures (see Fig. 2). This notion is predicated on our observation of highly similar spatial patterns of activity for each condition. As such, this conclusion runs counter to those of some previous studies applying hemodynamic methods to the Poffenberger Paradigm (Marzi et al. 1999; Tettamanti et al. 2002). Likewise, the comparison between the different activation maps from specific conditions revealed no significant differences in ipsilateral visual or motor areas related to the crossed versus uncrossed comparison (see Fig. 4). Moreover, this comparison did not yield any regions selectively activated by the crossed condition. Rather, we consistently observed an enhanced response to LVF stimulation, irrespective of the response hand, in visual areas of the right hemisphere. However, we would note that we cannot exclude the possibility that this stronger activity masked some small differences in the activation pattern related to interhemispheric interactions specific to the "crossed" conditions.

In terms of variation in the strength of responses in already active structures as an explanation of the CUD, our analyses did reveal differences when trials were separately analyzed according to their reaction times. Specifically, the fastest third of trials yielded a CUD of

Table 6 Average peak latencies (in seconds ± SD) of BOLD signals in the regions of interest

Condition	V1 right	V1 left	V5 right	V5 left	SMA	M1 right	M1 left
RH-RVF	5.11 ± 1.47	3.83 ± 1.17	3.46 ± 1.05	3.60 ± 1.11	4.32 ± 0.62	N/A	5.03 ± 0.73
RH-LVF	3.97 ± 0.80	4.43 ± 1.19	3.86 ± 1.26	3.52 ± 0.89	4.41 ± 0.50	N/A	5.05 ± 0.54
LH-RVF	5.05 ± 1.73	4.36 ± 0.48	4.14 ± 1.42	4.47 ± 1.20	4.59 ± 0.63	5.50 ± 0.83	N/A
LH-LVF	4.40 ± 0.83	5.80 ± 1.54	3.80 ± 0.98	3.21 ± 1.11	4.51 ± 0.51	5.43 ± 0.66	N/A

< 1 ms, the middle third a CUD of ~2 ms, and the slowest third a CUD of ~9 ms. In terms of CUD effects on the BOLD response, only slow trials resulted in significant activation differences (i.e. stronger responses to the crossed than uncross conditions), which were located within right extrastriate visual areas (BA 19 and 37). This pattern is in keeping with the proposition put forward by Saron and colleagues, based on a case-study analysis of event-related potentials of healthy individuals (Saron et al. 2003a), that cortical activation patterns are influenced by reaction times. Specifically, slower reaction times were proposed to rely on more posterior cerebral interhemispheric pathways, a notion supported by our results. In addition, the significant correlation between behavioral and BOLD indices of CUD within BA37 for the slowest third of trials further suggests that differential responses within this area are linked to behavioral outcome. A further implication of this finding is that visual cortices play a critical role in visuo-motor interhemispheric interactions. We return to these points below.

We found no evidence for activations in the corpus callosum, even when more relaxed statistical thresholding was applied. This contrasts with previous studies (Tettamanti et al. 2002; Weber et al. 2005). In addition to the general debate concerning whether BOLD responses within the white matter are physiologically reasonable (cf. Tettamanti et al. 2002), one of the possible explanations for this discrepancy can be found in the different methodologies employed in these studies. Tettamanti et al. (2002), as well as Weber et al. (2005), used a block-designed paradigm that is known to be more sensitive than event-related protocols, and activations in the white matter are considerably smaller than those in the gray matter (Preibisch and Haase 2001). On the other hand, event-related protocols are not biased by the shift of attention implicit in a block-designed paradigm, which has been shown to play an important role in the recruitment of cortical brain areas (Weber et al. 2005). It is further possible that this difference between event-related and blocked designs and/or the type of motor response required are the bases for the discrepancy between RT distributions between our study and those of Marzi's group. Another possibility is that the long ISI of the present study does not adequately tax the brain systems underlying signal changes within the corpus callosum. Despite the absence of differential activity within the corpus callosum, we would emphasize that a role for callosal fibers in interhemispheric interactions is supported by our data demonstrating a predominant role of visuo-visuo interhemispheric interactions (see below).

Further investigation will be required to replicate and detail these findings. For example, one possibility is that differential activations were observed for slow trials simply because the CUD in reaction times was sufficiently large, whereas such was effectively absent for fast and middle trials. Nonetheless, the present findings highlight the importance of considering the impact of intrasubject performance variations on patterns of brain activation. As such, our findings (albeit with a limited number of trials) also suggest that both reaction time indices of CUD and also interhemispheric activations may not be constant across an individual's reaction time distribution (see Iacoboni and Zaidel 2000 for evidence to the contrary).

In terms of the dynamics of responses in already active structures, the event-related design and high temporal sampling of the BOLD response allowed us to examine this possibility (albeit with substantially less temporal resolution than other—most notably electromagnetic—techniques). Here, we formulate some speculative comments on the dynamics of brain responses across multiple functional areas (see Table 6). As mentioned briefly above, it was only in V1 where peak latencies of the BOLD signal were statistically different across conditions. This is in keeping with the current understanding of contralateral representations of the visual hemifields and the lack of direct ipsilateral projections (either via naso-temporal overlap or callosal fibers beyond the representation of the vertical meridian) within V1 (e.g. Clarke and Miklossy 1990; Brysbaert 1994; Tootell et al. 1998). Moreover, each experimental condition exhibited a homologous ordinal sequence of peak latencies across these functional brain regions. Although the precise coupling between hemodynamic measures and neural activity remains to be fully resolved, previous studies have demonstrated the interpretability of temporal information in the BOLD signal in terms of relative latency differences between brain regions (e.g. Menon et al. 1998; Henson et al. 2002; Ritzl et al. 2003; Formisano and Goebel 2003), despite the unresolved question concerning the variability of the BOLD response across different brain areas. In the present study, the observed sequence across areas is consistent with observations of rapid visual response propagation using electrophysiological methods (e.g. Buchner et al. 1997; Nowak and Bullier 1997; Schroeder et al. 1998; ffytche et al. 2000; Morand et al. 2000; Foxe and Simpson, 2002; Michel et al. 2004). Interestingly, while we found nearly homologous BOLD responses for V5 bilaterally (both in terms of magnitude and peak latency), those from V1 differed between the contra- and ipsi-lateral hemispheres. One implication, which is supported by both anatomical (e.g. Clarke and Miklossy 1990) and functional data (e.g. Ipata et al. 1997; Tootell et al. 1998), is that there exist distinct interhemispheric channels even within the visual system. Visual areas, including some bilaterally, and SMA may thus work in a continuous stream that need not be directly linked with the timing of responses in M1 and by extension, reaction time. In support, electrophysiological investigations in both humans (e.g. Saron et al. 2001; Foxe and Simpson 2002; Thut et al. 1999; Blanke et al. 1999) and non-human primates (e.g. Schroeder et al. 1998; Bullier 2001) indicate that premotor regions, including SMA and frontal eye field (FEF), are active nearly simultaneously with visual regions.

The present data likewise provide evidence regarding the likely functional level of interhemispheric interac-

tions. On the one hand, the activation maps from each condition versus 'rest' revealed bilateral occipital activation in response to a briefly and laterally presented visual stimulus both in the ''crossed'' and in the ''uncrossed'' conditions. Conjointly, responses within motor cortex were consistently lateralized to the hemisphere contralateral to the responding hand, even in the case of ''crossed'' conditions. A strong implication of these results is that the predominant interhemispheric interactions occur between visual brain areas, in agreement with previous studies (Mordkoff et al. 1996; Marzi et al. 1998; Braun et al. 1999; Brandt et al. 2000; Murray et al. 2001), rather than motor areas (e.g. Thut et al. 1999; Tettamanti et al. 2002; Iacoboni and Zaidel 2003). Further supporting this conclusion is our observation of differential activation within visual areas following the crossed versus uncrossed comparison with trials leading to slow reaction times. However, as we observed this pattern with a relatively low number of trials, we cannot unequivocally rule out the possibility of other interhemispheric pathways that may further vary between individuals and/or as a function of finer reaction time subdivisions. Nonetheless, these data provide support for the proposition of Saron and colleagues [that posterior interhemispheric pathways predominate trials leading to slower reaction times (Saron et al. 2003a)]. We would note that additional transfer mechanisms involving the SMA cannot be excluded based on the present results, since we were unable to resolve hemispheric differences within the SMA. However, peak responses in SMA were consistently delayed relative to those in visual areas, and putative interhemispheric interactions involving the SMA may play a secondary role in visuo-motor routing. Further experiments that continue to capitalize on the event-related design of the present experiment will be required to more fully resolve this question.

The collective results permit some comments on models of visuo-motor interactions. First, the spatial activation patterns support the hypothesis that interhemispheric interactions take place in response to unilateral visual stimuli for both crossed and also uncrossed conditions to the same degree; to the extent that the intensity of the BOLD response accurately reflects neural response intensity. This pattern is in solid agreement with notions of parallel distributed processing within the visual system (e.g. Felleman and Van Essen 1991; Schroeder et al. 1998; Foxe and Simpson 2001) and extends these findings to suggest that brief unilateral visual stimulation produces volleys of responses in both cerebral hemispheres. Second, the spatial pattern of activations included lateralized responses within motor cortex and bilateral responses within visual cortices. This pattern provides additional evidence that interhemispheric interactions are predominantly between visual cortical regions and that visuo-motor integration likely occurs within a hemisphere (though we cannot unequivocally exclude the possibility of heterotopic interhemispheric interactions or such mediation via the SMA). Moreover, since crossed–uncrossed differences in peak BOLD responses were observed only within V1 (among those areas tested; see Fig. 6 and Table 6), a model of interhemispheric interactions occurring predominantly at a functionally extrastriate visual level is again supported. An additional speculative possibility is that this interhemispheric signal not only triggers visuo-motor integration, but also top-down modulation within ipsilateral V1. Third, our data would indicate that CUD differences in BOLD response that are apparent for different portions of the RT distribution reflect modulations in the strength of responses of the same brain network, rather than the selective activation of brain regions when reaction times are delayed. These data do not provide evidence of functionally distinct interhemispheric pathways that vary with reaction time. Rather, reaction time appears to modulate the relative strength of responses within a subset of brain regions—i.e. within visual extrastriate regions of the right hemisphere. One possibility is that activation accumulates and triggers enhanced activity within BA37 when motor responses are not initiated quickly. However, as we mentioned above, we cannot exclude the possibility that the CUD difference observed here is related instead to the (on average) larger CUD, rather than being linked to slower RT trials.

In summary, the collective results favor a parallel, distributed model of brain activation. Visuo-motor processing during a simple reaction time paradigm consistently resulted in bilateral brain responses (particularly within visual cortices) not only for the ''crossed'' but also the ''uncrossed'' conditions, providing evidence that a simple model of visuo-motor pathways is insufficient. The presence of interhemiphseric interactions and its consequent bilateral activity is not determined by the crossed anatomic projections of the primary visual and motor pathways. Distinct visuo-motor networks need not be engaged to mediate behavioral responses for the crossed visual field/response hand condition. While anatomical connectivity heavily influences the spatial pattern of activated visuo-motor pathways, behavioral and functional parameters appear to also affect the strength and dynamics of responses within these pathways. While the present study examined the case of visuo-motor routing, future experiments that similarly capitalize on the spatial as well as temporal information within the BOLD response, as well as single-subject analyses, will undoubtedly shed further light on the full breadth of brain function and processing pathways.

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