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Visuo-motor integration in humans: Cortical patterns of response lateralisation and functional connectivity

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ABSTRACT

Purpose: We assessed response and functional connectivity patterns of different parts of the visual and motor cortices during visuo-motor integration with particular focus on the intraparietal sulcus (IPS).
Methods: Brain activity was measured during a visuo-motor task in 14 subjects using event-related fMRI. During central fixation, a blue or red target embedded in an array of grey distractors was presented for 250 ms in either the left or right visual hemifield. After a delay, the subjects were prompted to press the upper or lower response button for targets in the upper and lower hemifield with the left or right thumb for blue and red targets, respectively. The fMRI responses were evaluated for different regions of interests (ROIs), and the functional connectivity of the IPS subregions with these ROIs was quantified.
Results: In an anterior IPS region and a region in the anterior premotor cortex, presumably the frontal eye fields (FEF), visually driven responses were dominant contralateral to both visual stimulus and effector. Thus, the anterior IPS combines, in contrast to the posterior IPS and the occipital cortex, response properties of cortex activated by visual input and by motor output. Further, functional connectivity with the motor areas was stronger for the anterior than for the posterior IPS regions.
Discussion: Anterior IPS and FEF appear to be of major relevance for relating visual and effector information during visuo-motor integration. Patient studies with the devised paradigm are expected to uncover the impact of pathophysiologies and plasticity on the observed cortical lateralisation patterns.

1. Introduction

Visual information is of crucial importance for the preparation, initiation, and guidance of motor actions and consequently a key aspect of behavioural neuroscience. It is therefore topical to identify the areas involved in visuo-motor integration, to detail their functional specialisation, and to uncover their functional connectivity within the underlying networks. There is general agreement that processes of visuo-motor integration are accomplished by a cortical network comprising posterior parietal and premotor areas (Andersen & Buneo, 2002; Battaglia-Mayer & Caminiti, 2002; Caminiti, Ferraina, & Mayer, 1998; Kalaska, Scott, Cisek, & Sergio, 1997; Medendorp, Beurze, Van Pelt, & Van Der Werf, 2008; Thoenissen, Zilles, & Toni, 2002; Wise, Boussaoud, Johnson, & Caminiti, 1997). Specifically, some areas of the intraparietal sulcus (IPS) appear to be of importance for making the visual information available for motor planning, while other IPS areas appear to be more involved in visual processing and attention control (Andersen & Buneo, 2002). To identify the role of these different areas in the process of visuo-motor integration, it is particularly promising to determine their functional specialisation in relation to their functional connectivity with other visual and motor areas.

One approach to determine whether an area is functionally specialised in processing of visual input, of visuo-motor integration and motor planning, or of motor execution, is the assessment of the lateralisation of brain activations. Information processing in both the visual system and the motor system typically follows characteristic patterns of lateralisation. In the motor system, the lateralisation refers to the effector representation. Activity in the motor cortex is associated with contralateral effector movement while activity in the cerebellum is associated with ipsilateral effector movement (Kolb & Wishaw, 1996). In the visual system, the lateralisation refers to the stimulus representation. Visually driven areas respond to stimuli presented in the contralateral visual hemifield. In numerous mapping studies in humans this representation principle was demonstrated for visual areas of the occipital cortex

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(DeYoe et al., 1996; Engel, Glover, & Wandell, 1997; Sereno et al., 1995; Tootell, Dale, Sereno, & Malach, 1996; Wandell, Dumoulin, & Brewer, 2007) and has recently been extended to the IPS. The IPS can be subdivided into multiple distinct visual hemifield representations, in particular, IPS0, IPS1, IPS2, IPS3, IPS4 (Hagler, Riecke, & Sereno, 2007; Hoffmann, Stadler, Kanowski, & Speck, 2009; Levy, Schluppeck, Heeger, & Glimcher, 2007; Merriam, Genovese, & Colby, 2003; Orban et al., 2006; Schluppeck, Glimcher, & Heeger, 2005; Sereno, Pitzalis, & Martinez, 2001; Silver, Ress, & Heeger, 2005; Swisher, Halko, Merabet, McMains, & Somers, 2007), and very recently IPS5 and SPL1 (Konen & Kastner, 2008a). Moreover, recent evidence suggests that some of its subregions are governed by lateralisation patterns that are typical for both the visual and the motor system (Beurze, de Lange, Toni, & Medendorp, 2007; Medendorp, Goltz, Crawford, & Vilis, 2005; Medendorp, Goltz, Vilis, & Crawford, 2003). These findings prompt the question, to which extent human IPS areas contribute to visual processing or to motor planning and how these areas are integrated in the respective cortical network comprising occipito-parietal and precentral cortices.

The aim of the present study was to detail the network involved in visuo-motor integration with a particular focus on the IPS. A combined approach was applied determining the stimulus and motor response related cortical activity on the one hand, and the functional connectivity patterns of IPS subregions on the other. For this purpose, we devised a paradigm that does not require highly experienced observers and therefore opens the possibility to assess the impact of visual pathway abnormalities on higher tier lateralisation properties in future patient studies.

2. Methods

2.1. Subjects

Fourteen subjects [mean age 33, range 24–44 years; six females, all right-handed (Oldfield, 1971)] with normal vision (visual acuity ≥1.0), or with refractive correction if necessary, gave their written informed consent to participate in the study. The procedures followed the tenets of the declaration of Helsinki (World Medical Association, 2000), and the protocol was approved by the Ethics Committee of the University of Magdeburg, Germany.

2.2. Paradigm and stimuli

The paradigm (see Fig. 1) was a delayed motor response task to a visual stimulus during fixation of a mark (a red cross on a grey disc, 0.6° diameter) centred on a black background. The subjects viewed the stimulus monocularly with the left eye, while the right eye was covered with an eye patch. Monocular stimulation was chosen to achieve a higher degree of comparability for future patient studies with the applied paradigm, as these typically require monocular stimulation. A jittered event-related design was used to allow for the separate assessment of cortical responses during visual stimulation and during button presses (indicated by the preceding visual stimulus) for four conditions: (1) visual stimulation in the left hemifield and button press with the left thumb; (2) vice versa; (3) visual stimulation in the left hemifield and button press with the right thumb; (4) vice versa. These four conditions were presented in a pseudo-randomised order to avoid systematic sequential effects and to permit the separation of their BOLD responses in the applied jittered event-related fMRI design (see below).

One stimulus trial comprised two phases: (A) a visual stimulation phase and (B) a button-press phase. (A) Visual stimulation phase: a stationary, coloured (blue or red) square target ($0.5^\circ \times 0.5^\circ$) embedded in an array ($6.5^\circ \times 6.5^\circ$; centred at 5.5° left or right of fixation) of 30 randomly repositioned (refresh rate: 12 Hz) grey square distractors ($0.5^\circ \times 0.5^\circ$), appeared for 250 ms at a pseudo-random position in the left or right visual hemifield. The rationale behind this visual stimulus was the following: a salient visual stimulus was chosen to reliably activate the visual cortex, even for short presentation durations, which prevent the subject from saccading at the stimulus. This stimulus allows for the assessment of the lateralisation pattern in the visually driven cortex. To engage an even more extensive visual processing network the subjects had to solve a target detection and localisation task within this stimulus. This task had to be demanding to some degree, but simple enough so that it would not to require highly experienced observers and could also be solved with impaired visual function, specifically, reduced visual acuity, in future patient studies. Furthermore, the target should code a specific action to be carried out with a specific effector. To achieve this, the subjects had to discriminate between target positions above or below the horizontal meridian, in order to learn which button-press action to perform (above the horizontal meridian for the upper button, below for the lower button), and to detect the colour of the target, in order to learn which effector (blue for left thumb and red for right thumb) to use for the button press. (B) Button-press phase: the colour of the fixation mark changes from grey to green for an epoch of 2 s prompting the subject to press the button corresponding to the colour and location of the target presented in the preceding visual stimulation phase. The response pad (fORP-Fiber Optic Response Pad, Current Design Inc., PA, USA) was invisible to the subjects. The task was simple enough to result in hit-rates around 95% in all four conditions with no significant differences between them (two-way ANOVA for repeated measures). Trials with incorrect responses were factored out in the fMRI data analysis.

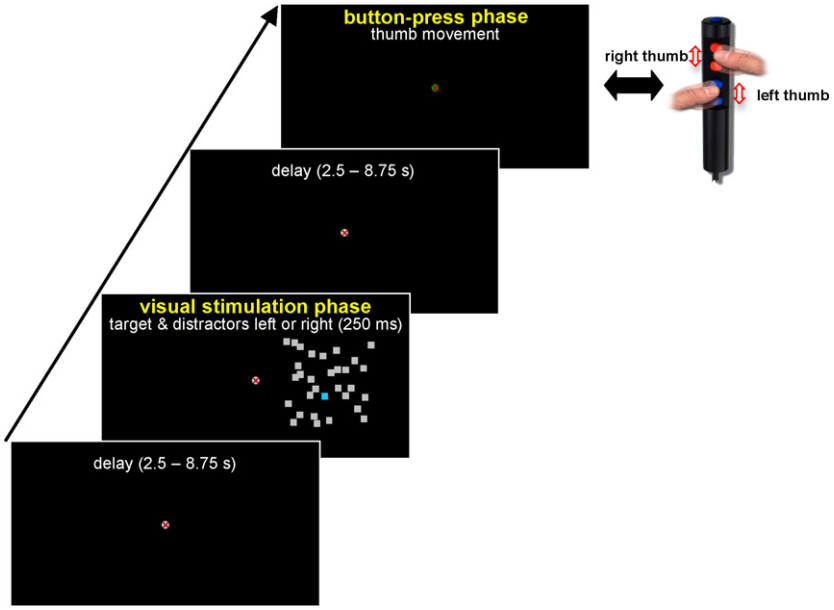

Fig. 1. Schematic of the visuo-motor event-related paradigm. Visual stimulation phase: during monocular fixation (OS) a coloured target (red or blue) embedded in an array of 30 blinking grey distractors appeared for 250 ms in either the right or left hemifield. Button-press phase: after a delay of 2.5–8.75 s the subjects were prompted by the colour change of the fixation dot to green to press a button on a keypad invisible to the subject. The correct response depended on the target presented in the preceding visual stimulation phase: for red and blue targets right or left thumb responses, respectively; for targets above and below the horizontal meridian, the upper or lower button. One trial is followed by another pair of visual stimulation and button-press phase in this circular design. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

In order to separate the fMRI signals in the visual stimulation phase from those in the button-press phase by applying the general linear model described below (Section 2.4), both phases were temporally jittered against each other with an inter-stimulus interval (ISI) ranging from 2.5 s to 8.75 s, in steps of 1.25 s with a mean ISI of 4.7 s. Using steps of 1.25 s allows for sampling of the hemodynamic function at TR/2 (TR = 2.5). Previous studies demonstrated that such a jitter allows for the reliable reconstruction and separation of the different event-related BOLD responses (Dale, 1999; Hinrichs, Scholz, Tempelmann, Woldorff, Dale & Heinze, 2000; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000).

The trials were presented in eight runs; each run took 5 min and consisted of 32 trials. Consequently, in each run 32 visual (of the visual stimulation phase) and 32 motor (of the button-press phase) responses were collected. The stimuli were presented at a frame rate of 60 Hz and back-projected at a viewing distance of 61 cm.

2.3. Functional magnetic resonance scanning

Functional images were acquired in a 3 T whole body MR scanner system (Siemens TRIO, Erlangen, Germany) equipped with a head volume coil. Axial T2* images were acquired parallel to the anterior- and posterior-commissure line using an echo planar imaging (EPI) mosaic sequence with 3.5 mm slice thickness (TR = 2.5 s; TE = 30 ms; 38 slices; 128 volumes; 64 × 64 acquisition matrix; FOV 224 mm).

2.4. Pre-processing and data analysis

SPM 5 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK) run with MatLab 7.3 (Mathworks, Natick, MA, USA) was used for the statistical analysis of the fMRI data. The data were statistically assessed as specified in Section 3 after pre-processing of the images (slice timing correction, realignment, normalization to a standard EPI-template, smoothing with a 7 mm full-width half-maximum Gaussian kernel). Statistical analysis was conducted in a two-stage mixed effects model. In the first (within-subject) stage, delta functions at stimulus onset for each event type (as specified in Section 2.2) were convolved with the canonical hemodynamic response function (HRF) provided by SPM5. The resulting time courses served as covariates for a general linear model (GLM). Additionally, the six rigid body parameters determined from realignment were included in the GLM as covariates of no interest, to reduce the confounding effects of head movements. Model estimation was performed using a standard least squares fit. In the second stage of the model, contrasts of parameter estimates of the comparisons of interest were submitted to second-level statistical analyses, treating individual subjects as random effects.

2.5. ROI analysis

For the quantitative assessment of the BOLD responses for the different conditions we specified regions of interest (ROIs) as detailed in Table 1 and determined the respective response magnitude as the percentage signal change (peak-BOLD response as determined from the beta-weights specified in the GLM; the maximum height of the reconstructed event was divided by the ROI's mean signal which served as baseline) for each subject using the MarsBaR ROI analysis toolbox (MARSeille Boîte À Région d'Intérêt-Devel; http://marsbar.sourceforge.net). The MNI coordinates of the ROI centres of the occipital and motor areas were determined as the locations of the local maxima of the activations within probability maps of the respective areas as specified with the WFU pick-atlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) or for area MT and the IPS areas, nearest to the coordinates reported in the studies by Dumoulin et al. (2000) and Swisher et al. (2007), respectively. In the IPS four local maxima were evident and ROIs of 5 mm radius were determined. These activations relate to the coordinates of the previously identified areas in the IPS (Wandell et al., 2007) determined by Swisher et al. (2007) as follows (similar coordinates were reported in other retinotopic mapping studies, e.g., Hagler et al., 2007; Konen & Kastner, 2008a; Levy et al., 2007; Silver et al., 2005): IPS terminal (IPSt) appeared to correspond to IPS0 [mean distance to the IPS0-centre coordinates $\pm 26 \pm 6/-79 \pm 6/31 \pm 7$: 7 mm, which is close to the S.D. of the IPS0 coordinates; the distance of IPSt to IPS1 is greater: 14 mm], IPS posterior (IPSp) to IPS1 [mean distance to the IPS1-centre coordinates $\pm 21 \pm 5/-68 \pm 7/52 \pm 8$: 5 mm, which is within the S.D. of the IPS1 coordinates], IPS median (IPSm) to IPS2 [mean distance to the IPS2-centre coordinates $\pm 21 \pm 5/-68 \pm 7/52 \pm 8$: 5 mm, which is within the S.D. of the IPS2 coordinates], and IPS anterior (IPSa) to IPS3/4 [mean distance to the IPS3- and IPS4-centre coordinates $\pm 25 \pm 7/-61 \pm 7/55 \pm 6$ and $\pm 26 \pm 6/-57 \pm 9/54 \pm 7$: 6 mm and 6 mm, which is within the S.D. of both the IPS3 and the IPS4 coordinates; consequently, it cannot be distinguished which of these two areas might be dominating the responses in this ROI]. The proximity of the MNI coordinates reported in the present investigation and in previous mapping studies suggests an equivalence of the respective IPS areas. It should be noted, however, that the IPS areas are ideally defined on the basis of the topographical organisation of their retinotopic maps and that, in particular in the anterior IPS, their location varies between subjects. Such effects of inter-individual variability are compensated for by the comparatively high number of subjects in the present study ($n = 14$) and in the reference study by Swisher et al. ($n = 20$). Still the equivalence of the retinotopically defined IPS areas with the activation maxima we observed is suggestive, but not definitive. To account for this, we adhered to an anatomical nomenclature, distinguishing between terminal, posterior, median, and anterior IPS, i.e., IPSt, IPSp, IPSm, and IPSa. The use of this nomenclature ($IPS_{t,p,m,a}$ vs. $IPS_{0,1,2,3}$) is not intended as an introduction of a novel naming scheme, but is intended to indicate that in the present study the visual areas are defined on an anatomical as opposed to a functional/topographical basis.

For the visual stimulation and the button-press phases, respectively, the percentage of the signal change within the respective ROIs was determined separately in each of the 14 subjects for the four conditions of the paradigm. The mean signal change across subjects (peak of the estimated BOLD responses, averaged across the entire ROIs) ±S.E.M. is depicted in the respective figures. Three-way ANOVAs for repeated measures (SuperANOVA 1.11, Abacus Concepts Inc., CA, USA) with the factors visual hemifield (right and left), hemisphere (ipsilateral and contralateral to the visual stimulus), and response hand (ipsilateral and contralateral to the visual stimulus) were conducted for the ROIs detailed in Table 1. In this analysis two interactions were of particular interest, namely that of visual hemifield × hemisphere and that of response thumb × hemisphere. The first interaction revealed, whether the response in ROI depended on the lateralisation of the visual stimulus, the second, whether it depended on the lateralisation of the effector.

Table 1
MNI coordinates of the regions of interest (ROIs).

Brain region	Right hemisphere			Left hemisphere			ROI radius (mm)
	x	*y*	*z*	*x*	*y*	*z*	
V1	10	−88	−2	−10	−90	2	10
MT	46	−74	8	−44	−74	0	10
IPSt	32	−76	32	−28	−74	26	5
IPSp	30	−70	40	−18	−66	42	5
IPSm	20	−68	56	−20	−72	56	5
IPSa	26	−60	51	−22	−60	48	5
PMa	28	−6	54	−34	−6	54	5
PMp	32	−14	62	−30	−14	62	5
SMA	5	−8	52	−5	−14	56	5
M1	38	−24	58	−34	−25	57	5

V1 = primary visual cortex; MT = middle temporal cortex; IPSt/p/m/a = intraparietal sulcus terminal/posterior/median/anterior; PMa/p = premotor area anterior/posterior; SMA = supplementary motor area; M1 = primary motor cortex.

2.6. Functional connectivity analysis

In order to assess whether two ROIs are functionally connected (Menon & Levitin, 2005; Schott et al., 2007), we took two approaches. Firstly, we extracted the adjusted time series for specific ROIs (IPSt, IPSp, IPSm, and IPSa, as specified in Table 1) of each hemisphere for each subject and for each of the eight runs. In a separate first-level GLM analysis for each subject, these time series were used as regressors in the design-matrix together with the six rigid body parameters determined from realignment as covariates of no interest, to reduce the confounding effects of head movements. Contrasts for bilateral functional ROI connectivity were determined in each subject. Subsequently, second-level group statistics were computed from the results of the first-level analysis, and the responses that were significantly linked to the time series of the ROIs were determined with separate one-sample *t*-tests for each of the three ROIs. Clusters of significant voxels were thresholded at a level of $p \leq 0.001$, corrected for false-detection-rate (FDR; see Fig. 5).

Secondly, in addition to the time series extracted for the IPS-ROIs, the time series were extracted for the ROIs V1, MT, PMa, PMp, and SMA. To test whether the correlations of the time series of these ROIs with IPSa differed from those with IPSt, Pearson's correlations were computed, the obtained correlation coefficients submitted to Fisher's *z*-transformation for correlation coefficients, and statistically compared with paired *t*-tests, corrected for multiple testing [serial Bonferroni correction (Holm, 1979)]. In Section 3 (Fig. 6), the functional connectivities for the ROIs of the same hemisphere are reported. Similar patterns of correlation measures were obtained for the ROIs on opposite hemispheres, but as expected, with generally smaller correlation coefficients (not shown in Fig. 6).

3. Results

An overview over the cortical responses during the visual stimulation phase as assessed with voxel-wise *t*-test group statistics is given in Fig. 2A. For both right and left hemifield stimulation, great expanses of bilateral occipito-parietal cortex were responsive (Fig. 2A, top). The comparison of left vs. right hemifield stimulation and vice versa revealed that a considerable proportion of these occipito-parietal responses was dominant on the hemisphere contralateral to the visual stimulus (Fig. 2A, bottom). In Fig. 2B the

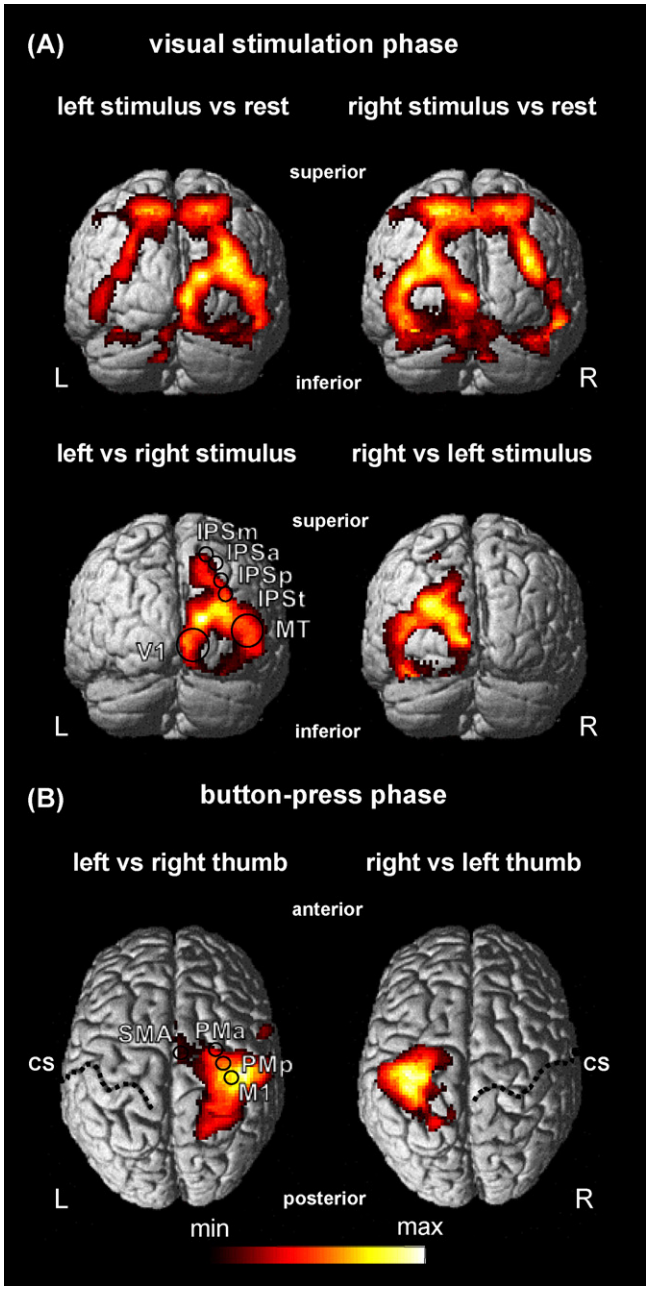

Fig. 2. Group statistic ($n = 14$) of the cortical responses for the visual stimulation phase (A) and the button-press phase (B). (A) Responses during the visual stimulation phase in a posterior view [responses were grouped according to the stimulated hemifield (left or right), regardless of the effector to be used in the on-coming button-press phase; range of scale bar: min t-value = 0; max t-value = 16]: the contrasts for stimulation in the left or right hemifield vs. rest reveal bilateral activations. The contrasts for stimulation in the left vs. stimulation in the right hemifield and vice versa reveal the dominance of activations in the hemisphere contralateral to the stimulated hemifield. It should be noted that, although IPSa and IPSm appear swapped in this posterior view, IPSm and IPSa do in fact progress from posterior to anterior, as is evident from Table 1. (B) Responses during the button-press phase in a superior view [responses were grouped according to the effector used (left or right), regardless of the hemifield that was stimulated during the visual stimulation phase; range of scale bar: min t-value = 0; max t-value = 23 and t-value = 10 for left vs. right and right vs. left thumb, respectively]: the contrasts for left vs. right thumb and vice versa reveal cortical activations contralateral to the effector. Additionally, in (A) and (B) the ROI localisations are indicated for the right hemisphere. L = left hemisphere, R = right hemisphere, CS = central sulcus; all data are thresholded at $p \leq 0.001$, uncorrected; cluster size $\geq$50 voxels.

voxel-wise group statistics of the cortical responses during the button-press phase are depicted. The comparison of left vs. right thumb button presses revealed responses from a cortical network including premotor and motor areas predominantly contralateral to the effector. In agreement with previous fMRI studies of motor function (Rotte, Kanowski, & Heinze, 2002), cerebellar responses were primarily lateralised to the hemisphere ipsilateral to the effector (not shown).

In order to quantify the response lateralisations during the visual stimulation and button-press phases, the percentage of the BOLD signal change was extracted for a set of ROIs of the occipito-parietal cortex (V1, MT, IPSt, IPSp, IPSm, and IPSa) and of the motor cortex (PMa, PMp, SMA, and M1) as detailed in Table 1. The dependence of the responses on the lateralisation of the visual stimulus and the effector is depicted in Figs. 3 and 4. For these depictions, responses from both hemispheres were averaged for each subject such as to obtain the response magnitudes ipsilateral and contralateral to the stimulus and to the effector, respectively. Subsequently these responses were averaged across subjects. The statistical significance of the dependence of the responses on stimulus and effector lateralisation was assessed from the interaction of stimulated visual hemifield and hemisphere and from the interaction of used thumb and hemisphere, respectively (three-way ANOVA for repeated measures).

For the visual stimulation phase, strong responses were obtained for V1, MT, IPSt, IPSp, IPSm, IPSa, PMa, and PMp, with the strongest responses evident for IPSm. The responses were significantly greater contralateral than ipsilateral to the stimulated visual hemifield in V1, MT, IPSt, IPSp, IPSm, IPSa, and PMa (for V1, MT, IPSt, IPSa $p \leq 0.0001$, for IPSp, IPSm $p \leq 0.0002$; see Fig. 3A), while the stimulus lateralisation did not affect the responses in PMp, SMA, and M1. Remarkably, the responses in some ROIs depended on the lateralisation of the effector to be used in the upcoming button-press phase as indicated by the visual stimulus. The responses were significantly greater contralateral than ipsilateral to the effector in IPSa, M1, PMa, PMp, and SMA (for IPSa $p \leq 0.0014$; for M1 $p \leq 0.0008$; for PMa $p \leq 0.0057$; for PMp $p \leq 0.0001$; for SMA $p \leq 0.0002$; see Fig. 3B). In contrast, the effector lateralisation did not affect the responses in V1, MT, IPSt, IPSp, and IPSm. Consequently, of the analysed ROIs, only the response lateralisations of IPSa and PMa depended on both the stimulus and the effector lateralisation.

For the button-press phase, the strongest responses were observed in PMp, SMA, and M1. Only minor responses were obtained for V1, MT, IPSt and IPSp. fMRI responses during the button-press phase did not depend on the stimulus lateralisation during the preceding visual stimulation phase, with the exception of V1 and MT, where responses to stimulation in the ipsilateral hemifield exceeded those to stimulation in the contralateral hemifield ($p \leq 0.0001$ and $p \leq 0.0011$, respectively; Fig. 4A). This result was confirmed by additional ROI analyses in BA17, BA18, and BA19: all three ROIs showed a lateralisation contralateral to the visual hemifield during the visual stimulation phase (BA17, BA18, and BA19: $p \leq 0.0001$), and an inverse lateralisation pattern during the button-press phase (BA17 and BA18: $p \leq 0.0001$; BA19: $p \leq 0.0017$). Remarkably, this paradoxical lateralisation pattern is absent in the IPS regions, which are particularly strongly driven during the visual stimulation phase. It is therefore unlikely, as already expected from the use of the jittered event-related fMRI design specified in Section 2, that the activity pattern observed in V1 and MT during the button-press phase is a direct consequence of the preceding visual stimulation. Instead, we suggest that this paradoxical lateralisation might result from a rebound effect in the button-press phase after suppression of ipsilateral cortical activity induced by the visual stimulation phase (Shmuel, Augath, Oeltermann, & Logothetis, 2006; Smith, Williams, & Singh, 2004). As expected, responses for but-

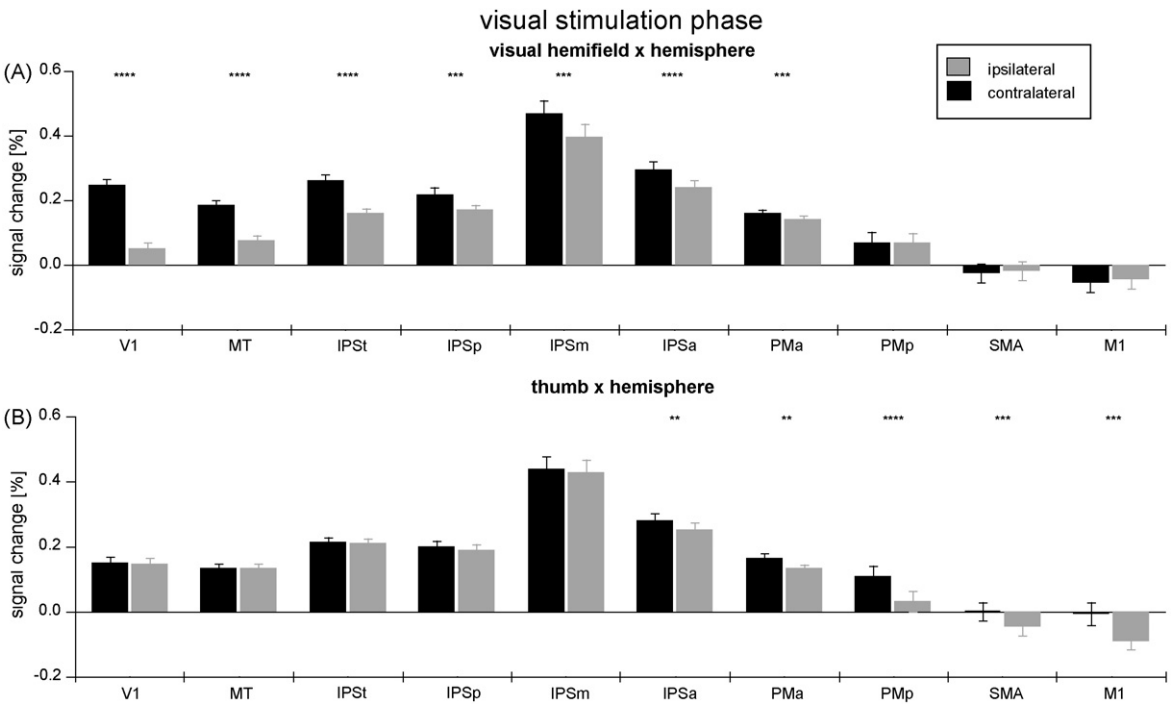

Fig. 3. Percentage peak-BOLD signal change of cortical responses during visual stimulation phase for the ROIs specified in Table 1 (means ± S.E.M. across 14 subjects): (A) Mean signal changes across the conditions with either contralateral (black) or ipsilateral (grey) visual stimulation. (B) Mean signal changes across the conditions with either contra- (black) or ipsilateral (grey) effector to be used in the upcoming button-press phase. The significance levels are indicated as determined with a three-way ANOVA for repeated measures of the interactions *visual hemifield* × *hemisphere* (A) and *thumb* × *hemisphere* (B): $^{****}p \leq 0.0001$, $^{***}p \leq 0.001$, $^{**}p \leq 0.01$.

ton presses with the contralateral thumb were significantly greater than those with the ipsilateral thumb in PMa, PMp, M1 ($p \leq 0.0001$), and SMA ($p \leq 0.0004$; see Fig. 4B), while the effector lateralisation did not affect the responses in V1, MT, IPSt, IPSp, IPSm, and IPSa.

Taken together, a dependence on both stimulus and effector lateralisation during the visual stimulation phase was evident only for IPSa and PMa. Additionally, in PMa a dependence on the effector lateralisation was also observed during the button-press phase. This suggests that IPSa is of particular importance for visuo-motor integration, while PMa is relevant for both visuo-motor integration and motor execution. As a consequence of this relation to motor output, we hypothesised that IPSa might be more strongly con-

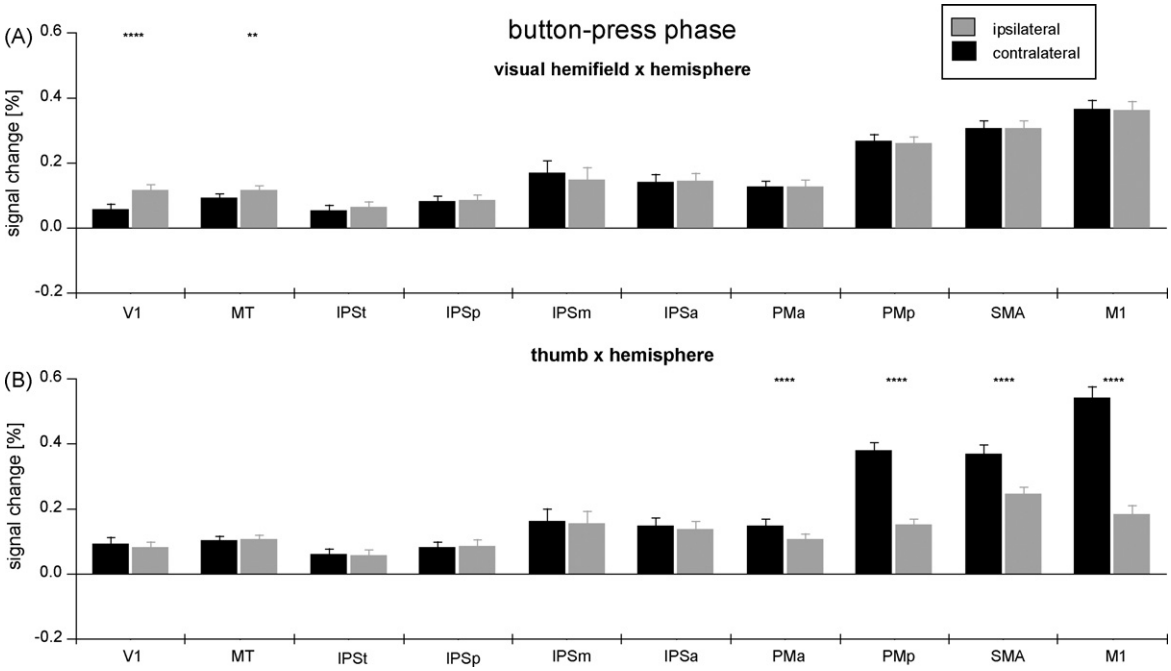

Fig. 4. Percentage peak-BOLD signal change of cortical responses during button-press phase for the ROIs specified in Table 1 (means ± S.E.M. across 14 subjects): (A) Mean signal changes across the conditions with either contralateral (black) or ipsilateral (grey) stimulation in the preceding visual stimulation phase. (B) Mean signal changes across the conditions with either contralateral (black) or ipsilateral (grey) effector used. The significance levels are indicated as determined with a three-way ANOVA for repeated measures of the interactions *visual hemifield* × *hemisphere* (A) and *thumb* × *hemisphere* (B): $^{****}p \leq 0.0001$, $^{**}p \leq 0.01$.

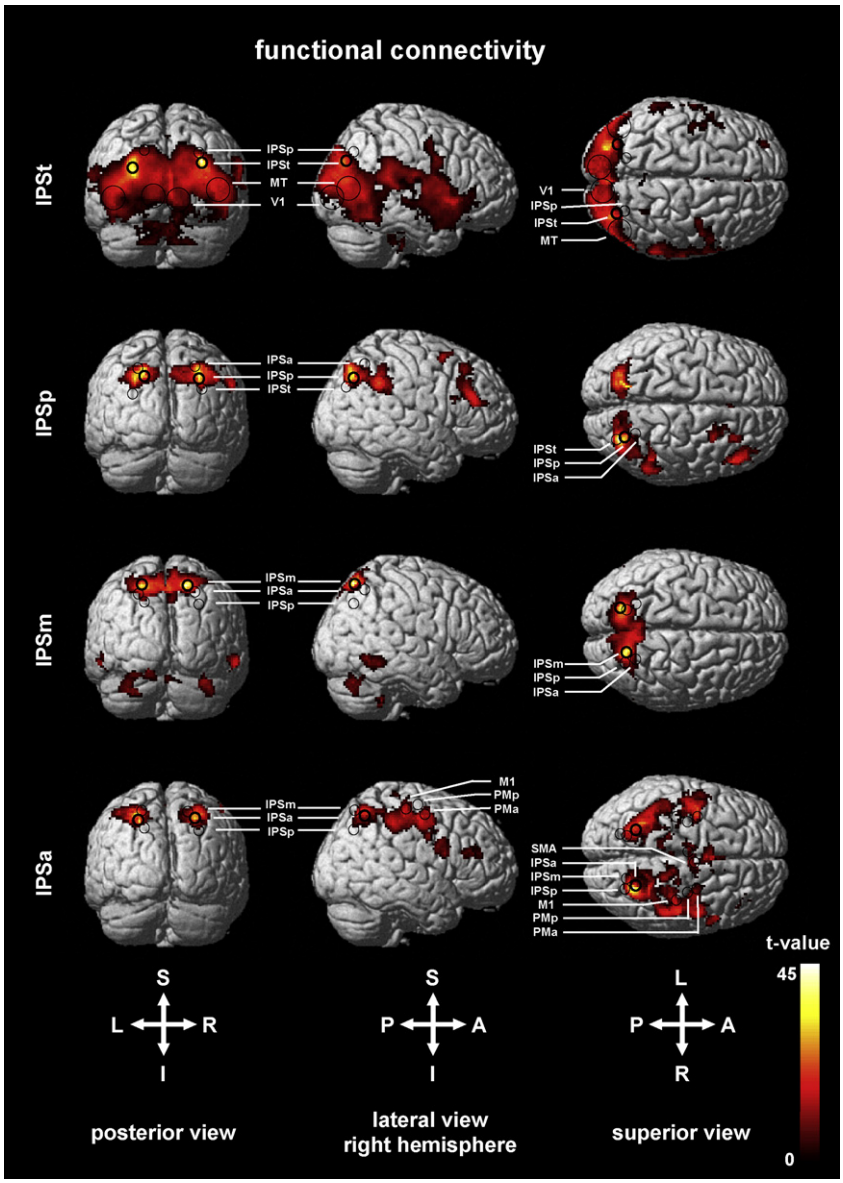

Fig. 5. Group statistic ($n = 14$) for the functional connectivity analysis of IPSt, IPSp, IPSm, and IPSa. Relevant ROIs are indicated by circles, the seeds are highlighted as bold circles. All data are thresholded at $p \leq 0.001$, corrected for FDR; cluster size ≥ 30 voxels. L = left hemisphere, R = right hemisphere, A = anterior, P = posterior, S = superior, I = inferior.

nected to premotor and supplementary motor cortices than more posterior IPS regions. This question was addressed by conducting a functional connectivity analysis. Specifically, we investigated whether the functional connectivity of IPSa to anterior areas might be stronger than that of the other examined parietal ROIs, namely IPSt, IPSp and IPSm. As depicted in Fig. 5, structures of the visual system were functionally connected with IPSt, while premotor and supplementary motor cortices primarily showed a functional connectivity with IPSa.

This result was confirmed and detailed by a quantitative comparison of the functional connectivity of IPSt and IPSa with the areas V1, MT, PMa, PMp, and SMA, using the ROIs specified in Table 1. As depicted in Fig. 6 the correlation with the MT time series was greater for IPSt than for IPSa (IPSt-MT vs. IPSa-MT: 0.70 vs. 0.60; $p < 0.05$), while the correlation with PMa and PMp was greater for IPSa than for IPSt (IPSt-PMa vs. IPSa-PMa: 0.61 vs. 0.67; $p \leq 0.05$, and IPSt-PMp vs. IPSa-PMp: 0.49 vs. 0.57; $p \leq 0.05$). These results indicate a sizable functional interaction of the activations in IPSa with those in the areas related to motor execution, a finding that highlights IPSa as a mediator during visually induced motor execution.

4. Discussion

In order to detail the network involved in visuo-motor integration, a combined approach was used to assess the stimulus and the motor response related activity on the one hand and the underlying functional connectivity on the other. Two regions were identified, namely IPSa and PMa, that incorporated functional response properties typical for both visual processing and motor execution and are therefore presumed to be specialised for visuo-motor integration and motor planning.

4.1. IPS network

In the present study, an extensive cortical network was activated during the visual stimulation phase. Remarkably, not the occipital regions showed the greatest response, but the examined intraparietal subregions IPSt, IPSp, IPSm, and IPSa. The strongest response was found in IPSm, the presumptive equivalent to area IPS2. This underlines that during the visual stimulation phase not only basic sensory processing was triggered, but also mechanisms

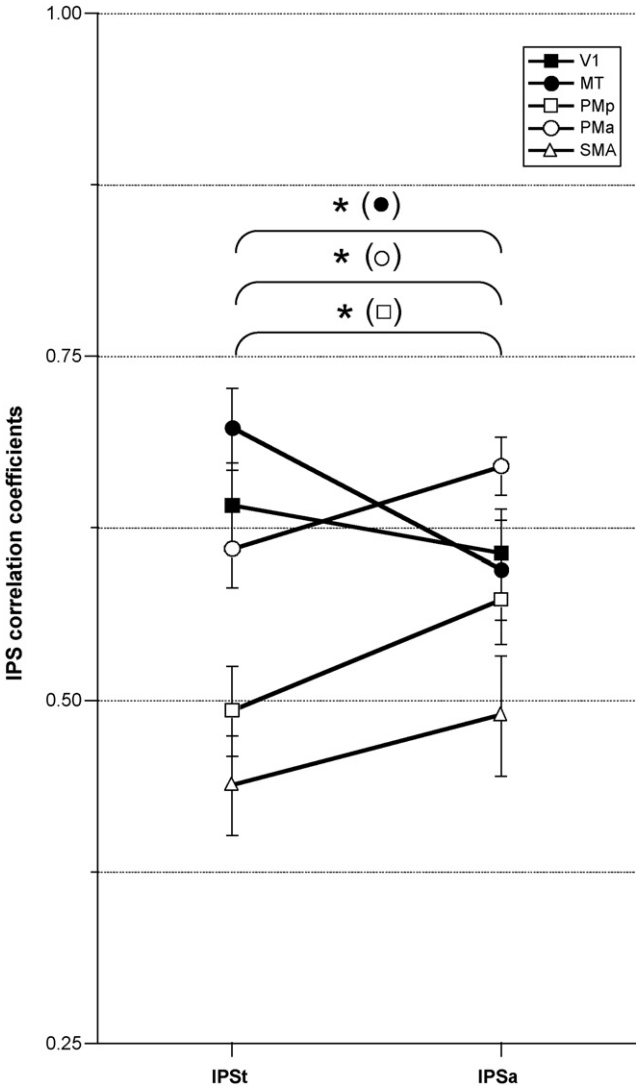

Fig. 6. Correlation of the time series of IPSt and IPSa, with those of V1, MT, PMa, PMp, and SMA (mean ± S.E.M. across 14 subjects; for details see Section 2). The significance levels are indicated as determined with paired *t*-tests, corrected for multiple testing [serial Bonferroni correction (Holm, 1979)]. Significant differences ($^*p \leq 0.05$) are indicated next to the respective symbol in brackets for the specific comparison.

known to engage parts of the intraparietal sulcus, such as attention, short term memory, feature extraction and visuo-motor integration (Claeys, Lindsey, De Schutter, & Orban, 2003; Corbetta, Kincade, & Shulman, 2002; Konen & Kastner, 2008b; Levy et al., 2007; Saygin & Sereno, 2008; Schluppeck et al., 2005; Sereno et al., 2001; Silver et al., 2005). In this context, it should be noted that, in the applied paradigm, the presentation of the task relevant stimulus will induce spatial attention shifts (Smith, Singh, & Greenlee, 2000), which are known to be closely associated with fronto-parietal network-activity (Kastner & Ungerleider, 2000; Saygin & Sereno, 2008) and thus likely to engage the IPS subregions. Clearly, the fact that the IPS subregions were most strongly driven during the visual stimulation phase indicates their central position in the networks for task relevant sensory processing of the visual stimulus, for shifting of attention, and for visuo-motor integration. Our connectivity analysis underlined this aspect: the functional connectivity between IPSa and MT fell short of that of IPSt and MT, indicating that IPSt is more involved in the network for sensory processing. In contrast, the functional connectivity of IPSt and PMa or PMp fell short of that of IPSa and PMa or PMp, indicating that IPSa contributed to the network of visuo-motor integration.

4.2. Functional specialisation of IPSa

In the IPS four subregions were examined, IPSt, IPSp, IPSm, and IPSa. Only IPSa depended in its response to visual stimulation on the lateralisation of both the visual stimulus presented and the effector to be used in the upcoming motor response, with maximal responses in the respective contralateral hemisphere. This lateralisation pattern applied only to the visual stimulation phase. During the button-press phase, responses in IPSa were smaller and independent of the lateralisation of effector and stimulus. Our findings thus demonstrate that IPSa is a visually driven subregion that is involved in visuo-motor integration, specifically for delayed motor responses to visual stimuli. The MNI coordinates of IPSa suggest an equivalence to the areas IPS3/4 described in previous retinotopic mapping studies as the location of its centre is within the S.D. of the locations of IPS3/4 as reported by Swisher et al. (2007). Furthermore, an IPS region with similar coordinates, i.e., its centre located within a distance of less than 10 mm from the IPSa centre, was previously attributed a role for reach planning (Beurze et al., 2007). For the responses of this region a lateralisation pattern similar to that of the IPSa responses was reported. Specifically, Beurze et al. demonstrated enhanced responses in this IPS region for both contralateral visual targets and contralateral effectors for reach planning. While their findings underline that this region is of relevance for visuo-motor integration during the planning phase of a reach towards remembered visual targets, our results indicate that this region is even of more general relevance: IPSa is involved in visuo-motor integration in absence of a target directed reaching movement, namely for simple visually induced button-press responses on a keypad that is located outside the visual field. While this is of basic interest for understanding the network underlying visuo-motor integration, it also has practical implications. In fMRI experiments with visual stimulation which require the subject to give motor feedback, the responses to the visual stimulus tend to be enhanced on the hemisphere contralateral to the effector used. As a matter of course, this does not only apply to IPSa, but also to more anterior regions concerned with motor responses, i.e., M1, PMa, PMp, SMA. Consequently, the bias of responses induced by the lateralisation of the effector must be taken into consideration, when the lateralisation of fMRI responses in paradigms with motor feedback is interpreted.

4.3. Functional specialisation of PMa

Not only the responses of IPSa to visual stimulation depended on the lateralisation of both the visual stimulus and the effector to be used in the upcoming motor response. The same lateralisation properties also applied to the responses of PMa, with the respective contralateral responses being maximal. This region, in terms of its coordinates, is likely to be an equivalent to the frontal eye fields [FEF; distance of PMa centre to FEF centre as determined by Kastner et al. (2007) is less than 10 mm], known to be activated by paradigms involving stimulation in the contralateral visual hemifield. FEF is not only involved in the planning and execution of memory guided saccades, but also in working memory tasks that do not require eye movements (Hagler & Sereno, 2006; Kastner et al., 2007). Further, like the subregions of the IPS, it is involved in the control of spatial attention (Kastner & Ungerleider, 2000; Saygin & Sereno, 2008). Remarkably, in addition to the lateralisation properties during the visual stimulation phase, PMa also exhibited lateralised responses during the button-press phase, with maximal responses contralateral to the effector used, a feature that is characteristic of cortical areas involved in motor execution. This indicates that in the processing chain from visual input to motor execution PMa is more involved in motor execution than IPSa.

4.4. Effector lateralisation and functional specialisation of motor areas

The button presses activated components of the motor system including the primary motor area, the dorsal premotor areas and the supplementary motor area. All of these areas were characterised by a strong response lateralisation contralateral to the effector in accordance with previous studies in humans (Alkadhi et al., 2002; Beurze et al., 2007; Colebatch, Deiber, Passingham, Friston, & Frackowiak, 1991; Hanakawa, Honda, Zito, Dimyan, & Hallett, 2006; Kuhtz-Buschbeck et al., 2003; Maccotta, Zacks, & Buckner, 2001; Michelon, Vettel, & Zacks, 2006) and non-human primates (Cisek, Crammond, & Kalaska, 2003; Hoshi & Tanji, 2006; Kazennikov et al., 1999; Kermadi, Liu, Tempini, Calciati, & Rouiller, 1998). Although there is a dominance of responses contralateral to the effector, we also observed BOLD responses ipsilateral to the effector. This has also been reported in previous studies on human and non-human primates, which demonstrated that the motor areas comprise both contralateral and bilateral neurons, with the strongest lateralisation in the primary motor area (Hoshi & Tanji, 2002; Kermadi et al., 1998; Kim et al., 1993).

All four motor areas show an effector specificity, but their response patterns indicate differences in their functional specialisations. While the primary and the supplementary motor areas responded only during motor execution, i.e., the button-press phase, the premotor areas also responded during motor planning, i.e., the visual stimulation phase. This result confirms previous reports in human and non-human primates that the dorsal premotor areas are involved in the sensory guidance of movements (Beurze et al., 2007; Donoghue & Sanes, 1994; Hoshi & Tanji, 2006; Hoshi & Tanji, 2007; Kalaska et al., 1997; Schubotz & von Cramon, 2001; Toni et al., 2002; Wise, di Pellegrino, & Boussaoud, 1996). Furthermore, the fact that the response lateralisation of PMa is both effector- and stimulus-dependent while that of PMp is only effector-dependent supports the view that the premotor cortex comprises an anterior part which is visually driven and a posterior part with motor preference (Matsumoto et al., 2003).

4.5. From sensory processing to motor execution—evidence from response lateralisations

To evaluate the lateralisation patterns of IPSa and PMa in the context of the activated network, the different regions investigated in the present study can be grouped according to their specific lateralisation patterns in the two phases, the visual stimulation phase and the button-press phase, as summarised in Table 2. Four lateralisation patterns are of particular interest, as they might reflect a processing chain from visual input, to visuo-motor integration, and finally to motor execution: (1) a group of regions with contralateral responses, exclusively to the visual stimulus during the visual stimulation phase, suggesting that they are visually driven: V1, MT, IPSt, IPSp, and IPSm. (2) IPSa, with contralateral responses, exclusively during the visual stimulation phase, to both the visual stimulus and the effector, suggesting that it is visually driven and involved in visuo-motor integration. (3) PMa, with contralateral responses during the visual stimulation phase to both the visual stimulus and the effector and during the button-press phase to the effector, suggesting that it is visually driven, and involved in both visuo-motor integration and motor execution. (4) A group of regions with weak responses during the visual stimulation phase and pronounced responses during the button-press phase, both lateralised exclusively contralateral to the effector, suggesting that these regions are involved in motor execution: PMp, SMA, and M1. Furthermore, it should be noted that the PMp responses during the visual stimulation phase clearly exceed those of SMA and M1. This indicates that PMp might also be involved in aspects of motor planning, as corroborated by previous investigations (Matsumoto et al., 2003).

Table 2
Contralateral response dominance during the visual stimulation and the button-press phase.

Brain region	Visual stimulation phase		Button-press phase
	Stimulus	Effector	Effector
V1	×		
MT	×		
IPSt	×		
IPSp	×		
IPSm	×		
IPSa	×	×	
PMa	×	×	×
PMp		×	×
SMA		×	×
M1		×	×

4.6. Applications of the presented paradigm in patient studies

We devised a paradigm, which allows for the separate assessment of the lateralisation of brain responses in a great expanse of cortex during visual stimulation and during the execution of motor actions. While it here served the identification of cortical regions that are involved in the process of visuo-motor integration in control subjects, it might also be of value for the investigation of lateralisation abnormalities. In particular, as the paradigm does not require highly experienced observers, it can also be applied to patient studies to evaluate the impact of pathophysiological processes and of plasticity on cortical lateralisation patterns. Potential applications might be the investigation of the consequences of visual field abnormalities or abnormally lateralised input to the primary visual cortex as typical for subjects with albinism (Hoffmann, Schmidtborn, & Morland, 2007a; Hoffmann, Seufert, & Schmidtborn, 2007b; Hoffmann, Tolhurst, Moore, & Morland, 2003) and achiasmia (Apkarian, Bour, Barth, Wenniger-Prick, & Verbeeten, 1995; Victor et al., 2000) on the lateralisation of both higher tier visual and motor areas. Respective studies are under way.

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