Hemispheric Asymmetries of Motor Versus Nonmotor Processes During (Visuo)Motor Control

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Abstract: Language and certain aspects of motor control are typically served by the left hemisphere, whereas visuospatial and attentional control are lateralized to the right. Here a (visuo)motor tracing task was used to identify hemispheric lateralization beyond the general, contralateral organization of the motor system. Functional magnetic resonance imaging (fMRI) was applied in 40 male right-handers (19–30 yrs) during line tracing with dominant and nondominant hand, with and without visual guidance. Results revealed a network of areas activating more in the right than left hemisphere, irrespective of the effector. Inferior portions of frontal gyrus and parietal lobe overlapped largely with a previously described ventral attention network responding to unexpected or behaviourally relevant stimuli. This demonstrates a hitherto unreported functionality of this circuit that also seems to activate when spatial information is continuously exploited to adapt motor behaviour. Second, activation of left dorsal premotor and postcentral regions during tracing with the nondominant left hand was more pronounced than that in their right hemisphere homologues during tracing with the dominant right hand. These activation asymmetries of motor areas ipsilateral to the moving hand could not be explained by asymmetries in skill performance, the degree of handedness, or interhemispheric interactions. The latter was measured by a double-pulse transcranial magnetic stimulation paradigm, whereby a conditioning stimulus was applied over one hemisphere and a test stimulus over the other. We propose that the left premotor areas contain action representations strongly related to movement implementation which are also accessed during movements performed with the left body side. *Hum Brain Mapp* 32:1311–1329, 2011. © 2010 Wiley-Liss, Inc.

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INTRODUCTION

Motor areas of the left hemisphere are strongly activated during movements performed with either the left or the right hand. This has been consistently reported by previous functional imaging (fMRI) [Cramer et al., 1999; Gut et al., 2007; Kim et al., 1993; Kobayashi et al., 2003; Li et al., 1996; Nirrkko et al., 2001; Singh et al., 1998; Solodkin et al., 2001; Van Impe et al., 2009; Verstynen et al., 2005] and other functional studies [Kawashima et al., 1993, 1998; Volkman et al., 1998]. Such left hemisphere involvement for movements with the right body side results from the contralateral organization of the motor system. However, its precise role in actions executed with the ipsilateral left body side remains unresolved. It has been shown that ipsilateral recruitment of the left hemisphere increases with movement complexity, particularly when complex sequencing or other finger coordination tasks are compared with simpler movements [Haaland, 2006; Haaland et al., 2004; Hesse et al., 2006; Hlustik et al., 2002; Kim et al., 1993; Singh et al., 1998; Verstynen et al., 2005]. Such studies frequently found increased left hemispheric activation within parieto-premotor circuits ipsilateral to the moving hand [Babiloni et al., 2003; Bohlhalter et al., 2009; Haaland et al., 2004; Hlustik et al., 2002; Johansen-Berg and Matthews, 2002; Kawashima et al., 1993, 1998; Nirrkko et al., 2001; Solodkin et al., 2001; Verstynen et al., 2005], most likely serving higher-order aspects of motor control such as planning of movement dynamics [Toni et al., 1999], response selection [Rushworth et al., 1997, 2001, 2003; Toni et al., 2001a] or representation of spatiotemporal movement formulae ["praxicons," Bohlhalter et al., 2009]. These findings concur with motor deficits observed in apraxic patients where left, but not right, parieto-premotor damage is prone to affect skilled movement production with either hand [Heilman et al., 1982, 2000; Kertesz and Hooper, 1982; Liepmann, 2001].

Some functional imaging studies have indicated that also the left (sensori)motor cortex ((S)M1) is more prominently activated by ipsilateral motor performance than the right SM1 [Babiloni et al., 2003; Cramer et al., 1999; Kawashima et al., 1993, 1998; Kim et al., 1993; Newton et al., 2005; Nirrkko et al., 2001; Verstynen et al., 2005]. These fMRI findings were further corroborated by transcranial magnetic stimulation (TMS) paradigms, indicating greater corticomotor excitability of the left than the right motor cortex during complex ipsilateral movements [Chen et al., 1997; Ghacibeh et al., 2007; Vines et al., 2008; Ziemann and Hallett, 2001].

Several mechanisms have been proposed as potential sources for this increased involvement of left motor areas.

According to the motor dominance theory, the left hemisphere is inherently more "motor capable" than the right such that left motor areas might support motor execution of both hands. An alternative yet partly complementary idea is that left hemisphere activation may reflect asymmetries in interhemispheric inhibition (IHI) [Duque et al., 2007]. In this view, motor cortices have similar capabilities for controlling the contralateral hand, but increased ipsilateral activation stems from asymmetric IHI whereby inhibition exerted from the dominant left hemisphere onto the nondominant right one is more powerful than vice versa [Ziemann and Hallett, 2001].

Only a few studies have directly compared ipsilateral brain activation as revealed by fMRI with IHI using a double-pulse TMS paradigm. With this TMS protocol, a test stimulus (TS) is applied over M1 of one hemisphere which is, in half of the trials, preceded by a conditioning stimulus over M1 of the other hemisphere. This protocol can be used to determine IHI from the left to the right hemisphere and vice versa. Kobayashi et al. [2003] applied fMRI during unilateral finger abduction/adduction movements and measured IHI at rest. They observed high ipsilateral activation in the left hemisphere during movements with the nondominant left hand specifically in those subjects that presented with increased IHI from the right to the left hemisphere. By contrast, Talelli et al. [2008] reported the opposite relationship in an elderly population: IHI from left to right M1 was reduced relative to young subjects when the right hand was isometrically contracted. Interestingly, this age-dependent relative IHI decrease was related to increased recruitment of ipsilateral primary and secondary motor cortices. Indirect evidence in agreement with this latter finding was provided by a fMRI study [Hayashi et al., 2008] investigating ipsilateral deactivations during unimanual finger tapping at progressively increasing movement frequencies. Left M1 became increasingly active (i.e. was disinhibited), when the ipsilateral hand tapped at higher frequencies, whereas right M1 became further deactivated. Thus, taken together, it remains inconclusive whether the differential modulation of the blood oxygen level-dependent (BOLD) signal in the left versus right ipsilateral hemisphere is substantially regulated by transcallosal mechanisms and more specifically by IHI.

Whereas since left-hemisphere motor dominance does not exclude the likelihood of right-hemisphere lateralization of attention system [Corbetta and Shulman, 2002; Culham et al., 2006; Marshall and Fink, 2003]. This notion originates from patient observations revealing right more than left hemisphere lesions to be associated with a prevalence of unilateral spatial neglect, which is characterized by deficits in attending or responding to stimuli in the contralesional

field [Corbetta et al., 2002b; Hillis et al., 2005; Karnath et al., 2004; Mesulam, 1999; Mort et al., 2003; Weintraub and Mesulam, 1987]. Previous fMRI research in healthy subjects has distinguished a dorsal (DAN) and a ventral attention network (VAN). DAN, with the intraparietal sulcus (IPS) and the frontal eye field (FEF) as core regions, has been proposed to exert top-down control of attention based on goals and advance knowledge [Corbetta and Shulman, 2002; Corbetta et al., 2008]. By contrast, VAN, which encompasses temporoparietal junction (TPJ) and ventral frontal cortex (VFC), has been described to operate in a bottom-up manner mediating stimulus-driven shifts in attention, by detecting behaviourally relevant, unpredictable events [Corbetta et al., 2008; Indovina and Macaluso, 2007]. In contrast to the largely bilateral spread of DAN, VAN lateralizes strongly to the right hemisphere. This raises the question whether goal-directed motor behaviour induces activation within the right hemisphere.

In the present study, we investigated hemispheric lateralization in the context of a continuous (visuo)motor task by applying fMRI in a large cohort of right-handed, young subjects ($n = 40$). The protocol required continuous tracing of a target pattern either with the preferred or non-preferred hand and alternating between presence and absence of online visual feedback. Two major questions were addressed.

First, despite a wide acceptance of right hemisphere dominance for the control of visuospatial attention, fMRI evidence for right-lateralized activity patterns in the context of ongoing motor control in space is limited. Thus, it was tested which areas would activate more prominently in one hemisphere than the other, regardless of whether the dominant or nondominant hand performed the task. This result pattern would indicate effector-independent, hemispheric specialization.

Second, we aimed at identifying the potential mechanisms underlying the relatively enhanced activity in the left compared with the right hemisphere when the ipsilateral hand performed the motor task. Specifically, it was investigated whether asymmetries of the BOLD response in ipsilateral motor areas reflect differential dexterity of the hands. Therefore, we correlated asymmetries in brain activation to asymmetries in motor performance when drawing with the left versus the right hand, as well as to the degree of handedness. Finally, we tested the hypothesis that functional asymmetries of the motor system relate to asymmetries in interhemispheric interactions as suggested by Ziemann and Hallett [2001]. To this end, asymmetries in BOLD response were correlated to those in IHI as measured by a double-pulse TMS protocol.

MATERIALS AND METHODS

Participant Characteristics

Forty healthy males participated in this study (mean age 22 yrs, SD 2.03, range 19–30). Subjects had no history of

neurological or psychiatric impairments nor visual deficits, and complied with the inclusion criteria for fMRI and TMS research. Degree of handedness was determined using the 10-item version of the Edinburgh handedness inventory [Oldfield, 1971]. All participants were strongly right-handed [Habib et al., 1995; LeMay, 1992] with a minimal score of 80% (mean 95%, SD 0.07). Applicants with intense past or present musical training were excluded. The experimental protocol was approved by the ethical commission (University Hospital Gasthuisberg, Leuven) in accordance with the Declaration of Helsinki and informed consent was obtained before participation.

Functional Imaging: Experimental Design and Procedure

Subjects were positioned supinely in the scanner with a bite-bar to constrain head movement while performing a drawing task that required tracing of a blocked line pattern. Tracing occurred on an MR-compatible touch-screen (Rotman Research Institute, Baycrest, Toronto, Fig. 1B) with a rubber-coated inkless pen wired to the device that was placed at the subject's hip level. The line pattern to be traced consisted of a composition of horizontal and vertical line segments (Fig. 1C; height: 1 cm, width: 7 cm, line thickness: 2 mm) which was permanently displayed on the device surface. Visual feedback was provided via a double mirror mounted on top of the head coil while auditory instructions and metronome pacing were received through headphones (Fig. 1A). Presentation software (Neurobehavioural Systems, Inc., Albany, CA) registered x,y -coordinates of the drawing output as measured by the touch-screen at a sampling rate of 100 Hz and a spatial resolution of 0.012 cm (Fig. 1D). Line tracing was initiated at the lower left corner when using the left hand and at the lower right for right hand performance. Tracing velocity was controlled by a high-pitched beep sounding every four seconds to indicate that either the lower left or lower right turning point of the pattern should be reached. Subjects were required to fluently trace the pattern back and forth, synchronized with metronome pacing and without lifting the pen from the screen. To minimize head movements as well as distortions of the magnetic field inside the scanner, tracing was performed by wrist and fingers only, with the upper-arm resting on the bed of the scanner and in close contact with the body. Moreover, subjects were instructed to keep the nonmoving hand motionless on the abdomen at all times, which was visually inspected by the experimenter. Before scanning, subjects familiarized themselves with the setup and practiced the behavioural task inside the scanner.

Task requirements

Each session comprised tracing (1) with the nondominant left hand (NDHt), (2) with the dominant right hand

Figure 1.

fMRI protocol setup. **A**, Subjects viewed their performance via a double mirror mounted onto the head coil. **B**, A MRI-compatible touch-screen was positioned at the level of the abdomen. **C**, The target pattern was to be traced from left to right and vice versa while metronome pacing (every 4 seconds) indicated when

the endpoints should be reached. **D**, Exemplary output of tracing performance with the dominant hand (DHT) and the nondominant hand (NDHT) and during presence (VF) or absence (NVF) of visual feedback. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(DHT), and (3) a rest condition, lasting 21 seconds each (seven volumes). In between these experimental conditions, subjects were instructed to switch the pen from one hand to the other during a 6-second interval (two volumes). At trial onset, each subsequent task condition was verbally announced via the headphones and metronome pacing was provided during all experimental conditions. Each condition was repeated five times within one session with pseudorandomized trial order across sessions. Sessions 1, 3, and 5 were performed with eyes open such that visual feedback (VF) was available, whereas sessions 2 and 4 were executed with the eyes closed, i.e. without visual guidance (NVF).

Behavioural analysis and statistics

Behavioural data were analyzed for 29 subjects (data were lost for the remaining 11 subjects due to hard disk failure of the kinematics computer). However, for all subjects, correct movement execution was ensured via visual inspection of the experimenter. A linear regression was calculated between the subject's drawing movements as measured by the touch-screen and the target pattern in x and y dimensions on a trial-by-trial basis. Minor yet systematic offsets between the patterns (e.g. tracing occurred systematically to the left of the line) were removed by subtracting the constant term as revealed by the regression equation. For each data point, the spatial error was determined as the minimal Euclidean distance between the measured x - y coordinates of the pen and the target pattern. The mean spatial error (ME) was calculated for each trial. To control whether subjects complied with metro-

nome pacing, we determined what percentage of the target pattern (traced trajectory path, TTP) was traced in between two beeps (100% = tracing from start to end point). For each subject, ME and TTP were averaged within DHT and NDHT conditions executed under visual guidance and subjected to dependent t -tests (α level = 0.05). Moreover, for each subject a behavioural lateralization index (LI_{Behav}) was calculated as follows:

$$LI_{\text{Behav}} = \frac{(ME_{\text{NDHT}}/TTP_{\text{NDHT}} - ME_{\text{DHT}}/TTP_{\text{DHT}})}{(ME_{\text{NDHT}}/TTP_{\text{NDHT}} + ME_{\text{DHT}}/TTP_{\text{DHT}})}$$

with $ME_{\text{NDHT,DHT}}$ and $TTP_{\text{NDHT,DHT}}$ denoting the mean error and percentage of drawn pattern averaged across trials during nondominant and dominant hand performance, respectively. This parameter ranges between -1 and 1 and captures the performance between hands such that positive values indicate more errors and/or slower tracing of the left hand, and negative values indicate more errors and/or slower tracing of the right hand. This LI_{Behav} was subjected to further analysis as described below (see Inter-hemispheric Inhibition as Measured by Double-Pulse TMS). Group results are reported as the mean value $\pm$ standard deviation.

Image Acquisition and Analysis

Scanning was performed on a 3T Philips Intera system (Best, The Netherlands) using a SENSE 8-channel head coil. T2*-weighted Echo Planar Imaging (EPI) MRI images were acquired with the following parameters: repetition

time (TR) 3000 ms, echo time (TE) 33 ms, field of view (FOV) $230 \times 230 \times 154$ (x, y, z), acquisition voxel size $2.21 \times 2.24 \times 3.5$ mm. Forty transverse slices with 3.5-mm slice thickness and a 0.35-mm interslice gap provided whole-brain coverage. One time-series consisted of 109 dynamic volumes (corresponding to 5.48 minutes) which were preceded by four dummy volumes, allowing the signal to reach steady state. Additionally, high-resolution anatomical images were acquired coronally using a 3D magnetization-prepared rapid acquisition gradient echo sequence (MPRage) with the following parameters: TR 9.8 ms, TE 4.6 ms, flip angle 8° , inversion time (TI) 921.7 ms, FOV 180×230 (x, z), with acquisition voxel size of 0.98×0.98 (x, z) and slice thickness of 1 mm.

Preprocessing

Image processing and statistical analyses were performed using Matlab R2007b (The Mathworks Inc., MA) and SPM5 (Statistical Parametric Mapping software, SPM: Wellcome Department of Imaging Neuroscience, London, UK; available at: <http://www.fil.ion.ucl.ac.uk/spm/>). Subject's EPI scans were spatially realigned to the first image of the first time series using second degree B-spline interpolation algorithms together with rigid body transformations (three translations and three rotations about each axis) to minimize head movement artifacts. Images were then spatially normalized [Friston et al., 1995a] to a symmetrical version of the Montreal Neurological Institute EPI brain template within the Talairach and Tournoux [1988] reference frame. Finally, images were smoothed by an isotropic 8 mm full-width-at-half-maximum Gaussian kernel.

Statistical Analyses

First-level analysis

Data analysis was performed in the context of the General Linear Model (GLM, Friston et al., 1995b). Each experimental condition (DHt, NDHt, rest) as well as the 6-second interval for switching the pen between hands were modeled as a box-car function convolved with the SPM standard hemodynamic response function. Physiological noise and low frequency drifts were reduced by applying a high-pass filter of 128 seconds. Movement parameters obtained during the spatial realignment were included as regressors of no interest. Contrasts of interest (DHt > rest, NDHt > rest) were calculated for each subject both across as well as within each visual feedback condition and were subsequently entered into second-level random effects (RFX) analyses.

Second-level RFX analysis

Basic network: Dominant versus nondominant hand. Simple *t*-tests were calculated separately for DHt > rest and NDHt > rest. Additionally, the effect of vision was

assessed by a simple *t*-test pooling VF versus NVF conditions across both hands (i.e. first-level contrast $[DHt_{VF} + NDHt_{VF}] - [DHt_{NVF} + NDHt_{NVF}]$). Anatomical inferences were drawn based on the neuroanatomy atlas of Duvernoy [1999] and the SPM Anatomy Toolbox v.1.5 [Eickhoff et al., 2005, 2007] when applicable.

Detecting activation asymmetries. A whole-brain approach was adopted for detecting asymmetric brain activation. To this end, the first-level contrast images of interest (i.e. $DHt_{VF} > \text{rest}$, $DHt_{NVF} > \text{rest}$, $NDHt_{VF} > \text{rest}$ and $NDHt_{NVF} > \text{rest}$) were left-right flipped allowing direct comparison of activation of one hemisphere with the other [Iidaka et al., 2004; Lux et al., 2004; Mechelli et al., 2005; Peyrin et al., 2004; Van Impe et al., 2009]. This method assumes that functionally homologous regions are located symmetrically in both hemispheres [Toro et al., 2008] and requires that EPI images are normalized to a symmetric template. Unimanual motor control evokes strong contralateral activity in most cortical motor regions thus complicating the detection of activation asymmetries beyond this well-documented lateralization. Therefore, it is meaningful to compare activation images revealed for left limb movements with the symmetrically flipped activation images revealed for right limb movements thus detecting effector-specific differences within the contra- or ipsilateral hemisphere. This method might lead to misinterpretations when motor tasks activate one hemisphere more than the other in an effector-independent way. To avoid this potential pitfall we performed first an analysis identifying hemispheric asymmetries which were *effector-independent* and, second, an additional analysis pinpointing *effector-specific* hemispheric asymmetries (Supp. Info., Fig. 1).

Effector-independent asymmetries between hemispheres : Right versus left hemisphere activation

We aimed at identifying brain areas showing a higher BOLD response in one hemisphere with respect to the other, irrespective of the performing hand, i.e. true hemispheric specialization. A two-step procedure was taken: first, we obtained which regions were activated more strongly in one hemisphere as opposed to homologous regions in the other hemisphere (e.g. $DHt > DHt_{flip}$). Subsequently, we determined whether this hemispheric lateralization was found independently of which effector performed the task, by means of a conjunction analysis $(DHt > DHt_{flip}) \cap (NDHt > NDHt_{flip})$ [Nichols et al., 2005]. Note that this approach allows to identify significant asymmetries in activation *between* hemispheres that are effector-independent and, therefore, point to true hemispheric specialization. The analysis was carried out in the context of a RFX ANOVA model, containing the contrast images DHt, DHt_{flip} , NDHt, $NDHt_{flip}$ and estimated under the assumption of dependent measurements and unequal variances. The threshold for significance was set at $P < 0.05$ FWE-corrected for multiple comparisons.

A laterality index comparing activation in the right versus left hemisphere (LI_{RL}) was calculated for all clusters surviving this statistical threshold [Jansen et al., 2006]. To obtain this index, the percentage signal change (PSC) was first extracted for the contrasts of interest from the first eigenvector of each cluster as well as of its symmetrically flipped homologue in the opposite hemisphere [Marsbar, Brett et al., 2002]. PSC was chosen instead of the extent of activated voxels as it is the more stable and reproducible measure [Cohen and DuBois, 1999]. LI_{RL} was then calculated as the differential PSC for the right (RH) versus left (LH) hemisphere: $LI_{RL} = (PSC_{RH} - PSC_{LH}) / (|PSC_{RH}| + |PSC_{LH}|)$. Fully right-lateralized activity is thus captured by a value of 1.0, full left-lateralization by -1.0 and full symmetry by a value of 0. For each subject, four LI_{RL} values were calculated corresponding to two effectors performing the task (DHT, NDHT) $\times$ 2 visual feedback conditions (VF, NVF).

Statistical analyses on those LIs were performed using Statistica 8 (StatSoft Inc., Tulsa). Since LI_{RL} values did not invariably meet the assumption of normality (Shapiro-Wilk's *W*-test), we used the nonparametric Wilcoxon test. For each area, it was examined (1) whether LI_{RL} differed significantly between DHT and NDHT; (2) whether LI_{RL} was decreased (i.e. more bilateral) for the VF relative to the NVF condition; and (3) whether an effector-by-vision interaction could be found. Bonferroni correction was applied when dependent contrasts were tested for multiple regions of interest (ROI) and the α -level was adjusted accordingly.

Hemispheric asymmetries for movements with the ipsi- and contralateral hand

Next, it was assessed whether the BOLD response of both the ipsi- and the contralateral hemisphere differed depending on whether the tracing task was executed with the nondominant versus the dominant hand. To this end, the left-right flipped contrast images representing (DHT-VF > rest)_{flip} and (DHT-NVF > rest)_{flip} were entered into a RFX 2 $\times$ 2 ANOVA together with the unflipped contrast images representing NDHT-VF > rest and NDHT-NVF > rest, thus corresponding to the factors hand and vision. Data were again analyzed as dependent measurements with unequal variance. Importantly, this analysis would also have yielded regions exhibiting effector-independent asymmetries (as determined by the previous analysis). To avoid these artificial results, areas exhibiting effector-independent asymmetries were excluded via a masking procedure (see Supp. Info., Fig. 1 for procedure).

The comparisons NDHT versus DHT_{flip} were then evaluated for detecting effector-specific differential activation in either the ipsi- or contralateral hemisphere. The threshold for significance was set at $P < 0.05$ after FWE correction for multiple comparisons. Within the clusters identified by the above analysis, PSC was extracted and laterality indices were obtained. For this effector-specific analysis, activation

was compared between the contra- versus the ipsilateral hemisphere (LI_{ci} for the contrasts of interest DHT-VF > rest, DHT-NVF > rest, NDHT-VF > rest, NDHT-NVF > rest). The LI_{ci} was calculated as follows: $LI_{ci} = (PSC_{contra} - PSC_{ipsi}) / (|PSC_{contra}| + |PSC_{ipsi}|)$, with higher LI_{ci} values signifying more elevated contralateral activation. As we had a strong a priori hypothesis for the primary motor cortex, the same analysis was performed for a predefined ROI, i.e. an 8-mm sphere centered at [-37, -21, 58] and corresponding to M1 as revealed by a meta-analysis by Mayka et al. [2006].

Interhemispheric Inhibition as Measured by Double-Pulse TMS

A double-pulse TMS protocol was applied to measure interhemispheric inhibition (IHI) as described previously [Vercauteren et al., 2008]. In short, an electromyogram (EMG) was recorded from the left and right abductor pollicis brevis (APB) (Mespec 8000, Mega Electronics Ltd., Kuopio, Finland; CED Power 1401, Cambridge Electronic Design, Cambridge, UK and Signal 4) while TMS was applied via two Magstim machines (Magstim 200, Magstim Company Ltd., Carmarthen, UK). First, the APB hotspot and rest motor threshold (RMT) were determined for each hemisphere in accordance with conventional protocols [Rossini et al., 1994]. A conditioning stimulus (CS) was delivered by a figure-of-eight coil (loop diameter: 50 mm) positioned tangentially over M1 of one hemisphere and a test stimulus (TS) by a second figure-of-eight coil (loop diameter: 70 mm) placed tangentially over M1 of the other hemisphere. CS intensity was set at 140% of the APB RMT in all conditions and TS intensity was set at 150% in the rest conditions. The stimulation intensity of the active conditions (see further) was decreased such that the test MEP amplitude was matched to the rest conditions, thus ensuring that %IHI was determined relative to comparable TS MEP amplitudes between conditions [Harris-Love et al., 2007]. The interstimulus interval between CS and TS was 10 ms. These parameters were chosen based on Wahl et al. [2007], who demonstrated that IHI as measured by this protocol correlates with corpus callosum organization. IHI was measured from the dominant to the nondominant hemisphere (IHI_{DtoND}) and vice versa (IHI_{NDtoD}), either when subjects were at rest or when the APB of the conditioned hemisphere was isometrically activated at 5% maximum voluntary contraction. For each condition we registered 12 unconditioned (i.e. TS alone) and 12 conditioned responses (i.e. TS was preceded by the CS). Trials with obvious background EMG were discarded and for the remaining trials, the MEP peak-to-peak amplitude was determined for the APB of the TS side within an interval of 15 to 65 ms after TMS stimulation. The percentage IHI was determined by $\%IHI = (1 - \text{conditioned MEP amplitude} / \text{nonconditioned MEP amplitude}) \times 100$, such that $IHI = 0\%$ indicates no inhibition and $IHI = 100\%$ indicates complete inhibition. One subject was excluded from the

analysis due to obvious background EMG in the majority of trials. Correlation analyses revealed a highly significant linear relationship between IHI measured at rest and during active contraction for both IHI_{DtoND} ($r = 0.71$, $P < 0.00001$) and IHI_{NDtoD} ($r = 0.63$, $P < 0.0001$). Here results will be reported after the obtained IHI values were averaged across both conditions and an IHI lateralization index (LI_{IHI}) was calculated according to $LI_{IHI} = (IHI_{NDtoD} - IHI_{DtoND}) / (|IHI_{NDtoD}| + |IHI_{DtoND}|)$. A positive LI_{IHI} reflects relatively more inhibition from the nondominant to the dominant hemisphere, whereas negative LI_{IHI} indicates the opposite asymmetry. These values were entered into a regression analysis.

Regression between LI_{ci} and IHI, performance, and handedness

It was hypothesized that activation of the ipsilateral motor regions would be particularly pronounced during NDH tracing. To further investigate the potential underlying mechanism, simple as well as multiple regression models were set up between LI_{ci} and LI_{Behav} , LI_{IHI} , and an handedness index as directly derived from the Oldfield score ($LI_{Oldfield}$). Bonferroni correction was applied for multiple testing of dependent variables and the α -level was adjusted accordingly.

RESULTS

Behavioural Results

First, all behavioural data underwent visual inspection. When the task was performed without visual feedback, subjects traced the memorized target pattern but drifted in space thus yielding a highly variable output pattern, in x - and y -direction (Fig. 1D, right). Therefore, it was not possible to reliably extract parameters describing the spatial accuracy such that only tracing movements with visual feedback were further analyzed. These results showed that the mean error (ME) was significantly increased and the percentage of traced trajectory path (TTP) significantly decreased ($P < 0.0005$) for NDHt (mean $\pm$ std ME_{NDHt} : 0.134 ± 0.015 , range 0.098–0.163; TTP_{NDHt} : 89.913 ± 5.551) as compared with DHt (ME_{DHt} : 0.106 ± 0.015 , range 0.077–0.137, TTP_{DHt} : 92.615 ± 4.927).

Basic Activation Network: Influence of Effector and Visual Feedback

Either tracing task (i.e. DHt > rest and NDHt > rest) activated a typical visuomotor network including contralateral primary and secondary motor areas, primary somatosensory cortex, dorsal as well as ventral frontoparietal networks and subcortical regions (Supp. Info., Fig. 2 and Table I). The availability of vision modulated brain activation such that task execution during VF as compared with

NVF produced increased BOLD responses in the superior parietal lobe bilaterally, bilateral occipital areas and right lingual gyrus, SMA, cingulum, posterior part of right inferior temporal gyrus, and cerebellar vermis (Supp. Info., Fig. 3 and Table II).

The reverse comparison (NVF > VF) revealed no significantly activated areas, even when the statistical threshold was lowered to $P \leq 0.001$ uncorrected for multiple comparisons.

Effector-Independent Asymmetries Between Hemispheres: Right Versus Left Hemisphere Activation

Areas lateralizing to one hemisphere irrespective of the effector (i.e. $DHt > DHt_{flip} \cap NDHt > NDHt_{flip}$) were found exclusively in the right hemisphere (Fig. 2A and Table I). They comprised inferior frontal gyrus (IFG, mainly BA 45 and 47), and middle and superior frontal gyrus (MFG, SFG). Additionally, activations were found in the anterior angular gyrus (ANG) and posterior supramarginal gyrus (SMG), in the posterior part of inferior temporal gyrus (PIT), lateral occipital complex, and in middle temporal gyrus (MTG). In the visual cortex, the superior part of middle occipital gyrus (MOG) was recruited, bordering IPS, and, finally, a small cluster ($kE = 8$) was activated in posterior cerebellum (VIII, not shown on overlay). An additional analysis confirmed that these differences across hemispheres were driven by significant activation of the right hemisphere, such that PSC values (pooled across visual feedback conditions) differed significantly from zero ($P \leq 0.003$, α -level = 0.004 after Bonferroni correction (Supp. Info., Fig. 4). By contrast, activity within the left hemisphere ROIs was close to baseline values. In this left hemisphere, no clusters common to $NDHt > NDHt_{flip}$ and $DHt > DHt_{flip}$ reached significance. LI_{RL} did not differ significantly between DHt and NDHt (Wilcoxon $z > 2.371$, $P < 0.018$ with adapted α -level = 0.007), except for PIT in the absence of visual feedback ($z = 2.861$, $P = 0.004$) (Table II), where right hemispheric activation was decreased for DHt relative to NDHt while left hemispheric activation remained unchanged. Visual inspection of LI_{RL} bar plots (Fig. 2B) moreover show that most regions exhibited increased right lateralization in the absence of visual feedback, during DHt and NDHt, except for PIT, SFG, and MOG. PIT and SFG showed the reversed pattern, irrespective of condition, i.e. increased right lateralization under visual guidance. For none of the regions, however, did this difference between VF and NVF achieve statistical significance after correction at the adapted $\alpha = 0.007$ ($z > 2.524$, $P > 0.012$, see Table II). Similarly, the hand $\times$ vision interaction did not reach significance for the LI_{RL} of any ROI ($z < 2.047$, $P > 0.041$, adjusted $\alpha = 0.007$).

Above-mentioned areas are in close proximity to a ventral attention network as reported previously (cf. infra). Prompted by this finding, we performed a separate analysis to verify

Figure 2.

Effector-independent BOLD responses and associated laterality indices (L_{RL}). **A**, conjunction analysis revealing regions that activate more in one hemisphere as opposed to homologue regions in the other, irrespective of the effector (conjoined: $NDHt > NDHt_{flip} \cap DHt > DHt_{flip}$, pFWE-corr. 0.05). MNI-stereotactically normalized coordinates were mapped onto Caret flatmap of the *right* hemisphere (available at: <http://brainmap.wustl.edu/caret>) [Van Essen, 2001, 2005]. No suprathreshold clusters were found for the left hemisphere. **B**, Corresponding laterality indices (L_{RL}) during nondominant left (NDHt,

orange) and dominant right hand (DHt, blue) performance, in the absence (NVF, shaded area) and presence of visual guidance (VF). A L_{RL} of +1 indicates full right lateralization, -1 full left lateralization, and 0 bilateral activation. CS: central sulcus, LS: lateral fissure, PIT: posterior inferior temporal gyrus, MOG: middle occipital gyrus, MTG: middle temporal gyrus, ANG: angular gyrus, MFG: middle frontal gyrus, IFG: inferior frontal gyrus, SFG: superior frontal gyrus. See Table I for ROI peak coordinates. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

whether classical key areas of the bilaterally responding dorsal attention network, i.e. the IPS and FEF, would likewise be activated. Significant bilateral activation was found

along the IPS ($x, y, z = -26, -56, 46; 26, -58, 52; t = 4.7$) as well as around the junction of the precentral and superior frontal sulcus ($x, y, z = -24, -10, 50; 24, -12, 50; t = 4.7$).

TABLE I. Cerebral activity evoked during $[NDHt > NDHt_{flip}]$ in conjunction with $[DHt > DHt_{flip}]$ (see Fig.2)

Anatomical region	Hemisphere	t-Value	P value ^a	Cluster size	Local maximum
Middle occipital gyrus	R	7.62	0.000	226	38 -80 34
Postinf temporal gyrus	R	7.19	0.000	238	54 -56 -16
Inf frontal gyrus, pars orbitalis	R	6.68	0.000	1,066	50 38 -6
Inf frontal gyrus, pars triangularis	R	6.02	0.000		54 24 2
Inf frontal gyrus, pars triangularis	R	5.86	0.000		48 42 6
Angular gyrus	R	5.99	0.000	381	54 -48 36
Supramarginal gyrus	R	4.95	0.013		64 -42 30
Angular gyrus	R	4.87	0.018		40 -60 40
Middle frontal gyrus	R	5.7	0.000	159	24 58 26
Cerebellum VIII	R	5.38	0.002	8	22 -42 -56
Middle temporal gyrus	R	4.94	0.014	18	50 -32 -12
Superior frontal gyrus	R	4.82	0.023	6	22 18 62

^apFWE < 0.05, corrected at the voxel level.

TABLE II. Wilcoxon-rank testing of LI_{RL} values: dominant versus nondominant hand (DHt vs. NDHt, with or without VF) and presence versus absence of visual feedback (VF vs. NVF, with DHt and NDHt)

	DHt vs. NDHt				VF vs. NVF			
	VF		NVF		DHt		NDHt	
	z-Value	P value	z-Value	P value	z-value	P value	z-Value	P value
PIT	1.654	0.098	2.861	0.004	0.934	0.350	0.438	0.662
MOG	0.229	0.819	2.371	<i>0.018</i>	1.601	0.109	0.205	0.837
MTG	1.568	0.117	0.586	0.558	0.911	0.362	2.524	<i>0.012</i>
ANG	1.742	0.081	2.026	<i>0.043</i>	2.026	<i>0.043</i>	2.000	<i>0.045</i>
MFG	1.720	0.085	1.018	0.309	0.227	0.820	0.992	0.321
IFG	1.548	0.122	1.430	0.153	1.682	0.093	1.903	0.057
SFG	0.505	0.614	0.995	0.320	0.410	0.682	1.635	0.102

P values surviving the adapted α -level of 0.007 are indicated in bold. P values significant before dependent testing correction ($\alpha = 0.05$) are italicized.

PIT, posterior inferior temporal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; ANG, angular gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SFG, superior frontal gyrus.

Hemispheric Asymmetries for Movements With the Ipsi- and Contralateral Hand

Nondominant hand tracing was accompanied with more bilateral activation than dominant hand execution. Thus, higher activation within the ipsilateral hemisphere was found during NDHt as compared with DHt ($NDHt > DHt_{flip}$, Table III). This comparison reached significance in typical motor areas such as the ipsilateral dorsal precentral gyrus corresponding to the dorsal premotor cortex (PMd), extending into SMA-proper and the caudal cingulate zone (CCZ) bordering the VCA line [Picard and Strick, 2001], as well as the ipsilateral dorsal postcentral gyrus (PoCG) (Fig. 3A). Accordingly, PSC derived from ROIs centered at the activation peak of each cluster (Fig. 3B) indicate that ipsilateral activations were higher for NDHt (orange) than during DHt (blue). By contrast, contralateral activations were slightly lower during NDHt than DHt. This general pattern of PSC was found for task performance with and without visual feedback. Even though M1 activation did not survive the stringent statistical threshold of the whole-brain analysis, PSC (extracted from a predefined ROI) was modulated in the same way as the pre- and postcentral areas (Fig. 3B). Finally, cerebellum and insula were activated more in the contralateral than the ipsilateral hemisphere (see Fig. 4). The opposite contrast ($NDHt < DHt_{flip}$) revealed no significantly activated areas.

For the cortical regions in the ipsilateral hemisphere, laterality indices (LI_{ci}) were calculated, such that larger LI_{ci} indicates enhanced contralateral activity (Fig. 5B, Table IV). LI_{ci} values were generally smaller during NDHt than DHt, indicating that the former induced more bilateral activation. Put differently, the left (ipsilateral) hemisphere was also active when the task was executed with the left hand and to a higher extent than right hemisphere regions during right hand execution, as indicated by the PSC anal-

ysis above. Significantly larger LI_{ci} values were found for DHt than NDHt in PMd, SMA, PoCG, and M1 when no visual feedback was provided (Wilcoxon $z > 3.11$, $P < 0.01$, α -level = 0.008) and in PMd and SMA also when visual feedback was available (Wilcoxon $z > 3.252$, $P \leq 0.001$, α -level = 0.008), while, for this condition, PoCG showed a trend towards significance (Wilcoxon $z > 2.58$, $P = 0.009$; see Table V). Thus, since the contralateral values were more elevated during DHt than during NDHt, LIs were higher during DHt than during NDHt, in line with our expectations. Lateralization was further influenced by visual feedback, be it to a different extent for DHt and NDHt. During DHt, LI_{ci} values of all ROIs were lower (due to increased bilateral activation) with visual feedback than without. This difference reached statistical significance for PMd and M1 ($z \geq 2.44$, $P < 0.015$). By contrast, availability of vision had less impact on LI_{ci} values revealed during NDHt: the only significant difference was observed for SMA, with slightly stronger contralateral than ipsilateral activation for the no-vision condition (SMA: $z = 0.2685$, $P = 0.007$; remaining regions: $z < 0.287$, $P \leq 0.774$).

Correlation and regression analyses tested whether this pronounced ipsilateral activation evoked by NDHt would correlate with interhemispheric inhibition, behavioural asymmetries, or handedness (results summary, see Supp. Info., Table III I). A linear regression revealed no significant relationship between LI_{Behav} and LI_{ci} determined during either feedback condition, for any of the ROIs ($R^2 \leq 0.048$, $P \leq 0.283$, see Supp. Info., Fig. 5 for M1). Similarly, there was no significant correlation between LI_{ci} during NDHt and LI_{IHI} for M1 (Supp. Info., Fig. 5) nor for the remaining ROIs ($LI_{ci} - IHI_{NDtoD}$ M1: $R^2 \leq 0.007$, $P \leq 0.616$, other: $R^2 \leq 0.100$, $P \leq 0.06$; $LI_{ci} - LI_{IHI}$ M1: $R^2 \leq 0.05$, $P \leq 0.283$, other: $R^2 \leq 0.043$, $P \leq 0.223$). Also other IHI parameters (e.g. representing the active condition or

TABLE III. Cerebral activity evoked during [NDHt > DHt_{flip}] and [DHt_{flip} > NDHt] in the hemisphere ipsilateral (IP) or contralateral (CON) to the performing effector

Anatomical region	Hemisphere	t-Value	P value ^a	Cluster size	Local maximum
NDHt > DHt _{flip}					
Cerebellum VIII	CON	11.73	0.000	32,056	24 -54 -54
Cerebellum VIII	CON	11.49	0.000		18 -60 -54
Precentral gyrus (PMd)	IP	7.5	0.000	919	-46 -8 -56
Superior frontal gyrus	IP	6.67	0.000		-22 -10 64
SMA-proper	IP	5.94	0.000		-8 -8 56
Middle frontal gyrus	CON	7.05	0.000	1,251	24 60 26
Middle frontal gyrus	CON	6.86	0.000		42 12 54
Superior frontal gyrus	CON	6.12	0.000		24 16 62
Inf frontal gyrus, pars orbitalis	CON	6.62	0.000	1,502	50 38 -6
Inf frontal gyrus, pars orbitalis	CON	6.28	0.000		44 48 -4
Inf frontal gyrus, pars triangularis	CON	6.1	0.000		52 22 2
Insula	CON	6.57	0.000	252	34 -24 18
Superior temporal gyrus	IP	5.63	0.001	200	-48 -38 14
Superior temporal gyrus	IP	5.32	0.003		-58 -22 6
Calcarine gyrus	CON	5.39	0.002	79	20 -100 -4
Parahippocampal gyrus	CON	5.38	0.002	48	20 10 -24
Inf frontal gyrus, pars orbitalis	CON	5.11	0.007		24 24 -24
Postcentral gyrus	IP	5.36	0.002	69	-30 -40 70
Middle occipital gyrus	IP	5.1	0.007	39	-48 -76 2
DHt _{flip} > NDHt					
Inf frontal gyrus, pars triangularis	IP	5.99	0.000	453	-48 42 6
Inf frontal gyrus, pars triangularis	IP	5.94	0.000		-50 40 -2
Middle orbital gyrus	IP	5.41	0.002		-44 48 -4
Middle occipital gyrus	IP	5.61	0.001	41	-36 -82 34
Inferior parietal lobe	IP	5.17	0.005	32	-56 -44 44

^ap_{FWE} < 0.05, corrected at the voxel level. kE = 20 voxels.

the difference between active and passive condition) did not significantly correlate with LI_{ci}. Finally, the correlation between LI_{ci} during NDHt and handedness level (LI_{Oldfield}) reached significance for PMd in the absence of vision, yet only without correction for multiple comparisons ($R^2 = 0.113$, $P = 0.045$; corrected α -level = 0.006). We additionally calculated a multiple regression model with LI_{ci} as dependent and LI_{Behav}, LI_{IHL}, and LI_{Oldfield} as independent variables. This analysis revealed no supplementary significant effects ($R^2 \leq 0.184$, $P \leq 0.049$, see Supp. Info., Table III II). Also more sensitive methods such as a double median-split based comparison of LI_{ci} during NDHt did not reveal significant differences for any of the ROIs.

DISCUSSION

This study aimed at identifying potential mechanisms of hemispheric asymmetries that underlie (visuo)motor control of the dominant and nondominant hand, surpassing the general contralateral organization of the motor system. Tracing with either hand evoked a strong BOLD response in left motor areas. Stringent statistical tests across hemispheres revealed that dorsal premotor and postcentral

areas were more strongly activated in the left than in the right hemisphere when the task was executed with the ipsilateral hand. This pattern could not be explained by the degree of handedness or the differential motor performance of both hands, nor does it seem to be significantly related to interhemispheric inhibition as measured by TMS during rest or isometric contraction. As an unexpected result, we identified a right-lateralized network activated by our sensorimotor task, centering around ventral temporoparietal and as well as ventral frontal areas that responded independently of which effector performed the tracing and of the availability of visual feedback.

Behavioural Performance

For the visual feedback condition, we compared measures of tracing variability and velocity across hands and found the nondominant hand to perform at a higher error rate and slightly reduced velocity, i.e. smaller completion of the traced trajectory path. This finding confirms the superiority of the dominant as opposed to the nondominant hand, as indicated by higher spatial accuracy and movement velocity, particularly for motor tasks with high

Figure 3.

Higher increase in ipsilateral motor activity during nondominant left than during dominant right hand tracing. **A**, Areas in the ipsilateral (left) hemisphere activating more strongly during tracing with the nondominant than dominant hand ($\text{NDHt} > \text{DHt}_{\text{flip}}$, $p_{\text{FWE-corr.}} = 0.05$). MNI-stereotactically normalized coordinates were mapped onto a Caret render of the *ipsilateral* left hemisphere (available at: <http://brainmap.wustl.edu/caret>) [Van Essen, 2001, 2005]. **B**, Mean percent signal change (PSC) and standard error derived from 8 mm-

ROIs centered around the maxima of each identified cluster and at M1, for the contrasts $\text{DHt} > \text{rest}$ and $\text{NDHt} > \text{rest}$, either with visual feedback (VF, upper panel) or without (NVF, lower panel). SMA-prop: SMA-proper, PMd: dorsal pre-motor cortex, M1: primary motor cortex, PoCG: postcentral gyrus. The M1 ROI (black) is a 8-mm sphere as determined in a meta-study by Mayka et al. [2006]. See Table III for ROI peak coordinates. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

demands on spatiotemporal control [Carson, 1989; Elliott et al., 1999; Hausmann et al., 2004; Phillips et al., 1999; Tremblay et al., 2005].

Figure 4.

Axial slice overlays of cerebellar activation during $\text{NDHt} > \text{DHt}_{\text{flip}}$. Activation overlays of $\text{NDHt} > \text{DHt}_{\text{flip}}$ on MNI brain template: compared with DHt , NDHt yielded proportionally more cerebellar activations, particularly in the contralateral hemisphere ($p_{\text{FWE}} = 0.05$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Functional Imaging Results

Right-lateralized network exhibiting effector-independent activation

Our data revealed that continuous tracing of a line pattern activates a right-lateralized network of mainly ventral frontoparietal areas (Fig. 2). Particularly, strong responses were found in the anterior parts of inferior frontal gyrus, pars orbitalis and triangularis, and inferior parietal lobe (ANG/SMG) extending toward the temporoparietal junction (TPJ). Both activation spots were located in close proximity (< 4 mm Euclidean distance) to two core regions of the ventral attentional system (VAN), i.e. TPJ and IFG as reported by Corbetta et al. [2002a]. An additional analysis (Supp. Info., Fig. 4) further confirmed that this asymmetry reflected true right hemisphere activation rather than deactivation of the homologue regions in the left hemisphere. Interestingly, lateralization of this network remained significant even without the availability of visual feedback. Thus, regardless of which hand was used to perform the task and irrespective of the availability of visual feedback, tracing activated classical core regions of the VAN.

Figure 5.

Laterality indices representing contralateral versus ipsilateral activation during NDHt and DHt (LI_{ci}). **A**, Same comparison as shown in Figure 3 (i.e. $NDHt > DHt_{flipped}$, $pFWE > 0.05$) overlaid on a representative brain in MNI space. PMd: dorsal premotor cortex, M1: primary motor cortex, SMA-prop: SMA proper, PoCG: postcentral Gyrus. See Table III for ROI peak coordinates. **B**, Laterality indices (LI_{ci}) for regions of interest (cf. Fig. 3) obtained during task execution with the nondominant left hand (NDHt, orange) and dominant right hand (DHt, blue), in the absence (NVF, shaded bars) and presence of visual guidance (VF). A LI_{ci} of +1 indicates contralateral activation only, -1 ipsilateral activation only, and 0 bilateral activation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

We also found significant bilateral activation along the intraparietal sulcus (IPS) as well as around the junction of the precentral and superior frontal sulcus, i.e. in close proximity (<5 mm for the IPS, <2 mm for FEF) to activation maxima of the dorsal attention network as identified by classical spatial attention paradigms. This network controls goal-oriented attention based upon intrinsic expectations and motivations and is mostly recruited by the appearance of anticipated stimuli and during preparation

TABLE IV. Group-based laterality indices (LI_{ci}) within functional motor cortical ROIs derived from comparison [$NDHt > DHt_{flipped}$] ($pFWE-corr = 0.05$, see Fig 5)

Region of interest	Feedback	DHt	NDHt
PMd	VF	0.45 ± 0.04	0.08 ± 0.03
	NVF	0.69 ± 0.04	0.10 ± 0.05
SMA-proper	VF	0.39 ± 0.06	0.04 ± 0.05
	NVF	0.55 ± 0.05	-0.07 ± 0.05
PoCG	VF	0.48 ± 0.07	0.11 ± 0.09
	NVF	0.62 ± 0.07	0.14 ± 0.09
M1	VF	0.58 ± 0.05	0.43 ± 0.05
	NVF	0.77 ± 0.05	0.42 ± 0.06

Values are mean $\pm$ SEM. A value of +1 corresponds to full contralateral recruitment, -1 to full ipsilateral recruitment, and 0 to a symmetrical distribution.

VF/NVF, during presence/absence of visual feedback; DHt/NDHt, during dominant/nondominant hand performance; PMd, dorsal premotor cortex; PoCG, postcentral gyrus; M1, primary motor cortex.

of intended shifts of attention [Corbetta et al., 2008]. Additionally, it is possible that this activation pattern is partly related to spatial memory demands, particularly in the condition without feedback [Corbetta et al., 2002a]. However, this effect might be small as the target pattern was relatively simple.

In summary, our bilateral DAN activation is not surprising considering its role in controlling spatially selective goal-driven attention. Recruitment of the VAN on the other hand was unexpected. Initially, VAN has been described as a system responding to behaviourally relevant but unexpected changes of stimuli (spatial and nonspatial features) that drive adjustments of attention [Corbetta and Shulman, 2002; Marois et al., 2000]. It interacts with DAN by interrupting goal-driven attention processes to allow stimulus-driven shifts of attention. Contrary to the majority of previously used task sets, our paradigm did not include unexpected events or stimuli. However, even though no overt events or stimuli were introduced

TABLE V. Wilcoxon-rank testing of LI_{ci} values: dominant versus nondominant hand tracing (DHt vs. NDHt) and presence versus absence of visual feedback (VF vs. NVF)

	DHt vs. NDHt				VF vs. NVF			
	VF		NVF		DHt		NDHt	
	z-Value	P value	z-Value	P value	z-value	P value	z-value	P value
PMd	4.459	0.000	4.730	0.000	4.509	0.000	0.098	0.922
SMA-proper	3.252	0.001	4.684	0.000	2.850	0.004	2.685	0.007
PoCG	2.582	<i>0.010</i>	3.111	0.002	1.921	0.055	0.287	0.774
M1	2.149	<i>0.032</i>	3.545	0.000	3.172	0.002	0.126	0.900

P values surviving the adapted α -level of 0.008 are indicated in bold. P values significant before dependent testing correction ($\alpha = 0.05$) are italicized.

PMd, dorsal premotor cortex; PoCG, postcentral gyrus; M1, primary motor cortex.

experimentally, behavioural events might have emerged during task execution. For instance, major changes in movement direction within a block such as corners or endpoints of the target pattern might constitute behaviourally relevant events. Those subtle continuity breaches might cause one form of reorienting that suffices to elicit the ventral system. This confirms the idea that DAN and VAN both emerge during paradigms that alternate between shifts of attention (DAN) and detection of relevant stimuli (VAN) [Corbetta et al., 2008; Hampshire et al., 2007; Shulman et al., 2003]. This interpretation would imply that VAN is also activated when spatial information is continuously used to modulate attention and to adapt behaviour accordingly. Similarly, Ogawa et al. [2006] found that the posterior parietal cortex (PPC), TPJ, occipitotemporal regions, and VFC of the right hemisphere were strongly activated when subjects moved a cursor along an intricate spatial template. However, contrary to our findings, this effect was more pronounced when visual feedback was present than when it was removed. This divergence might result from methodological differences since our statistical analysis focused on direct hemispheric asymmetries. Moreover, the occlusions of the template pattern in their paradigm were relatively short, but the durations could not be anticipated. Consequently, the unexpected reoccurrence of visual information might have been a behaviourally relevant event, contributing to the strong activation of VAN in the study of Ogawa et al. [2006]. By contrast, the no-feedback condition in our study lasted 21 seconds and was fully predictable. Another study by Astafiev et al. [2003] compared visuomotor responses (right hand pointing) with spatial shifts of attention and found response-independent, shared activation of FEF and IPS only. However, also here hemispheric asymmetries toward the right hemisphere were not investigated explicitly.

It is possible that eye movements accompanying fine-motor control of hand and fingers have co-contributed to the right-lateralized activation. Previous studies found that regions frequently associated with eye movements such as lateral intraparietal sulcus and FEF are mainly found bilaterally [Corbetta et al., 1998; Nobre et al., 2000]. However, a recent study by Petit et al. [2009] determined activations associated with making saccades to visual targets. Its authors found that activations caused by saccade execution were lateralized to the right hemisphere. In particular, two activation peaks identified in occipitotemporal areas were in close proximity to our coordinates located in MOG and PIT. Thus, it is likely that regions within the occipitotemporal cortex process general visuospatial aspects which are effector-independent and/or contribute to eye movement control. By contrast, frontoparietal areas identified in our study differed from those reported by Petit et al. [2009] confirming that these circuits exhibit effector specificity such that hand movement activates different subregions than saccades [Culham et al., 2006]. Our results suggest that VAN is activated during a tracing task spanning the left and right hemifield, a paradigm which is characteristically impaired in patients suffering from spatial hemineglect due to lesions in the right hemisphere. Typically,

such patients would draw only the right half of a picture (e.g. during the clock test) or would use only the right half of a paper when writing to dictation. This behavioural expression of neglect impairing goal-directed behaviour in space seems to point at a predominant dysfunction of the DAN. In agreement with this view, IPS has been identified as a core region related to neglect by both voxel-based lesion symptom mapping in patients and functional imaging of spatial attention paradigms in healthy subjects [Molenberghs et al., 2008]. On the other hand, neglect is also frequently associated with lesions of the right ventral attention system [ventral frontal or temporoparietal cortex, Husain and Kennard, 1996; Karnath et al., 2004; Mort et al., 2003], and can manifest itself even when DAN is structurally unaffected [Corbetta et al., 2005; Husain and Rorden, 2003; Milner and McIntosh, 2004]. This apparent paradox has been partly unravelled by recent research indicating that neglect results from disturbed interactions between the ventral and dorsal attention system: behavioural deficits correlated with dysfunctional connectivity within the right VAN and/or interhemispherically across parietal DAN regions, which was caused by structural damage to either system or to connecting fiber tracts, such as the superior longitudinal and arcuate fasciculus [He et al., 2007]. Our findings might support this view as we show for the first time that a drawing task, similar to clinical tests for hemineglect, does engage a right-lateralized ventral attention system conjointly with the bilaterally activated dorsal attention system.

Hemispheric asymmetries during ipsilateral movements

Tracing movements with the subdominant as compared with the dominant hand revealed enhanced ipsilateral recruitment of PMd, SMA, and postcentral gyrus (PoCG) in the left relative to the right hemisphere, as well as larger contralateral activation in the right than in the left cerebellum (Figs. 3 and 5). Importantly, these results were obtained through a direct statistical comparison of the left versus right hemisphere during movements of the ipsilateral limb. This asymmetry was markedly pronounced for PMd and SMA irrespective of the visual feedback condition, whereas for PoCG statistical significance was reached only when tracing was performed with the eyes closed (Fig. 5). Previous research has strongly suggested that M1 exhibits a similar functional asymmetry toward the left hemisphere [Babiloni et al., 2003; Dassonville et al., 1997; Haaland et al., 2004; Kawashima et al., 1993, 1998; Kim et al., 1993; Li et al., 1996; Singh et al., 1998; Verstynen et al., 2005]. However, this could only be confirmed statistically for the lateralization indices calculated from the BOLD response within an a priori-defined region of interest, and only when the task was executed without visual feedback. Thus, we infer that the most pronounced cortical asymmetry of ipsilateral activation was found for the

premotor areas. Theoretically, several mechanisms might have contributed to this effect.

First, it could be argued that involuntary co-contractions of the right hand contributed to increased left motor activity during NDHt. This factor was not controlled for as our scan-setup was not equipped for simultaneous EMG measurements. However, subjects were explicitly instructed to keep the nonactive hand still at all times, and compliance was visually inspected by the experimenter. Moreover, any boost in EMG activity caused by unintended mirror movements would likely have yielded strong suprathreshold activity in the execution-region M1, which was not the case.

Second, factors unrelated to manual control such as saccade-related activation might have confounded the comparison between ipsilateral activation for writing with the left versus right hand. However, the eye movement pattern was probably highly similar for both writing conditions. Moreover, the activation peaks identified in this comparison (i.e. left PMd, SMA, PoCG) are classically associated with hand rather than eye movement control. Likewise the theoretical possibility that dorsal PMd activation reflects a verbalization strategy during the more demanding condition is deemed unlikely since we did not find concurrent activation in classical language regions such as Broca's area. Premotor involvement has been demonstrated by some studies investigating language [e.g. Hanakawa et al., 2002, 2003], however, these regions are observed far more ventrally than our PMd location. Additionally, this type of motor activation might be more related to preparatory processes than verbalization per se [Rushworth et al., 2001].

Third, it has been shown previously that enhanced difficulty during motor performance results in increased bilateral activation [Gut et al., 2007; Haaland et al., 2004; Verstynen et al., 2005] particularly in secondary motor areas [Haaland et al., 2004]. Consequently, enhanced left hemisphere activation might simply relate to the relatively increased difficulty when the task was executed with the nondominant left hand. We tested this possibility, but found no relationship between asymmetries of motor performance to those of the BOLD response, suggesting that performance differences between hands are not a major driving force for increased left ipsilateral activation. This is in agreement with previous findings, demonstrating similar hemispheric asymmetries as those reported here, even with identical task performance across effectors [Verstynen et al., 2005].

Fourth, no significant correlation between asymmetries in ipsilateral BOLD response and the extent of right handedness were detected. This finding requires further confirmation since our subject sample was a relatively homogenous group of strongly right-handed individuals. Nevertheless, it is in agreement with the notion that left-hemisphere motor dominance is observed irrespective of handedness [Kim et al., 1993; Verstynen et al., 2005].

Fifth, we tested the hypothesis that ipsilateral activation of the left hemisphere reflects inhibitory mechanisms regulating information interchange between both hemispheres.

No significant relationship was detected between ipsilateral BOLD asymmetries and IHI as measured by TMS. Previous studies using double-pulse TMS during rest revealed mixed results as to whether IHI from the dominant to the nondominant hemisphere is significantly higher than in the opposite direction [Baumer et al., 2007; Netz et al., 1995, 1999] or not [De Gennaro et al., 2004; Ferbert et al., 1992; Salerno and Georgesco, 1996; Ugawa et al., 1993]. This inconsistency might result from high interindividual variability of IHI or from cross-study differences in stimulation parameters. We have applied parameters as reported by Wahl et al. [2007], who demonstrated that IHI correlated with the integrity of white matter tracts connecting both M1s as revealed by diffusion tensor imaging. In particular, we used an interstimulation interval of 10 ms, which allowed us to test only one of two potentially different neural populations mediating transcallosal inhibition. The application of a longer interstimulus interval (≥ 40 ms) tests a different pool of IHI-related neurons and a recent study [Talelli et al., 2008] revealed first evidence that this second mechanism might be more closely related to the ipsilateral BOLD response than IHI measured with a 10-ms interval. However, this effect could only be demonstrated for old versus young subjects while performing a grasping task with the dominant hand. More research is required to investigate whether IHI, as measured with long interstimulus intervals, is related to the increase in BOLD response of the left hemisphere when motor tasks are executed with the ipsilateral body side.

We could not confirm the results of Kobayashi et al. [2003] who proposed that high ipsilateral activation of the left hemisphere would reflect increased interhemispheric inhibition as a mechanism to counteract mirror movements. However, their result was based on a relatively small subject sample and is somewhat incongruent with other TMS studies revealing increased corticomotor excitability of M1 and decreased intracortical inhibition of the left hemisphere when movements were performed with the ipsilateral body side [Ziemann and Hallett, 2001]. In summary, our study revealed no convincing relationship between hemispheric asymmetries of IHI measured at rest or during isometric contractions and asymmetries of the BOLD response during tracing with the ipsilateral hand. Based on the relatively large sample size in our study, we consider this negative finding to be reliable. One important limitation of our study, however, is that IHI measurements were performed at rest or when subjects performed simple, isometric contractions ipsilateral to the hemisphere where the test stimulus was applied. This is more likely to measure a general "default" state of interhemispheric inhibition which might reflect structural rather than functional connectivity between the hemispheres, at least in healthy subjects. By contrast, it was shown that hemispheric asymmetries of IHI are more consistently modulated when measured in the context of a motor task [Duque et al., 2007; Koch et al., 2006]. In light of these findings, it is

likely that the prominent left hemispheric BOLD response during ipsilateral movements might relate, at least partly, to transcallosal mechanisms, be it in a highly task-specific manner.

Finally, previous research has suggested that motor planning and control rely particularly on parieto-premotor networks in the left hemisphere, such that these circuits are activated for movements executed with either hand [Serrien et al., 2006]. Our results are generally in line with this notion, most notably with respect to the premotor areas [Babiloni et al., 2003; Dassonville et al., 1997; Haaland et al., 2004; Kawashima et al., 1993, 1998; Kim et al., 1993; Solodkin et al., 2001; Verstynen et al., 2005; Viviani et al., 1998]. Left PMd dominance has been repeatedly reported during movement selection based on arbitrary cues [Deiber et al., 1996; Kloppel et al., 2007; Krams et al., 1998; O'Shea et al., 2007; Rushworth et al., 2003; Schluter et al., 2001; Toni et al., 2001b; Wise et al., 1997]. Moreover, a similar activation increase in left parietopremotor circuits was also found for tasks requiring the performance of complex [Haaland et al., 2004; Rijntjes et al., 1999; Verstynen et al., 2005] or novel [Swinen et al., 2009] movement paradigms. It has been proposed that left premotor cortex holds action representations that, during movement execution, can be retrieved in an effector-independent manner [Hlustik et al., 2002; Kuhtz-Buschbeck et al., 2003; Rijntjes et al., 1999; Schluter et al., 2001; Swinnen et al., 2009; Viviani et al., 1998]. Rijntjes et al. [1999] applied fMRI during signing with hand or toe in order to distinguish effector-independent from effector-dependent regions engaged in movement coding. Having established that the premotor hand area was recruited also during foot movement, the authors concluded that this region contains a movement code, or praxicon, which is accessible by various effectors. This has led to the notion that higher-order areas of the left hemisphere might represent actions at an abstract, effector-independent level in the form of such praxicons or movement formulas. Most notably for left parietal areas, this view has been endorsed by different lines of research. Clinical support comes from the finding that damage to left parietal cortex leads to bilateral instead of mere contralateral deficits, such as in ideomotor apraxia [Haaland et al., 2000; Heilman et al., 1982, 2000; Liepmann, 2001]. Particularly impaired are tasks such as gesture production [Buccino et al., 2004], tool-use pantomime [Fridman et al., 2006; Hermsdörfer et al., 2007; Johnson-Frey et al., 2005], and sequencing [Kolb and Milner, 1981].

Although the notion of action representation in the parietal cortex has received considerable experimental support [Creem-Regehr, 2009], the precise role of the premotor cortex is less clear. Hierarchical concepts of parietal-premotor circuits [Crammond and Kalaska, 2000; Toni et al., 2001b; Wise et al., 1997] suggest that premotor areas might be primarily involved in movement selection and preparation before execution rather than in goal representations and motor planning [Rushworth et al., 2003; Thoenissen et al., 2002]. As our study revealed hemispheric asymmetries for premotor but not for posterior parietal regions, it can be

hypothesized that the tracing task essentially required the skilful execution of a predetermined action which was more proficiently implemented by the dominant than by the nondominant hand. Left premotor cortex might thus provide additional resources at the level of movement implementation rather than at higher-level action representation. These resources might be accessible via ipsilateral corticospinal pathways or via dense transcallosal projections typically found for PMd and SMA.

Removal of visual feedback emphasized lateralization effects in PMd, SMA, M1, and PoCG. This effect was expected since visual processing activates the dorsal stream as well as interconnected frontal areas bilaterally, such that lateralization is reduced. Without visual feedback, asymmetric ipsilateral activation was found also for M1 and PoCG, with the latter falling into BA1, which is part of the primary somatosensory cortex [Eickhoff et al., 2005, 2007]. This result suggests that primary sensorimotor areas tend to be left-lateralized when movements are guided by proprioceptive information.

Interpretational Issues

As our study did not include left-handers, it is unclear whether this group would exhibit similar hemispheric asymmetries in the context of our task. Research on functional [Kim et al., 1993; Solodkin et al., 2001] or anatomical [Amunts et al., 2000] motor asymmetry, or lateralization of language and handedness [Dassonville et al., 1997] suggests that hemispheric asymmetries might be less pronounced and more variable in left- than right-handers. However, early [Kim et al., 1993] as well as more recent [Verstynen et al., 2005] functional imaging studies involving left-handers suggest that dominance of the left hemisphere for skilled motor movement is a universal feature rather than an aspect of handedness.

Furthermore, since the neural substrates for high-precision movements such as writing/drawing do not necessarily overlap with those of reaching/grasping movements, it remains uncertain to what extent currently observed hemispheric asymmetries generalize to other tasks. It is important to keep in mind that different sensorimotor tasks are controlled by specialized subregions within the parietal, temporal, and frontal cortex [Culham et al., 2006; Goodale and Milner, 1992], which might depend not only on the sensorimotor demands per se but also on how the task is conceptualized [Alexander et al., 1992; Goldenberg and Hagmann, 1997; Grossi et al., 1999] or whether movements are performed in near versus far space [Weiss et al., 2000] or toward central versus peripheral targets [Khan et al., 2005].

SUMMARY AND CONCLUSIONS

This study identified hemispheric asymmetries in right-handed subjects while tracing a line pattern either with the dominant or nondominant hand. First, a right-lateralized

circuit centered around ventral frontoparietal cortex and corresponding to a previously identified ventral attention network (VAN) was activated regardless of the performing effector. This is the first study to demonstrate activation of this right-lateralized attention circuit during a (visuo)motor task. Moreover, our data suggest that this network responds not merely to unexpected, behaviourally relevant stimuli but also when spatial information is continuously exploited to modulate attention and to adapt behaviour.

Second, ipsilateral activity of motor areas was higher in the left hemisphere during nondominant hand tracing than in the right hemisphere when tracing with the dominant hand. This left dominant activation increase showed no significant association with interhemispheric inhibition as measured during rest/isometric contraction, to movement performance, or to handedness. We argue that the left hemisphere contains action representations that might contain information strongly related to movement implementation and that are also accessed during movements performed with the left body side.

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