



Handedness and effective connectivity of the motor system



Eva-Maria Pool^a, Anne K. Rehme^a, Gereon R. Fink^{b,c}, Simon B. Eickhoff^{c,d}, Christian Grefkes^{a,b,c,*}

^a Neuromodulation & Neurorehabilitation, Max Planck Institute for Neurological Research, 50931 Cologne, Germany

^b Department of Neurology, University of Cologne, 50924 Cologne, Germany

^c Institute of Neuroscience and Medicine (INM-1, INM-3), Jülich Research Centre, 52428 Jülich, Germany

^d Institute of Clinical Neuroscience and Medical Psychology, Heinrich Heine University, 40225 Düsseldorf, Germany

ARTICLE INFO

Article history:

Accepted 16 May 2014

Available online 23 May 2014

Keywords:

Dynamic causal modeling

Premotor cortex

Motor putamen

Right-handers

Left-handers

ABSTRACT

Handedness denotes the individual predisposition to consistently use the left or right hand for most types of skilled movements. A putative neurobiological mechanism for handedness consists in hemisphere-specific differences in network dynamics that govern unimanual movements.

We, therefore, used functional magnetic resonance imaging and dynamic causal modeling to investigate effective connectivity between key motor areas during fist closures of the dominant or non-dominant hand performed by 18 right- and 18 left-handers. Handedness was assessed employing the Edinburgh-Handedness-Inventory (EHI). The network of interest consisted of key motor regions in both hemispheres including the primary motor cortex (M1), supplementary motor area (SMA), ventral premotor cortex (PMv), motor putamen (Put) and motor cerebellum (Cb).

The connectivity analysis revealed that in right-handed subjects movements of the dominant hand were associated with significantly stronger coupling of contralateral (left, i.e., dominant) SMA with ipsilateral SMA, ipsilateral PMv, contralateral motor putamen and contralateral M1 compared to equivalent connections in left-handers. The degree of handedness as indexed by the individual EHI scores also correlated with coupling parameters of these connections. In contrast, we found no differences between right- and left-handers when testing for the effect of movement speed on effective connectivity.

In conclusion, the data show that handedness is associated with differences in effective connectivity within the human motor network with a prominent role of SMA in right-handers. Left-handers featured less asymmetry in effective connectivity implying different hemispheric mechanisms underlying hand motor control compared to right-handers.

© 2014 Elsevier Inc. All rights reserved.

Introduction

Handedness is a fundamental, behavioral characteristic of the motor system that evolves even before birth and stabilizes during early childhood (Fagard, 2013). While to date a formal definition of handedness is missing, it is widely accepted that handedness includes that (i) one hand is consistently preferred for carrying out a particular task, (ii) the same hand is chosen for the majority of tasks to be performed, and (iii) this hand is more proficient than the other in task performance (Hammond, 2002; Serrien et al., 2006). Experimental evidence suggests that this intrinsic behavioral phenomenon is associated with asymmetries in the structural and functional organization of the cerebral cortex (Amunts et al., 1996; Eickhoff et al., 2008; Hammond, 2002). For example, anatomical studies revealed a deeper central sulcus in the dominant compared to the non-dominant hemisphere in both right- and left-handers

(Amunts et al., 1996). Furthermore, neuroimaging studies demonstrated an influence of hand dominance on neural activity (Dassonville et al., 1997; Kim et al., 1993; Solodkin et al., 2001; Volkmann et al., 1998). In both right- and left-handers, dominant hand movements were shown to be associated with a greater volume of the hand representation in the contralateral primary motor cortex (M1) (Dassonville et al., 1997; Volkmann et al., 1998). Solodkin and colleagues mapped brain activation patterns in right- and left-handers during single and sequential finger movements and found larger volumes of activation and less hemispheric lateralization in left-handers (Solodkin et al., 2001). The latter finding is compatible with behavioral data demonstrating that hand preference in left-handers is often expressed to a lesser degree than in right-handers (Borod et al., 1984). Finally, transcranial magnetic stimulation (TMS) paradigms provided evidence for handedness-related asymmetries in cortical excitability (Brouwer et al., 2001; Ziemann and Hallett, 2001). Ziemann and Hallett (2001) demonstrated that performing a complex motor task with one hand increases the excitability of the motor cortex contralateral to the inactive hand. This increase was significantly smaller when the task was performed with the dominant (right) as opposed to the non-dominant (left) hand (Ziemann and Hallett, 2001). The authors

* Corresponding author at: Department of Neurology, University Hospital Cologne, Kerpener Straße 62, 50924 Cologne, Germany. Fax: +49 221 478 7005.

E-mail address: christian.grefkes@uk-koeln.de (C. Grefkes).

hypothesized that the dominant (left) motor cortex exerts more inhibitory control upon the contralateral motor cortex controlling the non-dominant left hand than vice versa. Taken together, the neural mechanisms for hand dominance might rest in hemispheric-specific differences of network dynamics that govern unimanual movements.

Accordingly, we here investigated whether the preference to use the right or left hand in everyday life is reflected by systematic differences in network interactions during unimanual movements. As outlined above, structural and functional neuroimaging studies have already addressed the neural correlates of handedness (Amunts et al., 1996; Dassonville et al., 1997; Kloppel et al., 2007; Solodkin et al., 2001; Volkmann et al., 1998). However, to date little is known about hand preference and the dynamics of the motor network. To this end, we addressed in a functional magnetic resonance imaging (fMRI) study the question whether there are differences in neural activity and interregional interaction of key motor regions between right- ($n = 18$) and left-handers ($n = 18$). Dynamic causal modeling (DCM) was used to assess effective connectivity, i.e., the causal influence that one area exerts upon activity of another (Friston et al., 2003), during unimanual movements of the dominant and non-dominant hands at different frequencies for a bihemispheric network consisting of key motor areas like M1, supplementary motor area (SMA), ventrolateral premotor cortex (PMv), motor putamen (Put) and motor cerebellum (Cb) (Grefkes et al., 2008; Passingham, 1997; Witt et al., 2008). We hypothesized that higher movement speed evokes a stronger BOLD signal especially in the contralateral primary sensorimotor cortex (Jancke et al., 1998; Sadato et al., 1996). Moreover, we hypothesized that movement-related connections are differentially modulated depending on whether subjects are right-handed or left-handed (Kloppel et al., 2007; Solodkin et al., 2001).

Materials and methods

Subjects

The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. Thirty-six subjects (18 right-handers [mean age 25.7 ± 3.0 SD; range: 22–34 years] and 18 left-handers [mean age 24.6 ± 2.6 SD; range: 19–30 years]) with no history of neurological or psychiatric disease gave written informed consent. The two groups were carefully matched for age, sex, and laterality of handedness. The fMRI and connectivity data of the right-handers were included in a previous publication (Pool et al., 2013).

Handedness measurements

Handedness was assessed by asking the subjects to complete the 10-item version of the Edinburgh-Handedness-Inventory (EHI) (Oldfield, 1971). The EHI assesses hand dominance in daily activities (e.g., writing, striking a match, holding a broom). The laterality quotient (LQ) of hand dominance ranges from -100 to 100 : an $LQ > 25$ indicates right-handedness, and an $LQ < -25$ indicates left-handedness (Pujol et al., 1999). In the present study, the median LQ of the right-handers group was 83 (range: 53 to 100) and the median LQ of the left-handers group was -73 (range: -30 to -100). We computed a Kruskal–Wallis H-test for non-parametric independent group comparisons which showed no significant difference in the degree of handedness between right- and left-handers ($P = 0.188$).

fMRI design

In order to probe neural activity in the motor system, we used a block-design task, where subjects were asked to perform fist closures with their right or left hand at three different frequencies: (i) 0.75 Hz, (ii) 1.5 Hz, and (iii) 3.0 Hz (Pool et al., 2013). The task to be performed

was announced on a shielded thin-film transistor (TFT) screen at the rear end of the scanner, which was visible via a mirror mounted to the MR head coil. Written instructions were displayed for 2 s indicating the hand to be moved in the upcoming block of trials. Then, the instructions were replaced by a white circle, which started to blink in red at the respective frequency. Blocks of fist closures (15 s) were separated by resting baselines (15 s plus a temporal jitter of 1–2.5 s) during which a black screen instructed the subjects to rest until the next instruction appeared. Each condition was repeated five times throughout the experiment. Block sequence was pseudo-randomized for each subject. The whole experiment consisted of 30 blocks and lasted ~18 min. Subjects were familiarized with the task twice, first outside the scanner, then inside the scanner. Each subject was able to perform the task without difficulties after a few practise trials due to the relative simplicity of the motor task.

Image acquisition and processing

Functional MR images were acquired on a Siemens Trio 3.0 T scanner using a gradient single-shot echo planar imaging (EPI) sequence with the following parameters: time of repetition (TR) = 2000 ms, time of echo (TE) = 3.0 ms, field of view (FOV) = 220×220 mm, flip angle = 90° , voxel size = $3.4 \times 3.4 \times 3.4$ mm³, volumes = 550 (3 dummy images), and slices = 32, interslice gap = 1 mm. Image slices were acquired in ascending order covering the whole brain from the cerebellum to the vertex. In addition, high-resolution T1-weighted structural images were acquired (TR = 2250 ms, TE = 3.93 ms, FOV = 256 mm, voxel size = $1.0 \times 1.0 \times 1.0$ mm³, slices = 176).

All analyses (fMRI, dynamic causal modeling) were carried out using Statistical Parametric Mapping (SPM8) (<http://www.fil.ion.ucl.ac.uk>; release 2009). We defined the “motor dominant hemisphere” as the hemisphere contralateral to the dominant hand (according to the EHI). To investigate the effect of hand dominance, the images of the left-handers were flipped at the midsagittal plane. Thus, for all subjects, after flipping the left hemisphere was defined to be the “motor dominant hemisphere”, while the right hemisphere corresponded to the “motor non-dominant hemisphere” contralateral to the non-dominant hand. After realignment of the EPI volumes and co-registration with the anatomical T1-weighted image, all volumes were spatially normalized to the standard template of the Montreal Neurological Institute employing the unified segmentation approach (Ashburner and Friston, 2005). Finally, data were smoothed using an isotropic Gaussian kernel of 8 mm full-width-at-half-maximum.

For statistical analyses, box-car vectors for each condition were convolved with a canonical hemodynamic response function as implemented in SPM8 to create the regressors of interest in the framework of the general linear model (GLM). We used a parametric analysis to identify neural activity that was modulated by different levels of movement frequency. SPMs were computed on a single subject level with onset regressors for each hand (dominant, non-dominant) and respective parametric regressors (1st order polynomial expansion) coding the frequency of a given condition (0.75 Hz, 1.5 Hz, and 3.0 Hz). The time series in each voxel were high-pass filtered at 1/128 Hz to remove low frequency drifts. Movement parameters as assessed by the realignment algorithm were treated as covariates to exclude movement-related variance from the image time series. Furthermore, the temporally jittered instruction period was separately modeled as an additional regressor, i.e., separated from the resting and the movement conditions, to capture BOLD variations related to it but not analyzed further in the group analysis.

The parameter estimates for all four conditions (main effect “dominant hand movements”, parametric modulation “dominant hand movements”, main effect “non-dominant hand movements”, parametric modulation “non-dominant hand movements”) were subsequently compared between the groups of left- and right-handers in a 2 (hand) \times 2 (main effect/modulation by movement frequency) \times 2 (group) full

factorial analysis of variance (ANOVA). Voxels were considered significant when passing a height threshold of $T > 4.2$ ($P < 0.05$, family wise error (FWE)-corrected at the voxel level).

Dynamic causal modeling

We used deterministic bilinear DCM (Friston et al., 2003) to assess effective connectivity between regions activated by the motor task. DCM is a hypothesis-driven approach to model effective connectivity between distinct brain regions. DCM provides three sets of parameters: (i) the endogenous coupling irrespective of the actual experimental condition (DCM A-matrix), (ii) the parameters for context-dependent changes in coupling evoked by the four experimental conditions (i.e., two main effects of hand movements (dominant hand, non-dominant hand)) and two parametric conditions, i.e., the frequency-dependent modulation (dominant hand, non-dominant hand) (DCM B-matrix), and (iii) the direct experimental input to the system that drives regional activity (DCM C-matrix).

As DCMs are computed at the single subject level, we extracted the first eigenvariate of the BOLD time-series, adjusted for effects of interest, from 8 regions-of-interest (ROIs) at subject specific coordinates. ROIs were defined as spheres (radius: 4 mm) centered upon individual activation maxima based on individually normalized SPMs. ROIs in the motor dominant hemisphere were identified using a conjunction analysis across all three movement frequencies of the dominant hand, while ROIs in the non-dominant hemisphere were identified in a conjunction analysis of the corresponding non-dominant hand conditions. The ROIs consisted of M1, SMA, PMv, motor putamen and motor cerebellum, i.e., core regions of the motor system engaged in isolated hand movements (Grefkes et al., 2008; Witt et al., 2008). We chose PMv as ROI rather than PMd as PMv neurons are especially engaged in grasping movements, while PMd neurons are predominantly engaged in arm/reaching movements (Grefkes and Fink, 2005; Rizzolatti and Luppino, 2001; Rottschy et al., 2013). The preference of PMv for hand motor function was also reflected by the BOLD fMRI data of the present study which clearly showed a separable PMv cluster while PMd was only weakly activated and the area of activation extended typically into the M1 activation cluster (Fig. 1).

As individual activation maxima may vary substantially across subjects (Eickhoff et al., 2009), we ensured comparability by selecting coordinates according to the following anatomical constraints: M1 on the rostral wall of the central sulcus at the “hand knob” formation (Yousry et al., 1997), SMA on the mesial wall within the interhemispheric fissure between the paracentral lobule (posterior landmark) and the anterior commissure (Picard and Strick, 2001), PMv situated in the precentral sulcus close to the inferior precentral gyrus and pars opercularis (Rizzolatti et al., 2002), the mediolateral central part of the putamen (Put) (Nambu et al., 2002) and the superior part of the anterior lobe of the cerebellum (Cb) (Diedrichsen et al., 2009). All ROIs were extracted in each subject from both hemispheres using a threshold of $P < 0.001$ (uncorrected). The coordinates of all individual ROIs are given in Supplemental Table 1.

Based on structural connectivity data derived from invasive studies in macaque monkeys (Akkal et al., 2007; Boussaoud et al., 2005; Hoshi et al., 2005; Kelly and Strick, 2003; Luppino et al., 1993; Middleton and Strick, 2000; Rouiller et al., 1994), we assumed endogenous connections (DCM A-matrix) as specified in Table 1. Note that connections between the cerebellum and cortical areas are relayed via the thalamus, and hence the coupling parameters from and to the cerebellum reflect the ‘net effect’ of this disynaptic connection. This notion also applies for any other indirect connection captured by the coupling parameters. We furthermore assumed a direct effect of the motor task (DCM C-matrix, input regions) on the activity of all premotor regions (dominant/non-dominant SMA, dominant/non-dominant PMv) (Goldman-Rakic et al., 1992; Wang et al., 2011).

Bayesian model selection

Based on the DCM A-matrix, we set up alternative models of varying complexity representing biologically plausible hypotheses on inter-regional coupling among ROIs during movements of the right or left hand at different frequencies (DCM B-matrix). Starting from a fully connected DCM B-matrix with 90 connections, we constructed 31 models according to (i) the presence of modulatory effects on inter-hemispheric connections, and (ii) the lateralization of coupling towards M1 contralateral to the moving hand (Supplemental Fig. 1; cf. Pool et al., 2013). At first, we omitted heterotopic interhemispheric connections between the premotor areas, putamen, cerebellum and M1 (models 2–5). Then we successively removed heterotopic interhemispheric connections between cortical and subcortical motor areas (models 6–11) as well as homotopic connections between motor areas (models 12–16). Finally, all interhemispheric connections were removed (model 16), resulting in very simple models with only a few connections. Afterwards, the same strategy was applied to lateralized models which contained connections only towards M1 contralateral to the moving hand (models 17–31). We then used random effects Bayesian model selection (BMS) to identify the model with the highest posterior evidence, that is, the model which is the most likely generative model given the data (Stephan et al., 2009). To compute the total mean variance explained by this model we used a `spm_dcm_fmri_check.m` script by Karl Friston (2012; <https://www.jiscmail.ac.uk/cgi-bin/webadmin?A2=spm;bebd494.1203>).

Statistical analysis of DCM coupling parameters

The coupling parameters of the most likely generative model were tested for statistical significance using a one sample *t*-test ($P < 0.05$, false discovery rate (FDR)-corrected for multiple comparisons). Connections that were linearly modulated by different hand movement frequencies were separately identified from the DCM B-matrix by parametric modulation effects for the dominant or non-dominant hand.

To test for differences in endogenous or task-dependent neural coupling between right- and left-handers, coupling strengths of corresponding connections were compared using independent 2-sample *t*-tests.

We additionally computed correlation analyses between EHI scores and (i) BOLD activity, and (ii) effective connectivity during movements of the dominant or non-dominant hand.

Results

Neural activity during unilateral fist closures

Visually paced fist closures of the dominant or the non-dominant hand were associated with enhanced BOLD activity in a network of cortical and subcortical areas comprising contralateral primary motor cortex (M1), bilateral supplementary motor area (SMA), and bilateral ventral premotor cortex (PMv), bilateral motor putamen (Put), bilateral anterior lobe of the cerebellum (Cb), and bilateral primary visual (V1) and extrastriate cortex ($P < 0.05$, FWE-corrected, Fig. 1A). Please note that hemispheres were flipped along the x-axis for the left-handers. There was no significant difference in BOLD activity when comparing right-handers with left-handers, neither for movements of the dominant hand, nor for movements of the non-dominant hand.

When testing for the effect of the parametric regressor reflecting different movement frequencies at 0.75 Hz, 1.5 Hz, or 3.0 Hz for dominant and non-dominant hand movements in left-handers and right-handers separately, we found significant clusters of voxels situated in contralateral M1 ($P < 0.05$, FWE-corrected, Fig. 1B):

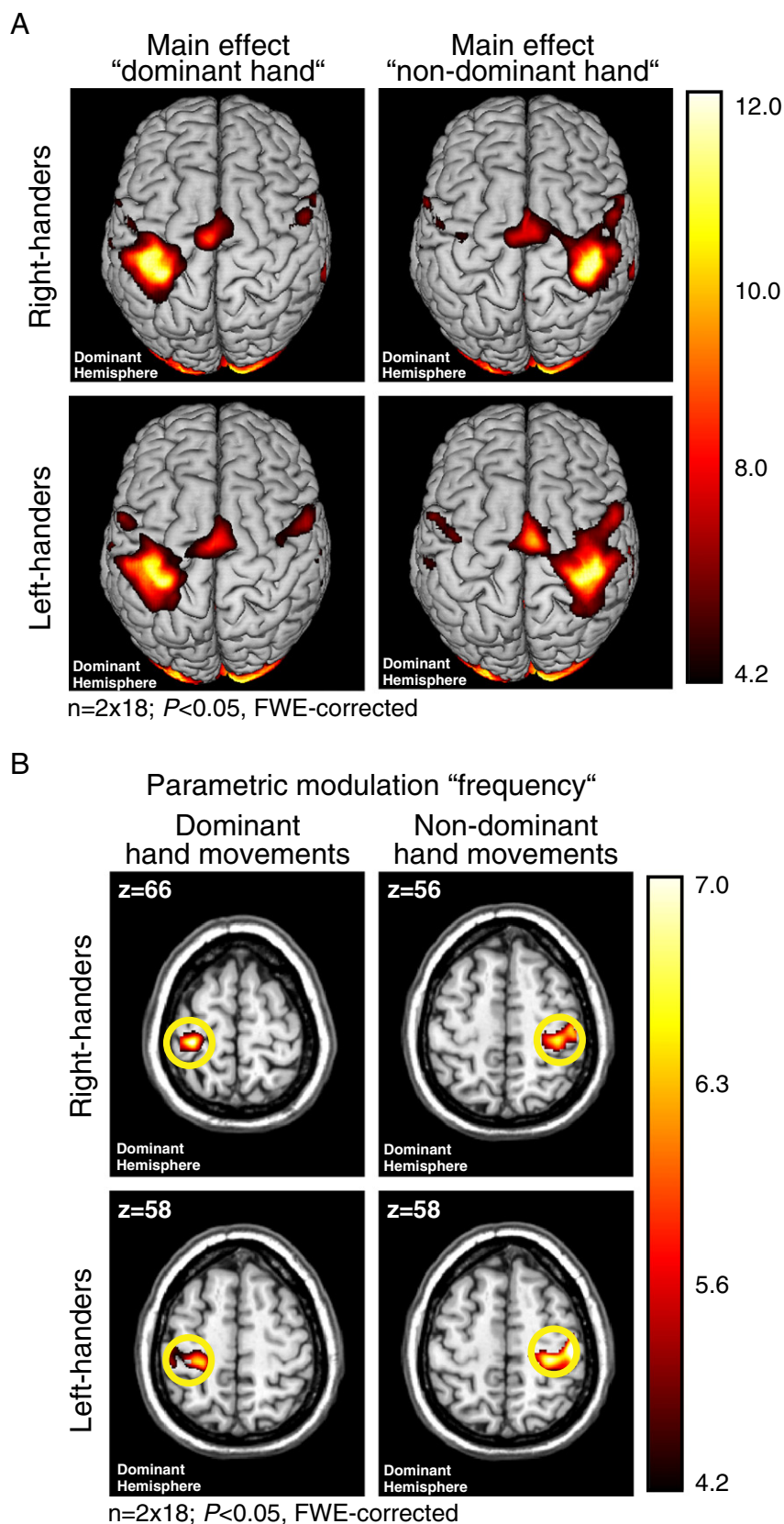


Fig. 1. Neural activity for A visually paced fist closures (main effect “hand”) and B the parametric modulation of “frequency” ($n = 2 \times 18$; $P < 0.05$, FWE-corrected).

BOLD activity in contralateral M1 positively correlated with higher movement frequencies. However, there were no significant group differences in frequency-dependent changes in BOLD

activity between right- and left-handers, neither for movements of the dominant hand, nor for movements of the non-dominant hand.

Table 1
Anatomical references for endogenous connectivity (DCM A-matrix).

Connection	Reference
SMA → PMv	Luppino et al. (1993)
SMA → M1	Rouiller et al. (1994)
SMA → Put	Akkal et al. (2007)
SMA → Cb	Akkal et al. (2007)
PMv → SMA	Boussaoud et al. (2005)
PMv → M1	Rouiller et al. (1994)
PMv → Put	Middleton and Strick (2000)
PMv → Cb	Middleton and Strick (2000)
M1 → SMA	Rouiller et al. (1994)
M1 → PMv	Rouiller et al. (1994)
M1 → Put	Middleton and Strick (2000)
M1 → Cb	Middleton and Strick (2000)
Put → SMA	Kelly and Strick (2003)
Put → PMv	Middleton and Strick (2000)
Put → M1	Middleton and Strick (2000)
Put → Cb	Hoshi et al. (2005)
Cb → SMA	Akkal et al. (2007)
Cb → PMv	Middleton and Strick (2000)
Cb → M1	Middleton and Strick (2000)
Cb → Put	Hoshi et al. (2005)

SMA = supplementary motor area, PMv = ventral premotor cortex, M1 = primary motor cortex, Put = motor putamen, Cb = motor cerebellum.

Connectivity analysis

Bayesian model selection

We used dynamic causal modeling (DCM) to estimate effective connectivity in a bilateral network of key motor areas. We evaluated

31 different network models (Supplemental Fig. 1) reflecting biologically plausible hypotheses about the context-specific modulations of inter-regional coupling. According to random-effects Bayesian model selection, the “fully connected” model (assuming connectivity between all ROIs) showed the highest exceedance probability of all tested models for the entire group as well as for right- and left-handers separately. It was hence considered the most likely generative model of our data (Fig. 2). With respect to the divergence between prior and posterior parameter distributions, we computed total mean variance explained and its standard-deviation. On average $39\% \pm 11\%$ of variance (range: 14–63%, Supplemental Fig. 2) was explained by the winner model.

Endogenous coupling (DCM A)

Fig. 3 displays the coupling parameters reflecting endogenous connectivity among the motor areas of interest independent of the conditional context (task/rest) ($P < 0.05$, FDR-corrected for multiple comparisons; see also Supplemental Table II for coupling strengths and P -values). The coupling parameters represent connection strengths, describing how fast and strong a response occurs in the target region (Friston et al., 2003). Positive coupling parameters (green arrows) suggest a facilitation of neural activity, whereas negative coupling parameters (red arrows) can be interpreted as inhibition of neural activity. The term “dominant hemisphere” was defined to refer to the hemisphere contralateral to the dominant hand.

In both right- and left-handers, endogenous coupling of neural activity between the motor areas of interest was symmetrically organized across hemispheres (left: dominant hemisphere). The most prominent positive influence on intrinsic M1 activity was exerted by ipsilateral SMA and PMv in both right- and left-handers. In contrast, endogenous coupling

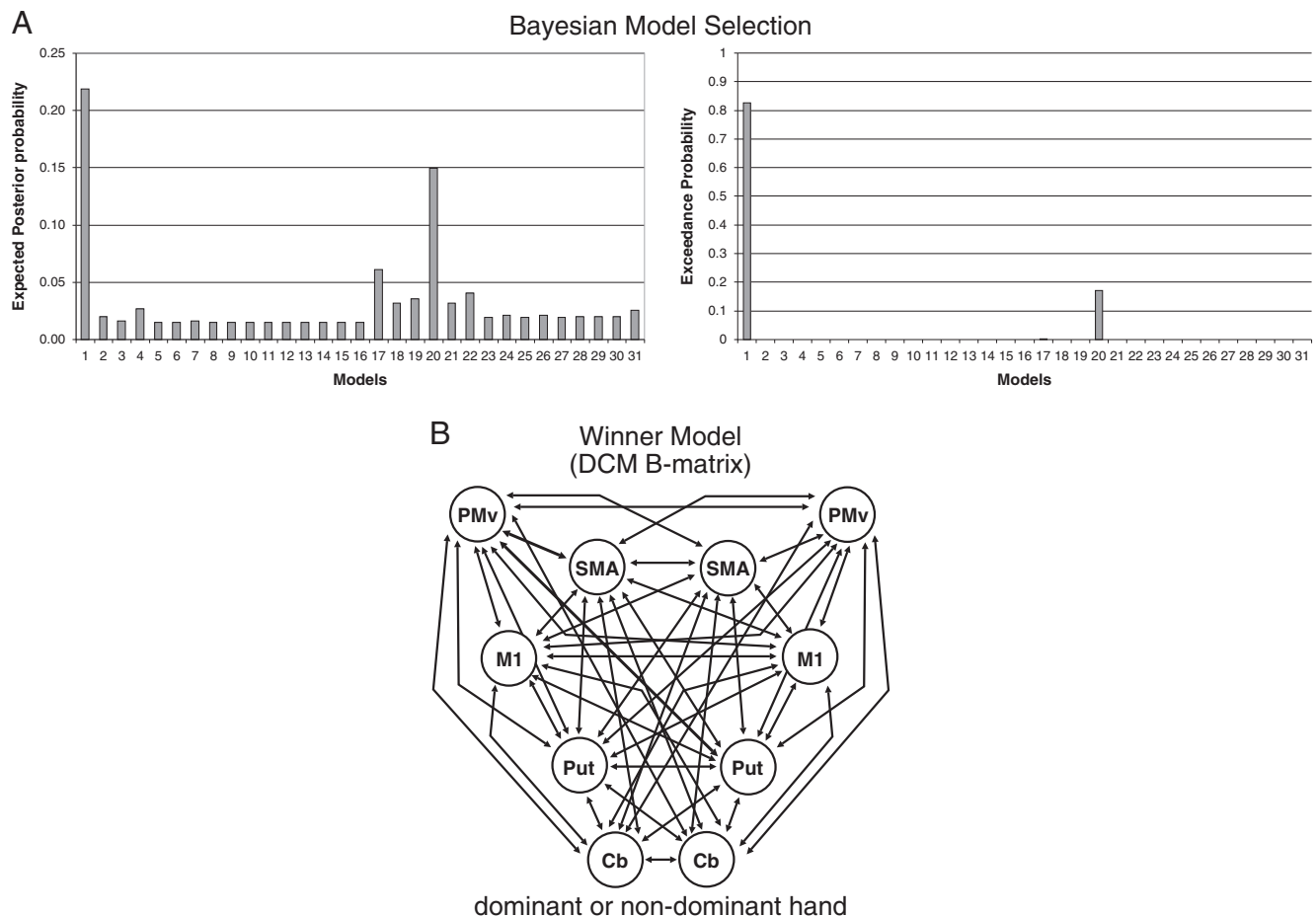


Fig. 2. A Bayesian model selection and B the winner model.

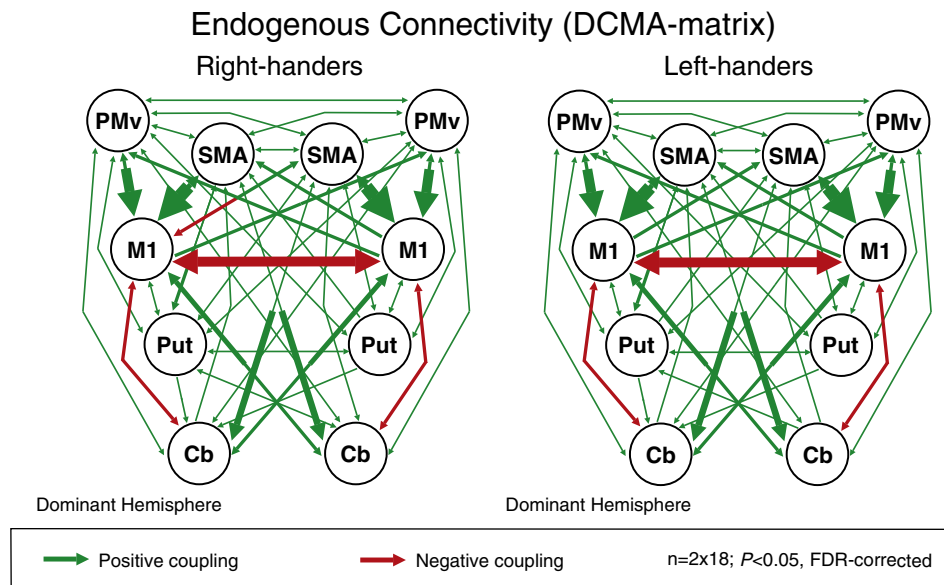


Fig. 3. Endogenous connectivity (DCM A-matrix; $n = 2 \times 18$; $P < 0.05$, FDR-corrected). Green arrows = positive coupling rates, red arrows = negative coupling rates. The width of each arrow corresponds to the coupling strength. In left-handers, the inhibitory connection ndSMA \rightarrow dM1 is significant at an uncorrected threshold ($P < 0.05$). For mean coupling parameters and P -values (one-sample t -test against zero) see Supplemental Table II.

between the putamen, cerebellum, and ipsilateral M1 was less pronounced. Intra-hemispheric interactions between M1–Put as well as inter-hemispheric interactions between SMA–M1 and M1–M1 were inhibitory.

Differences between right- and left-handers (DCM A)

When testing for differences between right- and left-handers, we found no significant handedness-dependent effects.

Task-induced changes in neural coupling (DCM B, main effect of hand)

Fig. 4 depicts the effect of unilateral fist closures on the interregional coupling between the motor areas of interest (DCM B-matrix) ($P < 0.05$, FDR-corrected; see also Supplemental Tables IIIa and IIIb for coupling strengths and P -values). When right-handers ($n = 18$) or left-handers ($n = 18$) moved their dominant hand, neural activity in the contralateral M1 was driven by stronger bilateral coupling with the SMA, PMv, putamen, and cerebellum. In contrast, the influence of premotor regions on M1 ipsilateral to the moving hand was negative suggesting that activity of this region was inhibited. Movements of the non-dominant hand evoked a mirror-reversed pattern of motor network modulations in both groups.

When comparing coupling parameters of the dominant hand with corresponding parameters of the non-dominant hand, we found a stronger excitatory influence on SMA exerted by contralateral M1, contralateral putamen, ipsilateral PMv, ipsilateral cerebellum and ipsilateral SMA ($P < 0.05$, FDR-corrected). In addition, there was a stronger influence from ipsilateral SMA onto ipsilateral cerebellum and both ipsi- and contralateral M1 ($P < 0.05$, FDR-corrected). Our data further revealed a significant stronger inhibitory influence from ipsilateral SMA towards ipsilateral M1 in right-handers while performing movements with the dominant (right) hand ($P < 0.05$, FDR-corrected). In left-handers, we did not find such differences between the dominant and non-dominant hand.

Differences between right- and left-handers (DCM B, main effect of hand)

When testing for differences between right- and left-handers, we found significant effects only for the dominant but not for the non-dominant hand. For dominant hand movements, neural coupling strength exerted from contralateral (dominant) SMA upon contralateral (dominant) M1 was significantly stronger in right-handers as compared to left-handers ($P < 0.05$, FDR-corrected; Fig. 5). Similarly, right-handers

featured significantly stronger influences exerted by contralateral M1, contralateral putamen, ipsilateral SMA as well as ipsilateral PMv onto contralateral SMA, and vice versa, during dominant hand movements. This means that particularly connections from and to contralateral (dominant) SMA showed stronger couplings when right-handers moved their dominant, right hand as compared to left-handers moving their dominant hand.

Spearman rank correlations between EHI scores and DCM parameters (Table 2, FDR-corrected for multiple comparisons) revealed significant correlations between EHI scores and coupling parameters for the same connections as reported above for the t -tests comparing neural coupling between right- and left-handers. This finding indicates that also the individual predisposition to preferentially use the right hand was linked to higher coupling parameters of contralateral SMA with other motor areas. In contrast, we found no significant correlations between EHI scores and DCM coupling parameters during movements of the non-dominant hand.

Frequency-dependent changes of neural coupling (DCM B-matrix, parametric modulation)

In a previous publication with a larger sample of subjects ($n = 36$) (Pool et al., 2013), we demonstrated that in right-handers movements at higher frequencies were associated with a linear increase in neural coupling strengths from contralateral premotor areas (SMA, PMv) towards contralateral M1. When testing for this frequency effect in the present data with a sub-sample of this group ($n = 18$), the DCM analysis confirmed that right-handers showed increasing excitatory influences from contralateral SMA and ipsilateral PMv onto contralateral M1 associated with higher frequencies during dominant hand movements ($P < 0.05$, FDR-corrected). During non-dominant hand movements, this effect was only significant from contralateral SMA onto contralateral M1 ($P < 0.05$, FDR-corrected). This constitutes a replication of our previous analysis with 36 right-handers (Pool et al., 2013). When testing for frequency-dependent coupling changes during movements of the dominant hand in left-handers, we found no significant effect after FDR correction ($P > 0.05$). At an uncorrected threshold ($P < 0.05$), the DCM analysis showed that increasing movement rate was associated with a stronger excitatory influence from contralateral PMv onto contralateral M1 as well as a stronger inhibitory influence from contralateral SMA onto ipsilateral M1. During movements of the non-dominant hand,

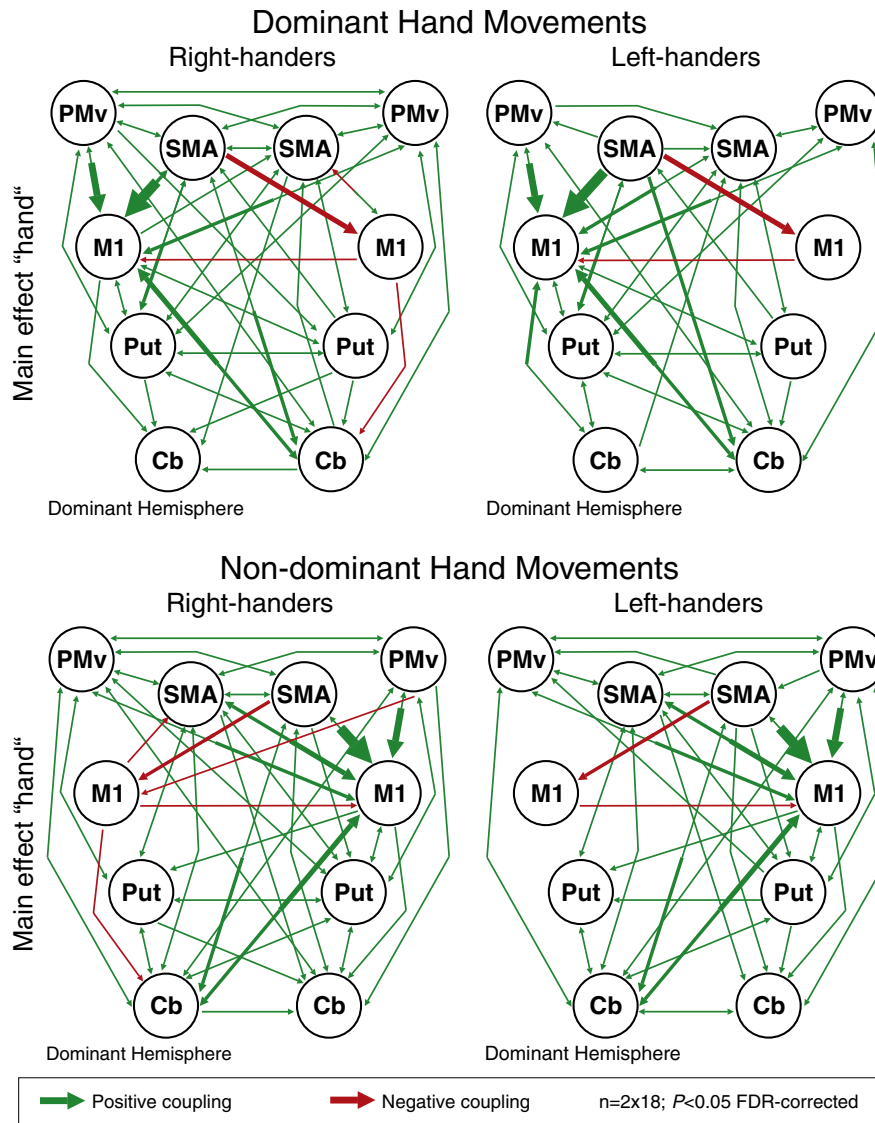


Fig. 4. Modulatory effects on effective connectivity (main effect “hand”) during right and left hand fist closures (DCM B-matrix; $n = 2 \times 18$; $P < 0.05$, FDR-corrected). Green arrows = positive coupling rate, red arrows = negative coupling rates. The width of each arrow corresponds to the coupling strength. For mean coupling parameters and P -values (one-sample t -test against zero) see Supplemental Tables IIIa and IIIb.

again no connection survived FDR correction. At uncorrected thresholds, a frequency-dependent effect could also be observed from contralateral SMA onto ipsilateral M1.

Differences between right- and left-handers (parametric modulation)

When testing for frequency-dependent differences between right- and left-handers, we found no significant effect after FDR correction ($P > 0.05$).

Discussion

We found that during dominant hand movements, neural coupling of contralateral (dominant) SMA with premotor areas, motor putamen and M1 was significantly higher in right-handers as compared to left-handers. Moreover, our results revealed a positive correlation between neural coupling strengths and the Edinburgh Handedness Inventory (EHI) scores during movements of the dominant hand. Together, our findings indicate that a stronger preference to use the right hand corresponds to stronger neural coupling of contralateral SMA when performing dominant hand movements.

Neural activity and handedness

Although several neuroimaging studies have already addressed the issue of handedness (Dassonville et al., 1997; Kim et al., 1993; Kloppel et al., 2007; Siebner et al., 2002; Solodkin et al., 2001; Volkmann et al., 1998), to date our understanding of the relationship between handedness and brain activation remains incomplete. For example, Kim and colleagues observed that right-handers relative to left-handers had larger ipsilateral activation volumes in M1 when performing a repetitive finger–thumb opposition task (Kim et al., 1993). In contrast, Solodkin et al. (2001) reported that right- and left-handers only showed differences in complex motor tasks, while simple hand movements – comparable to those implemented in the present study – did not evoke significant differences in neural activity (Solodkin et al., 2001). In line with the latter finding, we did not find any statistically significant differences in activation clusters between right- and left-handers. The relative simplicity of the task used in the present study also implies that any differences between right- and left-handers were not due to differences in task complexity, but rather reflect “true” differences in neural coupling.

Differences between right- and left-handers

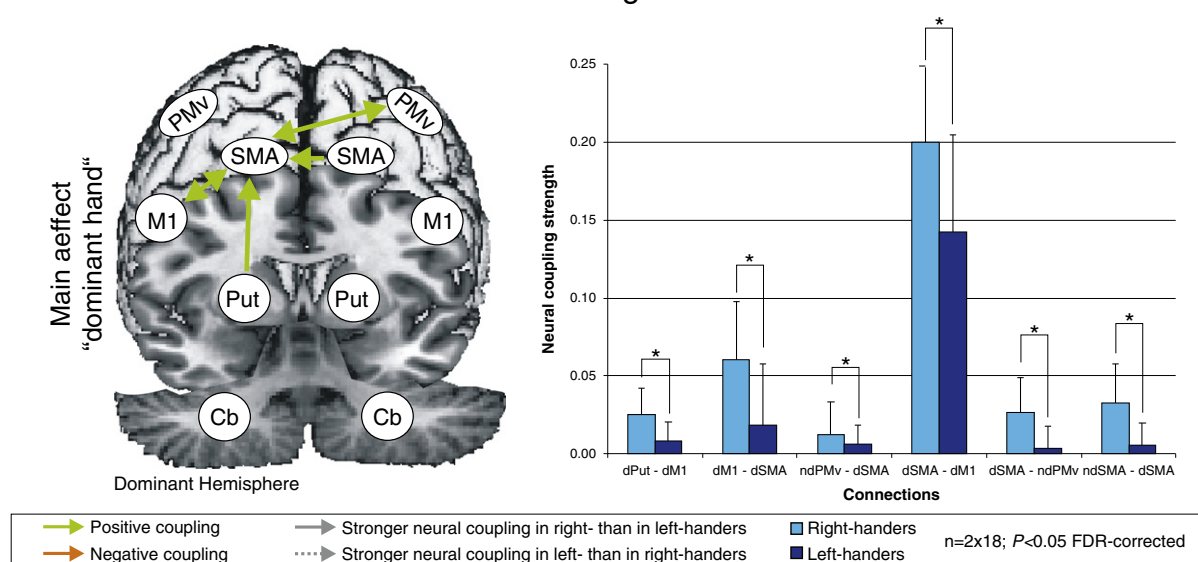


Fig. 5. Differences between right- and left-handers when performing dominant hand movements (* $P < 0.05$, FDR-corrected).

Effective connectivity and handedness

Neural coupling between SMA and M1

At the connectivity level, contralateral SMA exerted a stronger excitatory influence upon contralateral M1 in right-handers as compared to left-handers, when performing dominant hand movements (Fig. 5). The SMA is strongly engaged in movement sequencing and pacing (Jakobs et al., 2009; Jenkins et al., 2000; Passingham, 1989). A number of studies have shown that especially neurons in SMA have hemispheric-specific functional properties (Dum and Strick, 2002; Fried et al., 1991; Hoshi and Tanji, 2004). For example, tract-tracing studies in monkeys revealed that SMA neurons exhibit dense axonal projections to M1 neurons, especially between the respective hand representations of the two areas (Dum and Strick, 2002). Moreover, Hoshi and Tanji (2004) investigated neuronal activity in monkeys performing a target-reach task by following two sets of instructions (the target location and the hand to use to reach the target). These data revealed a selective activity of SMA neurons for either the ipsilateral or the contralateral arm, indicating that the SMA participates in selecting which hand has to be used (Hoshi and Tanji, 2004).

Furthermore, several fMRI studies reported a dominant role of left SMA in right-handers (Babiloni et al., 2003; Jancke et al., 2000; Rogers et al., 2004). Rogers et al. (2004) investigated effective connectivity between SMA and sensorimotor cortex in right-handers using structural equation modeling (Rogers et al., 2004). The authors observed that the positive influence of contralateral SMA on contralateral sensorimotor

cortex was stronger during movements of the dominant right hand compared to corresponding connections during movements of the non-dominant left hand. Similar effects were also found in the present study for right-handers. Our data furthermore revealed a stronger inhibitory influence from ipsilateral SMA towards ipsilateral M1 during dominant hand movements as compared to non-dominant hand movements.

In contrast to right-handers, left-handers showed no significant changes in effective connectivity between movements of their dominant or non-dominant hand suggesting that left-handers featured a lack of lateralization to the dominant hand-hemisphere system. This functional finding fits with structural data reported in anatomical studies showing that left-handers compared to right-handers featured less asymmetry with respect to the volume of intracortical connections in the hemisphere contralateral to the preferred hand (Amunts et al., 1996).

Neural coupling between premotor areas and SMA

Interestingly, we found that effective connectivity among the premotor areas of interest was significantly stronger in subjects who preferred their right hand for manual skills, especially with respect to the SMA contralateral to the dominant hand. Several studies already demonstrated that premotor areas, in general, are richly interconnected (Dum and Strick, 2005). The SMA, of all premotor regions, has the densest and most balanced reciprocal connections with the contralateral SMA, premotor cortex as well as with M1 (Boussaoud et al., 2005; Dum and Strick, 2005; Luppino et al., 1993; Rouiller et al., 1994). Major connections between the SMA and PMv have been reported in macaques (Johnson and Ferraina, 1996; Kurata, 1991) and galagos (Fang et al., 2005). These findings correspond well to our connectivity results suggesting a general principle of brain organization with a prominent role of contralateral (dominant) SMA that is stronger interconnected with ipsilateral PMv and ipsilateral SMA in right-handers when performing dominant hand movements as compared to left-handers (Fig. 5). Hence, the degree of effective connectivity of contralateral SMA corresponds to right-handedness and might, therefore, be important for hemispheric-specific control of dominant hand movements in right-handers. In contrast, this effect could not be observed in the opposite direction. Our results thus indicate a differential recruitment profile for left-handers reflected by a weaker effective connectivity network of contralateral SMA when performing dominant hand movements. Corresponding to this, Buckingham and colleagues investigated motor attention in right- and left-handers by combining a discontinuous double-step reaching task

Table 2
Spearman rank correlations between EHI scores and effective connectivity.

Dominant hand movements		Non-dominant hand movements	
dM1 - dSMA	Spearman-Rho	.562	No significant correlations with EHI
	p-value	.012*	
ndSMA - dSMA	Spearman-Rho	.572	
	p-value	.019*	
ndPMv - dSMA	Spearman-Rho	.487	
	p-value	.045*	
dPut - dSMA	Spearman-Rho	.537	
	p-value	.017*	

(d = dominant hemisphere, contralateral to the dominant hand; nd = non-dominant hemisphere, contralateral to the non-dominant hand).

* $P < 0.05$, FDR-corrected for multiple comparisons; $n = 28$.

with a Posner-style hand cueing paradigm (Buckingham et al., 2011). The authors demonstrated that right-handers needed more time to inhibit their dominant hand, indicating that their dominant hand was more readily primed to move than their non-dominant hand while left-handers showed neither of these asymmetries, indicating that they lack an equivalent attentional bias for the dominant hand (Buckingham et al., 2011). This finding nicely fits our observation of generally stronger intra- and interhemispheric effective connectivity in right-handers during movements of the dominant hand.

Neural coupling between putamen and SMA

In addition to cortical areas, we found that effective connectivity from contralateral putamen on contralateral SMA was also significantly stronger in subjects who preferred their right hand. The putamen receives somatotopic projections from the sensorimotor cortex and is involved in the facilitation and inhibition of actions (Alexander and Crutcher, 1990). Studies further suggested a role of the putamen in the automation of previously learned movements (Griffiths et al., 1994) as well as in timing mechanisms (Macar et al., 2004; Rao et al., 2001). For example, Macar and colleagues used event-related fMRI to investigate healthy right-handed subjects when performing a timing task and a force task (Macar et al., 2004). As expected, the authors revealed an important role of the putamen in timing mechanisms, but also observed prominent activation of SMA during the timing task (Macar et al., 2004). The authors concluded that timing processes could be subserved by a striato-thalamo-cortical pathway including the SMA. Similar effects might also underlie the stronger influence exerted by the putamen onto SMA in right-handers for the dominant hand, as observed in the present study. Moreover, de la Fuente-Fernandez et al. (2000) investigated healthy right-handed subjects by using [^{18}F]fluorodopa positron emission tomography and showed that the degree of right hand preference correlated with fluorodopa uptake in the left putamen. This finding is well in line with our results and suggests a role of the putamen in motor lateralization (de la Fuente-Fernandez et al., 2000).

Limitations and conclusion

One limitation of our study pertains to the limited number of areas included in the connectivity model. Areas known to be involved in the motor control of even simple hand movements, e.g. prefrontal and parietal cortices (Filimon, 2010; Goldman-Rakic, 1987), had to be excluded from the analysis because of the technical and computational limitations of DCM in its current implementation. In DCM, model complexity is penalized by more conservative shrinkage priors which make it more difficult for a given connection to become significant. The reason for this is that the priors on the connectivity parameters ensure that the system remains stable (Friston et al., 2003). Hence, the number of included regions in DCM is always a trade-off between model fit and generalizability. Therefore, that we found significant connections despite a rather complex model (10 regions, 90 connections) highlights the robustness of the data. Moreover, left-handers featured less asymmetry in effective connectivity, despite clear preference to use their left hand for everyday life tasks. We cannot disentangle whether this effect arises from the fact that left-handers live in an environment that is rather made for right-handers (and hence they are more often forced to use their non-dominant right hand which might also affect cortical connectivity). However, the relative simplicity of the motor task used in the present study makes it rather unlikely that relevant use-dependent effects in every-day life may have influenced the differences found between right- and left-handed subjects. It is interesting to note that differences between right- and left-handers were only evident in the connectivity data but not in the “classical” BOLD activation analysis. That connectivity analyses of motor system activity can have higher sensitivity compared to activation analyses has also been shown by Sharma et al. (2009). A reason for that might rest in the region of interest approach used in DCM which corrects for residual interindividual variability in the precise

anatomical location of premotor areas in individual subjects. Likewise, in DCM, the hemodynamic response function (HRF) is computed for each and every ROI separately (Friston et al., 2003) in contrast to the “classical” activation analysis, which uses a canonical HRF for all voxels. Hence, DCM better accounts for variability of the HRF between regions, which might further increase its sensitivity for detecting differences between groups of subjects.

In conclusion, the present study suggests that handedness is associated with differences in effective connectivity within the human motor network. Our results reveal a general principle of brain organization with a prominent role of dominant SMA in right-handers. Moreover, our data indicate a strong lateralization in the dominant hand-hemisphere system when performing dominant hand movements. Left-handers showed a weaker asymmetry in motor network connectivity implying different hemispheric mechanism of hand motor control as compared to right-handers.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2014.05.048>.

Acknowledgments

We thank our volunteers and are grateful to Dr Marc Tittgemeyer and the MR staff for the support. CG was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft GR 3285/2-1). SBE was supported by the Deutsche Forschungsgemeinschaft (DFG, EI 816/4-1; S.B.E. and LA 3071/3-1), the National Institute of Mental Health (R01-MH074457) and the Helmholtz Initiative on Systems Biology. GRF gratefully acknowledges support from the Marga and Walter Boll Stiftung.

Declaration of conflict of interests

The authors declare that they have no competing interests.

References

- Akkal, D., Dum, R.P., Strick, P.L., 2007. Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. *J. Neurosci.* 27 (40), 10659–10673.
- Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci.* 13 (7), 266–271.
- Amunts, K., Schlaug, G., Schleicher, A., Steinmetz, H., Dabringhaus, A., Roland, P.E., Zilles, K., 1996. Asymmetry in the human motor cortex and handedness. *Neuroimage* 4 (3 Pt 1), 216–222.
- Ashburner, J., Friston, K.J., 2005. Unified segmentation. *Neuroimage* 26 (3), 839–851.
- Babiloni, C., Carducci, F., Del Gratta, C., Demartin, M., Romani, G.L., Babiloni, F., Rossini, P.M., 2003. Hemispherical asymmetry in human SMA during voluntary simple unilateral movements. An fMRI study. *Cortex* 39 (2), 293–305.
- Borod, J.C., Caron, H.S., Koff, E., 1984. Left-handers and right-handers compared on performance and preference measures of lateral dominance. *Br. J. Psychol.* 75 (Pt 2), 177–186.
- Boussaoud, D., Tanne-Gariepy, J., Wannier, T., Rouiller, E.M., 2005. Callosal connections of dorsal versus ventral premotor areas in the macaque monkey: a multiple retrograde tracing study. *BMC Neurosci.* 6, 67.
- Brouwer, B., Sale, M.V., Nordstrom, M.A., 2001. Asymmetry of motor cortex excitability during a simple motor task: relationships with handedness and manual performance. *Exp. Brain Res.* 138 (4), 467–476.
- Buckingham, G., Main, J.C., Carey, D.P., 2011. Asymmetries in motor attention during a cued bimanual reaching task: left and right handers compared. *Cortex* 47 (4), 432–440.
- Dassonville, P., Zhu, X.H., Uurbil, K., Kim, S.G., Ashe, J., 1997. Functional activation in motor cortex reflects the direction and the degree of handedness. *Proc. Natl. Acad. Sci. U. S. A.* 94 (25), 14015–14018.
- de la Fuente-Fernandez, R., Kishore, A., Calne, D.B., Ruth, T.J., Stoessl, A.J., 2000. Nigrostriatal dopamine system and motor lateralization. *Behav. Brain Res.* 112 (1–2), 63–68.
- Diedrichsen, J., Balsters, J.H., Flavell, J., Cussans, E., Ramnani, N., 2009. A probabilistic MR atlas of the human cerebellum. *Neuroimage* 46 (1), 39–46.
- Dum, R.P., Strick, P.L., 2002. Motor areas in the frontal lobe of the primate. *Physiol. Behav.* 77 (4–5), 677–682.
- Dum, R.P., Strick, P.L., 2005. Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. *J. Neurosci.* 25 (6), 1375–1386.
- Eickhoff, S.B., Grefkes, C., Fink, G.R., Zilles, K., 2008. Functional lateralization of face, hand, and trunk representation in anatomically defined human somatosensory areas. *Cereb. Cortex* 18 (12), 2820–2830.

- Eickhoff, S.B., Heim, S., Zilles, K., Amunts, K., 2009. A systems perspective on the effective connectivity of overt speech production. *Philos. Trans. A Math. Phys. Eng. Sci.* 367 (1896), 2399–2421.
- Fagard, J., 2013. The nature and nurture of human infant hand preference. *Ann. N. Y. Acad. Sci.* 1288, 114–123.
- Fang, P.C., Stepniewska, I., Kaas, J.H., 2005. Ipsilateral cortical connections of motor, premotor, frontal eye, and posterior parietal fields in a prosimian primate, *Otolemur garnetti*. *J. Comp. Neurol.* 490 (3), 305–333.
- Filimon, F., 2010. Human cortical control of hand movements: parietofrontal networks for reaching, grasping, and pointing. *Neuroscientist* 16 (4), 388–407.
- Fried, I., Katz, A., McCarthy, G., Sass, K.J., Williamson, P., Spencer, S.S., Spencer, D.D., 1991. Functional organization of human supplementary motor cortex studied by electrical stimulation. *J. Neurosci.* 11 (11), 3656–3666.
- Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. *Neuroimage* 19 (4), 1273–1302.
- Goldman-Rakic, P.S., 1987. Motor control function of the prefrontal cortex. *Ciba Found. Symp.* 132, 187–200.
- Goldman-Rakic, P.S., Bates, J.F., Chafee, M.V., 1992. The prefrontal cortex and internally generated motor acts. *Curr. Opin. Neurobiol.* 2 (6), 830–835.
- Grefkes, C., Fink, G.R., 2005. The functional organization of the intraparietal sulcus in humans and monkeys. *J. Anat.* 207 (1), 3–17.
- Grefkes, C., Eickhoff, S.B., Nowak, D.A., Dafotakis, M., Fink, G.R., 2008. Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. *Neuroimage* 41 (4), 1382–1394.
- Griffiths, P.D., Perry, R.H., Crossman, A.R., 1994. A detailed anatomical analysis of neurotransmitter receptors in the putamen and caudate in Parkinson's disease and Alzheimer's disease. *Neurosci. Lett.* 169 (1–2), 68–72.
- Hammond, G., 2002. Correlates of human handedness in primary motor cortex: a review and hypothesis. *Neurosci. Biobehav. Rev.* 26 (3), 285–292.
- Hoshi, E., Tanji, J., 2004. Differential roles of neuronal activity in the supplementary and presupplementary motor areas: from information retrieval to motor planning and execution. *J. Neurophysiol.* 92 (6), 3482–3499.
- Hoshi, E., Tremblay, L., Feger, J., Carras, P.L., Strick, P.L., 2005. The cerebellum communicates with the basal ganglia. *Nat. Neurosci.* 8 (11), 1491–1493.
- Jakobs, O., Wang, L.E., Dafotakis, M., Grefkes, C., Zilles, K., Eickhoff, S.B., 2009. Effects of timing and movement uncertainty implicate the temporo-parietal junction in the prediction of forthcoming motor actions. *Neuroimage* 47 (2), 667–677.
- Jancke, L., Specht, K., Mirzazade, S., Loose, R., Himmelbach, M., Lutz, K., Shah, N.J., 1998. A parametric analysis of the 'rate effect' in the sensorimotor cortex: a functional magnetic resonance imaging analysis in human subjects. *Neurosci. Lett.* 252 (1), 37–40.
- Jancke, L., Peters, M., Himmelbach, M., Nosselt, T., Shah, J., Steinmetz, H., 2000. fMRI study of bimanual coordination. *Neuropsychologia* 38 (2), 164–174.
- Jenkins, I.H., Jahanshahi, M., Jueptner, M., Passingham, R.E., Brooks, D.J., 2000. Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow. *Brain* 123 (Pt 6), 1216–1228.
- Johnson, P.B., Ferraina, S., 1996. Cortical networks for visual reaching: intrinsic frontal lobe connectivity. *Eur. J. Neurosci.* 8 (7), 1358–1362.
- Kelly, R.M., Strick, P.L., 2003. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *J. Neurosci.* 23 (23), 8432–8444.
- Kim, S.G., Ashe, J., Hendrich, K., Ellermann, J.M., Merkle, H., Ugurbil, K., Georgopoulos, A.P., 1993. Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. *Science* 261 (5121), 615–617.
- Kloppel, S., van Eimeren, T., Glauche, V., Vongers, A., Munchau, A., Frackowiak, R.S., Buchel, C., Weiller, C., Siebner, H.R., 2007. The effect of handedness on cortical motor activation during simple bilateral movements. *Neuroimage* 34 (1), 274–280.
- Kurata, K., 1991. Corticocortical inputs to the dorsal and ventral aspects of the premotor cortex of macaque monkeys. *Neurosci. Res.* 12 (1), 263–280.
- Luppino, G., Matelli, M., Camarda, R., Rizzolatti, G., 1993. Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *J. Comp. Neurol.* 338 (1), 114–140.
- Macar, F., Anton, J.L., Bonnet, M., Vidal, F., 2004. Timing functions of the supplementary motor area: an event-related fMRI study. *Brain Res. Cogn. Brain Res.* 21 (2), 206–215.
- Middleton, F.A., Strick, P.L., 2000. Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res. Brain Res. Rev.* 31 (2–3), 236–250.
- Nambu, A., Kaneda, K., Tokuno, H., Takada, M., 2002. Organization of corticostriatal motor inputs in monkey putamen. *J. Neurophysiol.* 88 (4), 1830–1842.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9 (1), 97–113.
- Passingham, R.E., 1989. Premotor cortex and the retrieval of movement. *Brain Behav. Evol.* 33 (2–3), 189–192.
- Passingham, R.E., 1997. Functional organisation of the motor system. In: Frackowiak, R.S.J., Friston, K.J., Frith, C.D., Dolan, R.J., Mazziotta, J.C. (Eds.), *Human Brain Function*. Academic Press, San Diego, pp. 243–274.
- Picard, N., Strick, P.L., 2001. Imaging the premotor areas. *Curr. Opin. Neurobiol.* 11 (6), 663–672.
- Pool, E.M., Rehme, A.K., Fink, G.R., Eickhoff, S.B., Grefkes, C., 2013. Network dynamics engaged in the modulation of motor behavior in healthy subjects. *Neuroimage* 82C, 68–76.
- Pujol, J., Deus, J., Losilla, J.M., Capdevila, A., 1999. Cerebral lateralization of language in normal left-handed people studied by functional MRI. *Neurology* 52 (5), 1038–1043.
- Rao, S.M., Mayer, A.R., Harrington, D.L., 2001. The evolution of brain activation during temporal processing. *Nat. Neurosci.* 4 (3), 317–323.
- Rizzolatti, G., Luppino, G., 2001. The cortical motor system. *Neuron* 31 (6), 889–901.
- Rizzolatti, G., Fogassi, L., Gallese, V., 2002. Motor and cognitive functions of the ventral premotor cortex. *Curr. Opin. Neurobiol.* 12 (2), 149–154.
- Rogers, B.P., Carew, J.D., Meyerand, M.E., 2004. Hemispheric asymmetry in supplementary motor area connectivity during unilateral finger movements. *Neuroimage* 22 (2), 855–859.
- Rottschy, C., Caspers, S., Roski, C., Reetz, K., Dogan, I., Schulz, J.B., Zilles, K., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2013. Differentiated parietal connectivity of frontal regions for "what" and "where" memory. *Brain Struct. Funct.* 218 (6), 1551–1567.
- Rouiller, E.M., Babalian, A., Kazennikov, O., Moret, V., Yu, X.H., Wiesendanger, M., 1994. Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. *Exp. Brain Res.* 102 (2), 227–243.
- Sadato, N., Ibanez, V., Deiber, M.P., Campbell, G., Leonardo, M., Hallett, M., 1996. Frequency-dependent changes of regional cerebral blood flow during finger movements. *J. Cereb. Blood Flow Metab.* 16 (1), 23–33.
- Serrien, D.J., Ivry, R.B., Swinnen, S.P., 2006. Dynamics of hemispheric specialization and integration in the context of motor control. *Nat. Rev. Neurosci.* 7 (2), 160–166.
- Sharma, N., Baron, J.C., Rowe, J.B., 2009. Motor imagery after stroke: relating outcome to motor network connectivity. *Ann. Neurol.* 66 (5), 604–616.
- Siebner, H.R., Limmer, C., Peinemann, A., Drzezga, A., Bloem, B.R., Schwaiger, M., Conrad, B., 2002. Long-term consequences of switching handedness: a positron emission tomography study on handwriting in "converted" left-handers. *J. Neurosci.* 22 (7), 2816–2825.
- Solodkin, A., Hlustik, P., Noll, D.C., Small, S.L., 2001. Lateralization of motor circuits and handedness during finger movements. *Eur. J. Neurol.* 8 (5), 425–434.
- Stephan, K.E., Penny, W.D., Daunizeau, J., Moran, R.J., Friston, K.J., 2009. Bayesian model selection for group studies. *Neuroimage* 46 (4), 1004–1017.
- Volkman, J., Schnitzler, A., Witte, O.W., Freund, H., 1998. Handedness and asymmetry of hand representation in human motor cortex. *J. Neurophysiol.* 79 (4), 2149–2154.
- Wang, L.E., Fink, G.R., Diekhoff, S., Rehme, A.K., Eickhoff, S.B., Grefkes, C., 2011. Noradrenergic enhancement improves motor network connectivity in stroke patients. *Ann. Neurol.* 69 (2), 375–388.
- Witt, S.T., Laird, A.R., Meyerand, M.E., 2008. Functional neuroimaging correlates of finger-tapping task variations: an ALE meta-analysis. *Neuroimage* 42 (1), 343–356.
- Yousry, T.A., Schmid, U.D., Alkadhi, H., Schmidt, D., Peraud, A., Buettner, A., Winkler, P., 1997. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain* 120 (Pt 1), 141–157.
- Ziemann, U., Hallett, M., 2001. Hemispheric asymmetry of ipsilateral motor cortex activation during unimanual motor tasks: further evidence for motor dominance. *Clin. Neurophysiol.* 112 (1), 107–113.