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Functional resting-state connectivity of the human motor network: Differences between right- and left-handers

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ABSTRACT

Handedness is associated with differences in activation levels in various motor tasks performed with the dominant or non-dominant hand. Here we tested whether handedness is reflected in the functional architecture of the motor system even in the absence of an overt motor task. Using resting-state functional magnetic resonance imaging we investigated 18 right- and 18 left-handers. Whole-brain functional connectivity maps of the primary motor cortex (M1), supplementary motor area (SMA), dorsolateral premotor cortex (PMd), pre-SMA, inferior frontal junction and motor putamen were compared between right- and left-handers. We further used a multivariate linear support vector machine (SVM) classifier to reveal the specificity of brain regions for classifying handedness based on individual resting-state maps. Using left M1 as seed region, functional connectivity analysis revealed stronger interhemispheric functional connectivity between left M1 and right PMd in right-handers as compared to left-handers. This connectivity cluster contributed to the individual classification of right- and left-handers with 86.2% accuracy. Consistently, also seeding from right PMd yielded a similar handedness-dependent effect in left M1, albeit with lower classification accuracy (78.1%). Control analyses of the other resting-state networks including the speech and the visual network revealed no significant differences in functional connectivity related to handedness. In conclusion, our data revealed an intrinsically higher functional connectivity in right-handers. These results may help to explain that hand preference is more lateralized in right-handers than in left-handers. Furthermore, enhanced functional connectivity between left M1 and right PMd may serve as an individual marker of handedness.

Introduction

Handedness, i.e., the preference to use one hand over the other, is associated with differences in activation levels in various motor tasks performed with the dominant or non-dominant hand (Hammond, 2002). One of the earliest observation of lateralized brain function was reported by Pierre-Paul Broca who on the basis of aphasia and left hemisphere damage concluded that the left hemisphere is responsible for language-related behavior in right-handed patients (Broca, 1863). Since then, several studies have confirmed that hemispheric asymmetries of both structural and functional cortical organization are related to handedness (Amunts et al., 1996; Hammond, 2002). Using magnetic resonance morphometry, Amunts et al. demonstrated that the depth of the central sulcus is related to handedness. In right-handers, the left central sulcus was deeper than the right, and vice versa in left-handers. Analysis of macrostructural asymmetry was complemented by converging results of an analysis of microstructure (i.e., tissue compartment containing dendrites, axons, and synapses) in Brodmann's area 4. Based on their findings Amunts et al. suggested that hand preference is associated with increased structural connectivity and an increased intrasulcal surface of the precentral gyrus in the dominant hemisphere (Amunts et al., 1996). Using functional magnetic resonance imaging (fMRI), Jäncke and colleagues investigated right-handers performing a sequence task (touching of all four fingers with the thumb) at two different frequencies (1.0 Hz and 3.0 Hz) (Jäncke et al., 1998). In right-handers they observed stronger right hemispheric activation when performing the task with the left hand compared to activity in the left hemisphere when performing the same task with the right hand (Jäncke et al., 1998). Solodkin and colleagues further revealed differences in the fMRI activation patterns between simple and complex digit movements in right- and left-handers: while simple movements did not show differences with respect to handedness, neural activations underlying complex movements were more extended in left-handers compared to right-handers (Solodkin et al., 2001). Liu and colleagues found greater interhemispheric asymmetry in functional

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resting-state-connectivity of attention-related areas in right-handers compared to left-handers (Liu et al., 2009). We recently showed that effective connectivity, i.e., the causal influence that one area exerts over another area, between motor areas was differentially modulated in right- and left-handers depending on whether movements were performed with the dominant or non-dominant hand (Pool et al., 2014). More precisely, effective 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) supplementary motor area (SMA) with ipsilateral SMA, ipsilateral ventral premotor cortex (PMv), contralateral motor putamen and contralateral primary motor cortex (M1) (compared to equivalent connections in left-handers). Individual hand dominance as assessed using the Edinburgh-Handedness-Inventory (EHI) for daily activities (e.g., writing, striking a match, holding a broom; Oldfield, 1971) also correlated with coupling parameters of these connections. In contrast, we did not observe differences between right- and left-handers when testing for the effect of movement speed on effective connectivity. Based on these observations we concluded that handedness is associated with differences in effective connectivity within the human motor network with a prominent role of left SMA in right-handers. The fact that left-handers featured less asymmetry in effective connectivity strongly suggested differential hemispheric mechanisms underlying hand motor control in left- and right-handers (Pool et al., 2014).

However, differences in task performance (either in absolute performance measures or in hidden parameters like attention and effort) are inherent putative confounds for all task-based fMRI studies (Lowe et al., 1998; Yan et al., 2012). For example, performing a standard motor task might be less demanding when using the dominant hand compared to the non-dominant hand, which may also affect neural activation levels, e.g., in frontoparietal areas. Therefore, resting-state fMRI seems an attractive approach to overcome putative confounds as it allows investigating networks independent from performance.

We, therefore, used resting-state fMRI in 18 right-handed and 18 left-handed healthy volunteers to investigate handedness-dependent effects on resting-state functional connectivity. Given the evidence suggesting a role of M1 in handedness (Amunts et al., 1996; Ziemann and Hallett, 2001), we hypothesized that also resting-state connectivity of M1 might differ between right- and left-handers. In addition, as also connectivity of higher motor areas could show differential connectivity profiles dependent on handedness, we included seed regions in SMA, dorsolateral premotor cortex (PMd), pre-SMA, inferior frontal junction and motor putamen into the analyses. To test whether effects were specifically related to the motor system, we also investigated resting-state functional connectivity maps of the visual system and the language system using the primary visual cortex (V1) and the pars triangularis of the inferior frontal gyrus (IFG) as seed regions.

Consistent with previous studies revealing a hemispheric asymmetry related to handedness during motor performance (Haaland et al., 2004; Jäncke et al., 1998; Solodkin et al., 2001) and structural investigations reporting handedness-related macroscopic and microscopic asymmetries (Amunts et al., 1996), we hypothesized that differences within the human motor network between right- and left-handers can already be detected in absence of an overt motor task. However, mass-univariate group comparisons are not able to reveal how strong a feature really contributes to the distinction between right- and left-handers at an individual subject level. In other words, finding a group difference for a specific brain regions does not tell us whether this brain region can also predict an unseen subject that is not part of the test sample. We, therefore, in addition used a multivariate linear support vector machine (SVM) classifier algorithm (Chang and Lin, 2011) to test whether resting-state functional connectivity between brain regions can predict handedness of individual subjects.

Material 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 (10 males; 22–33 years old; mean age 26.1 ± 3.0 SD) and 18 left-handers (7 males; 19–30 years old; mean age 24.3 ± 2.6 SD)] with no history of neurological or psychiatric disease gave informed consent. Activation data of frequency-dependent modulation were previously published for this cohort of subjects (Pool et al., 2013, 2014).

To ensure that there were no significant differences in head movement parameters between right- and left-handed subjects we compared framewise displacement (FD) and root-mean-square (RMS) of the realignment parameters of the resting-state data in a two-sample *t*-test. Both tests showed no significant differences between groups (FD: $P = 0.302$; RMS: $P = 0.259$) (Power et al., 2012; Van Dijk et al., 2012).

Handedness measurements

Handedness was assessed by asking the subjects to complete the Edinburgh-Handedness-Inventory (EHI) (Oldfield, 1971). The EHI is a test to assess 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: A LQ > 25 indicates right-handedness, a LQ < -25 left-handedness (Pujol et al., 1999). The median LQ value of the right-handers was *88* (range: 53 to 100) and the median LQ of the left-handers was -71 (range: -30 to -100). We computed Mood's median test for non-parametric group comparisons, showing no significant difference between the median degree of handedness of right- and left-handers ($P = 0.176$).

Data acquisition

All subjects underwent resting-state functional magnetic resonance imaging (rs-fMRI). MR images were acquired on a Siemens Trio 3.0 T scanner (Siemens Medical Solutions, Erlangen, Germany). The resting-state paradigm was measured using a gradient echo planar imaging (EPI) sequence with the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 220 mm, 32 slices, $3.4 \times 3.4 \times 3.4$ mm^3 voxel size, 1 mm gap, flip angle = 90°, rs-fMRI: 184 volumes (three dummy images). The slices covered the whole brain extending from the vertex to lower parts of the cerebellum.

For the resting-state assessment, subjects were instructed to remain motionless and to fixate on a red cross on a black screen for about 6 min. We choose a scanning time around 6 min because longer scanning times do not improve the signal-to-noise of the data, but promote fatigue of the subjects (Van Dijk et al., 2010).

Image preprocessing

The resting-state fMRI data were conjointly preprocessed using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). After realignment of the EPI volumes and co-registration, 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.

Data analyses

fMRI resting-state data

Variance that could be explained by known confounds was removed from each voxel of the fMRI time-series. Confound regressors included