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Transcallosal connection patterns of opposite dorsal premotor regions support a lateralized specialization for action and perception.

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ABSTRACT

Lateralization of higher brain functions requires that a dominant hemisphere collects relevant information from both sides. The right dorsal premotor cortex (PMd), particularly implicated in visuomotor transformations, was hypothesized to be optimally located to converge visuospatial information from both hemispheres for goal-directed movement. This was assessed by probabilistic tractography and a novel analysis enabling group comparisons of whole-brain connectivity distributions of the left and right PMd in standard space (16 subjects). The resulting dominance of contralateral PMd connections was characterized by right PMd connections with left visual and parietal areas, indeed supporting a dominant role in visuomotor transformations, while the left PMd showed dominant contralateral connections with the frontal lobe. Ipsilateral right PMd connections were also stronger with posterior parietal regions, relative to the left PMd connections, while ipsilateral connections of the left PMd were stronger with particularly the anterior cingulate, the ventral premotor and anterior parietal cortex. The pattern of dominant right PMd connections thus points at a specific role in guiding perceptual information into the motor system, while the left PMd connections are consistent with action dominance based on a lead in motor intention and fine precision skills.

INTRODUCTION

The relation between movements and sensation of a given body-side and functions of the contralateral hemisphere reflects an essential characteristic of cerebral lateralization. Beyond this symmetrical division, each of the two hemispheres shows specialization with a lateralized dominance, particularly in the human brain. Where the left hemisphere is generally dominant in manual skill and language, a dominant right-hemisphere function concerns the integration of more global spatial sensory information in motor action. Information concerning extrapersonal space is particularly obtained by visual senses, while somatosensory stimuli provide information about personal space (Bottini et al., 2009). Particularly for visuomotor integration right hemisphere dominance has been well described (Callaert et al., 2011; Corballis, 2003). Symptoms resulting from lesions of the right hemisphere, particularly when the parietal cortex is involved, indeed include visuospatial disorientation and visuomotor deficit, but also contralateral neglect (Bogen and Gazzangia, 1965; Corbetta and Shulman, 2011; Franco and Sperry, 1977; Halligan et al., 2003; Perenin and Vighetto, 1988; Rossetti et al., 2003; Vallar and Perani, 1986). In this respect, the intact right hemisphere has been proposed to be more visually 'intelligent' than the left, equivalent to the superior capacities of the left hemisphere in other cognitive domains (Corballis, 2003). How such segregated hemisphere specializations are integrated in whole-brain neuronal networks, empowering one's sense of unity in perception and action (Bogen and Gazzangia, 1965; Franco and Sperry, 1977; Gazzaniga, 2005), remains an issue to be solved. In the present study, we are able to demonstrate differences between the left and right dorsal premotor cortex (PMd) regarding their patterns of connections in ipsilateral and contralateral hemispheres. These characteristic distributions represent a possible flow of information from two hemispheres to each of the two PMd's, consistent with the distinction of perceptual dominance of the right and a more

internally anchored action dominance of the left hemisphere concerning goal-directed movements.

Dorsal parietal-premotor circuitry plays a specific role in processing spatial aspects of visuomotor transformations (Binkofski et al., 1999; de Jong et al., 1999; Galletti et al., 2001; Johnson et al., 1996; Shipp et al., 1998; Wise et al., 1997). While in humans the right hemisphere is dominant in such transformations, goal-directed actions within extrapersonal space implies perception of, as well as movements made into both visual hemifields. This means that the right hemisphere uses information about the outside world derived from both hemispheres. The right PMd is thus logically positioned to support visuomotor integration and guide the resulting movement instructions also to the opposite PMd (Boussaoud et al., 2005). Similarly, the stronger involvement of the right PMd in complex bilateral movements, relative to the left PMd, suggests more efficient access to bilateral hemisphere information (de Jong et al., 2002; Sadato et al., 1997; van den Berg et al., 2010; Wenderoth et al., 2004). We therefore hypothesized that, in addition to ipsilateral parietal input, the right PMd receives more sensory information from the left hemisphere compared to the contralateral input received by the left PMd. Although the left PMd contributes to specific left-hemisphere functions, such as language and dexterous skill (Mechelli et al., 2005; Saur et al., 2008), the ventral premotor cortex is more involved in these functions and has stronger connections within the ipsilateral hemisphere (Tomassini et al., 2007).

In order to compare the ipsi- and contralateral hemisphere connections with each of the two PMd's, we employed probabilistic diffusion tensor imaging (DTI) and a novel analysis. In this study, a whole brain connectivity distribution was generated with the PMd as seed region. Next, normalized whole-brain connectivity distributions were implemented in the

construction of group maps. The latter were used for voxel-based statistical testing of a lateralized dominance of connections with either the right or left PMd.

METHODS

Subjects

Sixteen healthy right-handed subjects, mean age 26.8 years (SD \pm 9.8), 9 females, participated in the study. None of the subjects had neurological or psychiatric disorders. All subjects were right-handed as indicated by the Edinburgh handedness inventory (Oldfield, 1971). The experiment was approved by the local Medical Ethical Committee. All subjects gave written informed consent according to the declaration of Helsinki.

Data acquisition

Data acquisition was performed using a 3 Tesla Philips MR system (Philips Medical Systems, Best, the Netherlands) with a 32-channel head coil. Anatomical images were based on a T1-weighted 3D ultrafast gradient echo sequence with repetition time 9 ms, echo time 3.5 ms, flip angle 8°, field of view 232 x 256 x 170 mm, 170 slices without slice gap and a voxelsize of 0.9 x 1 x 1 mm. Images for DTI were acquired with a diffusion weighted spin echo sequence. The protocol comprised 60 independent diffusion gradient directions with b values of 1000 s/mm² followed by a b_0 image. Further scanning parameters were repetition time 8830 ms, echo time 61 ms, flip angle 90°, field of view 240 x 240 x 138, 55 slices without slice gap and a voxelsize of 2.5 x 2.5 x 2.5 mm. To assess quality of the diffusion data, signal-to-noise ratios (SNR) were calculated by $SNR = S/\sigma$ where S is the signal in a 2D region of interest of 10 x 10 = 100 voxels with maximal uniform brain signal and σ is the standard deviation of those 100 voxels (Lagana et al., 2010). The same 2D region was used to calculate the SNR for each diffusion direction as SNR might vary among directions (Lagana et al., 2010). The

resultant total mean SNR was 7.7 (\pm 1.3) with 5.1 as minimal value 10.0 as maximal value for one direction.

Image processing

Diffusion images were processed using tools from the FMRIB Software Library (FSL) version 4.1.9 (www.fmrib.ox.ac.uk/fsl). Diffusion images were realigned to the b_0 -image to compensate for eddy currents and motion (Jenkinson and Smith, 2001). The brain images were automatically extracted from the entire head images (Smith, 2002) and manually corrected. We calculated probabilistic distributions on multiple fiber directions at each voxel in the diffusion data using a multiple-fiber extraction (Behrens et al., 2003; Behrens et al., 2007) with gradients corrected for slice angulations. A Bayesian estimation of diffusion parameters obtained using sampling technique (BEDPOST) was conducted, which includes modeling of crossing fibers in each voxel (Woolrich et al., 2009). For each subject, T1 images were co-registered with diffusion images by a nonlinear transformation preceded by a linear transformation. We used the default functions FNIRT and FLIRT respectively, provided by FSL (Jenkinson and Smith, 2001). The same procedure was done to co-register T1 images to MNI. Both steps resulted in a transformation matrix, which was used to convert diffusion images to MNI or back through the T1 transformation matrices.

Each subject's T1-weighted image was automatically segmented using the FSL FAST function (Zhang et al., 2001). Gray and white matter were dilated with 1 x 1 x 1 mm and a threshold was set at 0.2. The overlap between these grey and white matter images was used to create a gray matter/white matter boundary mask. Standard anatomical MNI space regions of interest of the PMd were derived from an existing binary human motor area template (Mayka et al., 2006), which was transformed to T1 anatomical images of each subject using the

nonlinear transformation matrix. The T1 PMd regions were multiplied with the gray matter/white matter boundary mask to select this part within the PMd. Thereafter, the gray matter/white matter PMd regions were nonlinear transformed to diffusion space.

Connections of the right and left PMd were analyzed with probabilistic tractography. We tracked from the grey matter/white matter boundary voxels within our PMd regions in native diffusion space to generate a connectivity distribution of those regions for each subject. Output generated a connectivity distribution summing the total number of generated tracts for all voxels within the seed region. A single voxel then displays the summed hits for all tracts (i.e. the number of tracts that have passed the voxel). As result, probabilistic tractography is influenced by the size of the seed region next to the number of samples done for each voxel within that seed region. For the latter, we used the default number of 5000 samples. Although the size of the left and right PMd template in MNI space was equal, transforming it to diffusion space resulted in some differences in size, which might induce a bias towards one side for the seed region size in diffusion space and thereby also for tractography results. The mean size of the right PMd in native diffusion space was 580 (± 103) voxels, while for the left it was 560 (± 101) voxels, which was not significantly different when compared with each other ($t(15)=1.25$, $p_{\text{two-tailed}}=0.231$). Furthermore, the right PMd was larger than the left in eight subjects (67 ± 57 voxels), while the left PMd was larger than the right in the other eight subjects (27 ± 23 voxels). This virtually eliminated the possibility of a bias in our diffusion seed region toward one side, thus avoiding a possible confounding bias in the two connectivity distributions. To eliminate the possibility of faulty tracking to the contralateral hemisphere through 'kissing' fibers in the brain stem, we included an exclusion mask in the midsagittal plane from the third ventricle downward through the brain stem between the cerebral peduncles, with a boundary anterior and posterior by the surrounding cerebrospinal

fluid. It should be noted that in this way tractography did not reach the contralateral cerebellum, thus excluding its assessment.

Comparison of left and right PMd connections

To compare the connectivity distribution of the right and left PMd, we used a novel approach to test hemisphere differences of connections at group level. Maps of generated tracts for each hemisphere were superimposed at each other in MNI space and tested for group differences using permutation statistics. To that end, first, the two separate images of the cerebral connectivity distribution for the right and left PMd were transformed from diffusion to MNI space through T1 by two nonlinear transformations. The original PMd tracts (transformed in MNI space) were visualized by calculating the median over all subjects for each voxel for both the right and left PMd (Fig.1). Intrinsically linked to the methods of probabilistic tractography, these median group images are prone to a distance bias because areas at larger distance from a given seed region are less likely to demonstrate their tracts as nearby areas. In our analysis, however, this issue did not play a role because left-right comparisons were made between tracts that both originated from symmetrically equal right and left PMd seed regions and passed distant voxels that were positioned in a similar symmetrical way, thus equally far from their seed PMd. We therefore only draw conclusions from the images originating from the statistically tested differences between the two PMd's. To test for such differences, we flipped the connectivity maps of the left PMd in MNI space. Furthermore, we separately subtracted for each subject (i) the right from the left mirrored and (ii) the left mirrored from the right connectivity maps. This resulted in two connectivity maps for each subject displaying the differences of the right and left mirrored PMd, now displayed in MNI space as ipsilateral and contralateral to the seed region. The two resulting connectivity distributions provided the input for the subsequently conducted voxel-based group testing of these

connectivity maps by using a one-sample non-parametric permutation test with 5000 permutations for each voxel (Nichols and Holmes, 2002). This resulted in an uncorrected p -values map of differences displaying which voxels showed more contribution to the right than left PMd in both the ipsi- and contralateral hemisphere and another uncorrected p -value map showing it the other way around, which voxels showed more contribution to the left than right PMd. A voxel-level threshold of $p < 0.001$ was used with a cluster extend threshold of 20 voxels to reduce false-positive results using MRICron (<http://www.mccauslandcenter.sc.edu/mricro/mricron/>). In this way we could assess whether resulting patterns in the statistical difference map were indeed characterized by an elongated 'fiber shape', reflecting the specific relation between adjacent voxels in a tract. Ignoring this physiological feature of a cluster and using e.g. a family-wise-error (FWE) correction for multiple comparisons might result in false negative findings. Furthermore, a mask was applied to exclude all voxels outside the brain.

RESULTS

The pattern of connections that originated from the right and left PMd seed regions showed major similarities (Fig.1). Eyeballing these original PMd tracts showed nevertheless subtle differences. For instance, right PMd tracts reached left parieto-occipital regions and the left postcentral gyrus, while the left PMd did not make these contralateral connections. The results of a formal assessment of such differences are presented in the following paragraphs.

Right PMd connectivity dominance

In general, the right PMd had more connections distributed within the left hemisphere compared to the contralateral hemisphere connections of the left PMd. These contralateral connections of the right PMd were particularly made with parietal and occipital cortex regions

(Fig.2; green clusters). The largest cluster comprised the posterior part of the fronto-occipital fasciculus ending along the calcarine sulcus, bordering the lingual, fusiform- and middle occipital gyri. This cluster also spread along the posterior segment of the intraparietal sulcus. Another dominant cluster in the contralateral hemisphere was seen around the central sulcus, both in the postcentral gyrus underlying the somato-sensory cortex, and in the precentral gyrus including the motor representation of the hand. Within the corpus callosum, the right PMd connections outnumbered those of the left PMd in the posterior midbody and splenium. In the ipsilateral hemisphere, a dominance of right PMd connections with occipito-parietal regions was also found, but this was less pronounced than for the connections with contralateral posterior brain regions (Fig.2).

Left PMd connectivity dominance

Although the right PMd was generally dominant with regard to the pattern of contralateral connections, a few contralateral connections of the left PMd with rostral parts of the prefrontal cortex were more intense compared to the right PMd equivalents (Fig.2; blue clusters). Such anterior dominance was also seen in the corpus callosum with left PMd connections outnumbering the right PMd connections in the genu of the corpus callosum. The left PMd, relative to the right PMd, showed more ipsilateral connections with medial premotor regions, comprising the anterior cingulate and pre-supplementary motor area (pre-SMA). Such dominance of left ipsilateral PMd connections was also seen for connections with the ventral premotor and anterior parietal cortex as well as a few temporal cortex regions. In addition, we saw ipsilateral connections in the cerebellum when the left PMd was defined as seed region. With regard to cerebellar connectivity, it should be kept in mind that its basic pattern of crossed cerebral-cerebellar connections could not be assessed due to the

midsagittal mask through brainstem and diencephalon, which was used to exclude faulty PMd tracking along 'kissing' fibers in the brainstem (Fig.2; red line).

DISCUSSION

The present study demonstrated a hemisphere-specific difference between the left and right PMd regarding the descriptive distribution of its connections. Although functional inferences made from anatomical differences have a speculative character, the dominance of connections between the right PMd and particularly contralateral occipito-parietal regions, relative to the contralateral connections of the left PMd, provide support for the hypothesis that the right PMd is dominant in the integration of visual information to prepare purposeful movements. Consistent with such dominance of connections with posterior brain regions, these right PMd connections outnumbered the left PMd connections in the posterior segments of the corpus callosum. Connections of the left PMd with the contralateral prefrontal regions were dominant to those of the right PMd with the prefrontal cortex, while transcallosal connections were stronger represented in the anterior callosal segments. Where previous tractography studies have identified the location of strong reciprocal connections within the corpus callosum that predominantly run between homologous areas of both hemispheres (Hofer and Frahm, 2006; Huang et al., 2005), our study enabled identification of lateralization differences between transcallosal connections of the right and left PMd. With respect to the concept 'connection', it might be noticed that tractography does not provide information about the direction of information flow along an identified tract, while it may not necessarily discriminate between monosynaptic connections and a connectional chain including synaptic intersections (Jbabdi and Johansen-Berg, 2011). The latter particularly concerns fibers entering the cortex. Synaptic intersection of a given white matter tract would imply passing gray matter, which is at odds with the methodological concept of DTI. We did indeed not see such crossing of gray matter

in our study. E.g., connections with the occipital lobe laterally passed the parieto-occipital sulcus.

Although the visual system already contributes to visuomotor control by maintaining a functional segregation between parvo- (color) and magnocellular (motion) processing streams, the parietal cortex is further implicated in higher order visuospatial and visuomotor processing along a dorsal visual stream (Goodale and Westwood, 2004; Halligan et al., 2003; Rossetti et al., 2003; Shipp et al., 1998). Integration of lateralized visual characteristics in whole-field visual processing may already take place along highly focused transcallosal connections between the occipital lobes (Clarke and Miklossy, 1990; van Essen and Zeki, 1978; Watson et al., 1993). A consequence of right-hemisphere dominance in human visuomotor integration is a more complex transcallosal innervation to enable efficient access to sensory information from both hemispheres as well as an effective transfer of movement parameters, not only to the adjacent right motor cortex but also to the left (pre)motor cortex. The latter is reflected by the right PMd connections with the precentral gyrus, of which the posterior surface contains the primary motor cortex, while the premotor cortex spans its anterior and lateral surfaces. The crucial role that we attributed to the right PMd concerning visuomotor transformations is thus supported by the identified pattern of dominant connections with particularly occipito-parietal regions relative to the left PMd connections.

Dominance of the contralateral connections with the right PMd not only concerned vision-related tracts. Additional PMd connections with parietal regions point at involvement of the right PMd in general sensorimotor processing, including the integration of somatosensory information. Right-sided dominance concerning the latter is consistent with right parietal-premotor circuitry previously described to be involved in the integration of proprioceptive

information in motor control (de Jong et al., 2002; Naito et al., 2005), which may be particularly beneficial for coordinating bilateral movement.

While sensorimotor transformations involved in motor preparation are often characterized by bottom-up processing, the same connections may facilitate a reciprocal information flow in a more top-down fashion. In attention, these two directions characterize the distinction between sensory driven and goal-directed attention respectively (Corbetta and Shulman, 2002). The dominance of contralateral connections of the right PMd with particularly posterior parts of the brain, relative to the left PMd connections, is indeed consistent with functional circuitry implicated in spatial attention (Gitelman et al., 1999; Raichle, 2011). In this way, hemisphere-specific characteristics of right PMd connectivity contributes to understanding neuronal mechanisms that underlie a lateralized higher-order brain function such as spatial processing in both sensorimotor transformations and attention.

For the left PMd, connections were stronger with prefrontal regions, relative to the prefrontal connections of the right PMd. This particularly concerned ipsilateral connections with cingulate motor areas and the pre-SMA, and contralateral connections with the lateral surface of the anterior prefrontal cortex. Although we did not start with a specific hypothesis concerning connections of the left PMd, stronger involvement in circuitry comprising these frontal regions fits left-hemisphere dominance underlying right-handedness. In this respect, medial premotor regions may contribute to right-hand dominance by accommodating a lead in the internal generation of action (Lau et al., 2004) as well as recruiting overlearned movement sequences (Boecker et al., 1998; Lewis et al., 2004). The dominance of left PMd connections with the ventral premotor and anterior parietal cortex in the ipsilateral hemisphere, relative to such connections of the right PMd in the opposite hemisphere, may further support a

contribution of specifically the left PMd to fine precision movements (Binkofski et al., 1999; Dafotakis et al., 2008; Raos et al., 2006; Sakata et al., 1997). A concerted function of the left PMd and medial premotor areas has also been associated with a left-hemisphere function such as speech (Hartwigsen et al., 2013; Vingerhoets et al., 2013). The presence of a dominant left hemisphere tract from the PMd to the temporal cortex may further support its involvement in 'classical' left-hemisphere networks underlying language (Hickok et al., 2011; Knecht et al., 2000).

CONCLUSION

To conclude, the patterns of particularly contralateral hemisphere connections of the right PMd indicated a lateralized dominance related to visuomotor control. This was based on the stronger connections of the right PMd with occipito-parietal regions of the opposite hemisphere. Relative to the connections of the right PMd, left PMd connections were stronger with prefrontal areas, ipsilateral ventral premotor and the anterior parietal cortex representing action dominance based on a lead in motor intention and fine precision skills. These two patterns of lateralized right and left PMd connections may thus reflect a hemisphere-specific dominance for perception and action, respectively.

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ABBREVIATIONS:

PMd=dorsal premotor cortex; DTI=diffusion tensor imaging; SNR=signal-to-noise ratio; pre-SMA=pre-supplementary motor area.

CONFLICT OF INTEREST:

None.

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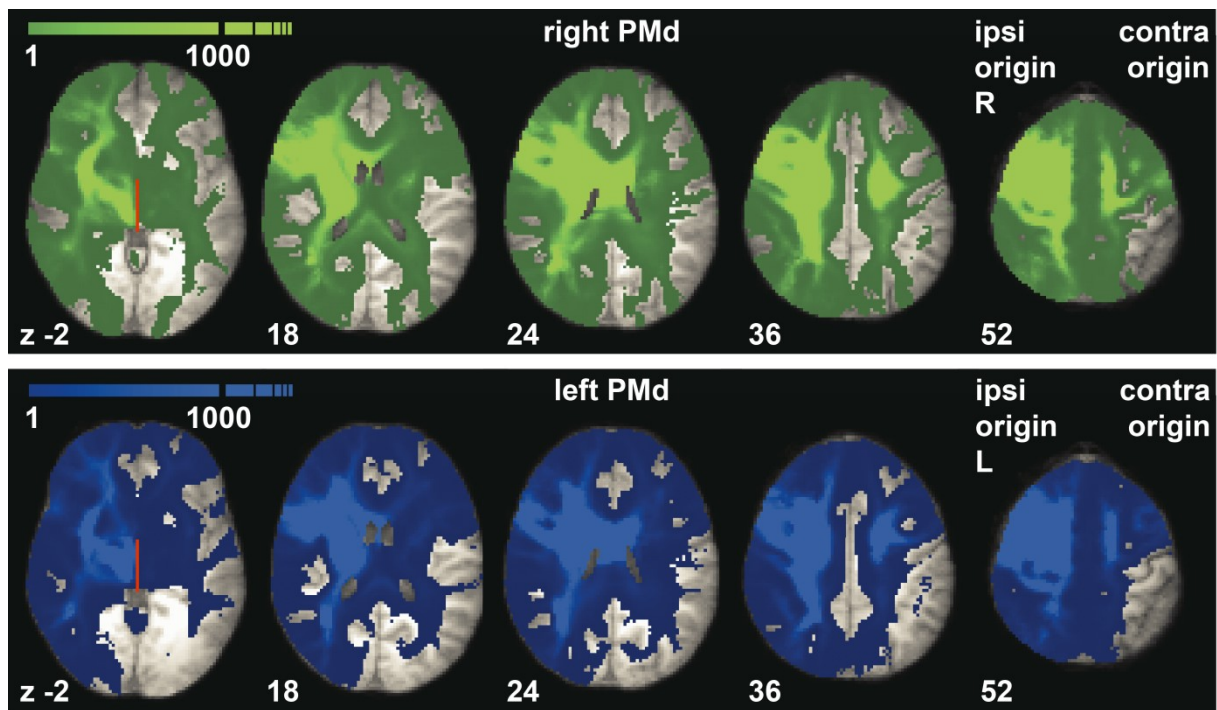
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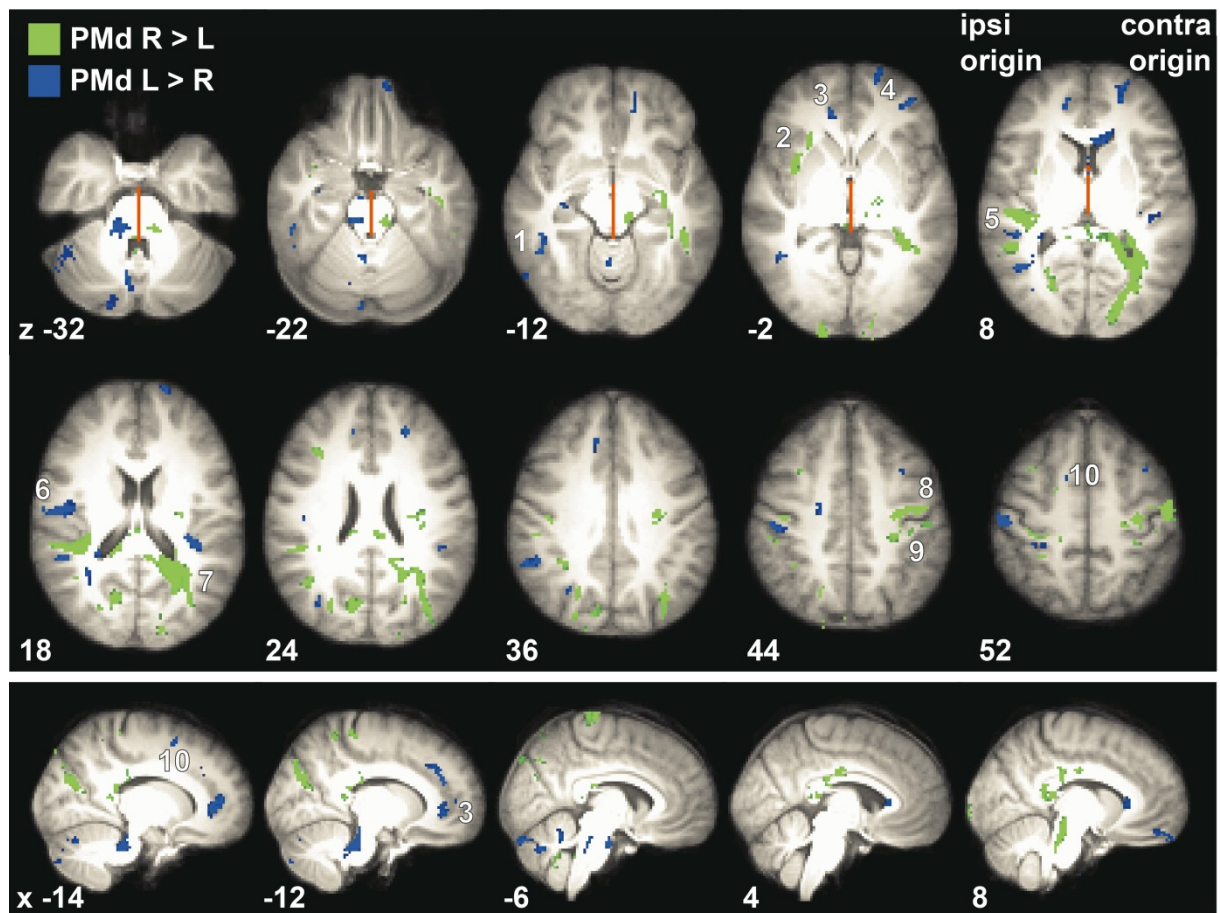
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Figure 1 - Tractography of the right and left premotor cortex



Median tractography values over all subjects for each voxel are shown for the right (green) and left (blue) dorsal premotor cortex (PMd). The left PMd is mirrored to ease comparison of the right and left PMd. Results are displayed on a mean T1 MR image of all 16 subjects transformed into standard MNI space. Positive z coordinates refer to the distance of transversal sections (in mm) superior to the plane traversing the anterior and posterior commissures. The color scale indicates the total number a tract passed a voxel. Values above 1000 are represented by the same color intensity. The contralateral cerebellum was not reached via the cerebral peduncles due to a midsagittal exclusion mask through the brain stem (red line). ipsi origin=ipsilateral to seed region; contra origin=contralateral to seed region; R=right side of the brain; L=left side of the brain.

Figure 2 - Differences in connectivity distributions of the left and right premotor cortex



Differences between the left (L) and right (R) dorsal premotor cortex (PMd) are shown on transversal sections of a mean group anatomy ($N=16$) in standard MNI space, which implies that a horizontal reference plane traverses the anterior and posterior commissures. The x, y, z coordinates (in mm) refer to the distance of respectively coronal, sagittal and transversal sections to the middle of the anterior commissure. Positive z and y coordinates indicate the position of sections respectively superior and anterior to the anterior commissure, while positive x coordinates indicate the distance to the mid-sagittal plane of sections contralateral to the PMd from which tracts originate. Thresholds are set at $p < 0.001$ with an extended voxel threshold of 20 voxels. The contralateral cerebellum was not reached via the cerebral peduncles due to a midsagittal exclusion mask through the brain stem (red line). 1=inferior temporal gyrus; 2=external capsule; 3=anterior cingulate gyrus; 4=superior and middle frontal

gyrus; 5=superior temporal gyrus; 6=ventral premotor cortex; 7=fronto-occipito fasciculus;
8=precentral gyrus; 9=postcentral gyrus; 10=pre-supplementary motor area.