

Hemispheric asymmetries of functional connectivity and grey matter volume in the default mode network

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ABSTRACT

Resting state networks such as the default mode network have been widely reported. Although a plethora of information on its functional relevance has been generated, little is known about lateralization or hemisphere asymmetry within the DMN. We used high-resolution resting state fMRI and T1 3D data to investigate such asymmetries in two groups of healthy subjects, one right-handed and one left-handed. Independent component analysis and the dual regression approach were carried out to identify functional asymmetries, while voxel-based morphometry was used to identify structural asymmetries in grey matter volume within the DMN. Greater leftward functional connectivity was observed in the posterior cingulate gyrus (PCG) for both groups. Leftward functional asymmetry was observed in the thalamus and rightward functional asymmetries were observed in the middle frontal and middle/superior temporal gyrus in the right-handed group. Rightward asymmetries in grey matter volume were observed in the posterior portion of the PCG for both groups. The right-handed group exhibited leftward structural asymmetries in the anterior portion of the PCG and in the middle frontal and posterior portion of the middle temporal gyrus, while rightward asymmetries were observed in the posterior portion of the PCG and anterior portions of temporal regions. These results suggest that functional connectivity and grey matter volume are not equally distributed between hemispheres within the DMN, and that functional asymmetries are not always reflected or determined by structural asymmetries.

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1. Introduction

The study and understanding of resting state networks (RSN), which are brain regions presenting strong temporal coherence in low-frequency fluctuations of the BOLD signal (Filippini et al., 2009), have increased dramatically in the last few years. One of the most studied RSN is the so-called default mode network (DMN) (Damoiseaux et al., 2006; Raichle, 2009; Raichle et al., 2001), which includes the prefrontal (PFG), anterior (ACG), and posterior cingulate (PCG), the lateral parietal (LPG), inferior (ITG) and middle temporal gyri (MTG), as well as the precuneus (Fransson & Marrelec, 2008), cerebellar areas, thalamic nuclei, and regions extending to the medial temporal lobe (Boly et al., 2008). Much of the available information describes the relationship between the DMN and neurological disorders (Zhang & Raichle, 2010) such

as Alzheimer's (Greicius, Srivastava, Reiss, & Menon, 2004; Sorg et al., 2007), Parkinson's disease (van Eimeren, Monchi, Ballanger, & Strafella, 2009), and autism (Assaf et al., 2010). Other studies of the DMN include heritability of its functional connectivity (Glahn et al., 2010), commonalities of functional architecture through meta-analysis (Biswal et al., 2010), and maturation processes (Fair et al., 2008). Although it is clear that the brain is asymmetric both in structure and function (Toga & Thompson, 2003) and that many studies report hemispheric dominance of higher cognitive skills such as language (Tzourio-Mazoyer et al., 2010), music perception (Yasui, Kaga, & Sakai, 2009), and somatosensory functions (Jung et al., 2003), little is known about lateralization or hemisphere asymmetry within the DMN.

Recently, resting state fMRI (rsfMRI) has shown hemispheric asymmetries in some functional properties, where intrinsic activity is stronger in one hemispheric region than in its contralateral homologue (Tommasi, 2009). Tian, Wang, Yan, and He (2011) showed that small world network properties such as degree and regional efficiency are not symmetric. More specifically, they described leftward asymmetry of these properties in the anterior cingulate and superior frontal gyrus, confidently reported to be part of the DMN (Fox & Raichle, 2007; Greicius, Krasnow, Reiss,

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& Menon, 2003). Similarly, Iturria-Medina et al. (2011) showed leftward structural asymmetry of the PCG using centrality. Leftward asymmetries in functional connectivity density (FCD) have also been reported in posterior cingulate cortices and a rightward FCD in the middle temporal gyrus, frontal regions, and precuneus along with other regions (Tomasi & Volkow, 2011).

Another study (Yan et al., 2009) examined hemispheric differences in connectivity patterns of the anterior cingulate cortex (ACC) with other regions, such as the dorsolateral prefrontal cortex, inferior parietal cortex, and dorsal posterior cingulate cortex, reporting leftward and rightward asymmetries. Using a similar technique, Liu, Stufflebeam, Sepulcre, Hedden, and Buckner (2009) compared functional connectivity between contralateral and ipsilateral pairs of regions of interest, describing leftward asymmetries along the cortical midline and rightward asymmetries in the occipital–parietal junction, angular gyrus, and insula. Other studies have detected hemispheric asymmetries of structural properties in other regions of the DMN; some report rightward asymmetries in grey matter volume and cortical thickness in the superior temporal gyrus (Luders et al., 2006; Watkins et al., 2001), whereas others report leftward structural asymmetries in this same region (Toga & Thompson, 2003). Luders et al. (2006) showed that cortical thickness in the middle and medial frontal gyri presents leftward asymmetry.

Independent component analysis (ICA) and dual regression (Cole, Smith, & Beckmann, 2010) are two robust approaches that can be used to investigate differences in resting-state activity between groups. More specifically, ICA estimates maximally independent components by identifying brain regions that show a strong temporal coherence in low-frequency fluctuations (less than 0.1 Hz) (Filippini et al., 2009). Dual regression generates individualized, session-specific time courses and spatial maps for each independent component in each subject's functional data set (Beckmann, DeLuca, Devlin, & Smith, 2005; Cole et al., 2010).

In addition to connectivity studies based on BOLD imaging, it is possible to study brain asymmetry with high resolution MRI. Voxel-based morphometry is a widely used approach that can be applied to high-resolution brain images in order to investigate differences in brain anatomy (Luders, Gaser, Jancke, & Schlaug, 2004; Takao, Abe, & Ohtomo, 2010). In the present study, ICA and dual regression were applied in order to identify the DMN and compare its functional connectivity properties between hemispheres, and voxel-based morphometry was used to compare grey matter volume between hemispheres within two groups of healthy subjects (one right-handed and one left-handed).

The purpose of this study is to compare resting state functional connectivity and grey matter volume between hemispheres in two populations (right- and left-handed subjects). The main hypothesis is that both of these parameters (functional connectivity and grey matter volume) are unequally distributed between hemispheres. More specifically, leftward functional asymmetries in the PCG are expected, as previous studies have shown asymmetries in resting-state functional properties (Liu et al., 2009; Tian et al., 2011; Tomasi & Volkow, 2011). Structural asymmetries are also likely, as asymmetries have been observed in regions associated with the DMN (Luders et al., 2006; Toga & Thompson, 2003; Watkins et al., 2001).

2. Materials and methods

2.1. Subjects

Two groups of rsfMRI and T1 3D high-resolution data obtained from healthy subjects were used in this study. Handedness of both groups was determined using the Edinburgh Handedness Inventory. The RH-FCP group included data from 171 right-handed subjects (105 women; 21.8 ± 2.72 years, ranging from 18 to 30 years) and the LH-FCP group from 27 left-handed subjects (18 women; 21 ± 2.01 years, ranging from 18 to 25 years). Data for both groups was selected from the publicly released 1000 Functional Connectomes Project (FCP)

(http://www.nitrc.org/projects/fcon_1000/; Cambridge Buckner data set) (Biswal et al., 2010). Participants gave their informed consent before entering the study. All procedures were approved by the Internal Review Board and were carried out according to the 1964 Declaration of Helsinki.

2.2. Image acquisition

Functional and structural images of both groups were acquired from the 1000 Functional Connectomes Project (Biswal et al., 2010). Functional images were collected using Echo Planar Imaging single shot sequence with TR = 3000 ms and 119 whole brain volumes with 47 slices. Final isometric resolution of structural images was $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$. During functional MRI acquisition, subjects in all groups were instructed to keep their eyes closed, to think about nothing in particular, and not to fall asleep.

2.3. Data analysis

2.3.1. Preprocessing of fMRI data and generation of the default mode network for each group

The data were analyzed using FSL 4.1.6 (Smith et al., 2004). Resting state fMRI data analysis was carried out using Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) (Beckmann et al., 2005). Preprocessing included motion correction, brain extraction, spatial smoothing using a Gaussian kernel of full-width at half-maximum of 5 mm, and high-pass temporal filtering. Images in the subject's space were registered to standard space by using the Nonlinear Image Registration Tool (FNIRT). Preprocessed data was temporally concatenated generating a single, 4D data set. Following concatenation, fMRI data was decomposed into resting state patterns of functional connectivity using ICA, generating 21 components for the RH and 25 for the LH group. The order of the components was estimated using the Laplace approximation. The DMN was identified for each group using the spatial extension of the DMN reported from previous studies (Beckmann et al., 2005; Cole et al., 2010; Damoiseaux et al., 2006).

2.3.2. Generation of subject-specific default mode and hemisphere comparison of functional properties

A dual-regression algorithm was applied to generate subject-specific temporal dynamics and associated DMN maps (Filippini et al., 2009; Veer et al., 2010). Subject-specific DMN estimates were flipped in the LR-direction and tested voxel-wise for differences versus non-flipped maps using randomized permutation methods (5000 permutations) (Nichols & Holmes, 2002) that included age and gender as confounding variables. This testing resulted in spatial maps characterizing hemisphere differences in functional connectivity for each group. Only voxels with $p < 0.05$, corrected for multiple comparisons using Threshold-Free Cluster Enhancement (TFCE), were considered as significant, and differences were masked according to the DMN of each group.

2.3.3. Processing of structural data and hemisphere comparison of structural properties

We used the voxel-based morphometry technique implemented by FSL (Smith et al., 2004) for structural analysis of grey matter volume. Images from each group were flipped left to right in order to compare structural differences between hemispheres. The brain was extracted using BET software (Smith, 2002). By using FAST4 (Zhang, Brady, & Smith, 2001) we segmented the data in order to sample different kinds of tissue. Grey matter images were selected and then aligned to standard space by non-linear registration. An average of these co-registered images was used to generate a specific template for the present study. Grey matter images were then co-registered to this template using non-linear co-registration. All possible changes in expansion and contraction were corrected through modulation (Good et al., 2001). All modulated images were concatenated into a single 4D image and then smoothed with a Gaussian kernel with a sigma of 3 mm. Finally, a paired t -test was applied to the 4D image using the randomized permutation method (Nichols & Holmes, 2002) to compare flipped versus non-flipped grey matter volumes with gender and age as confounding variables. This resulted in spatial maps representing the hemispheric differences in grey matter volume of each group.

3. Results

3.1. Identification of the default mode network

In both the left- (LH) and right-handed (RH) groups, the medial frontal gyrus (medFG), PCG, cingulate gyrus (CG), angular gyrus (AG) as well as the precuneus, LPG, MTG, and thalamic nuclei were identified as part of the DMN (Figs. 1A and 2 and Table 1). All these regions have been widely reported to be part of the DMN (Beckmann et al., 2005; Cole et al., 2010; Damoiseaux et al., 2006; Greicius et al., 2003).

Table 1

Coordinates of local minima of p (corrected) for regions of the DMN showing hemispheric asymmetries in functional connectivity for the RH and LH groups. Left > Right: leftward asymmetry of functional connectivity. Right > Left: rightward asymmetry of functional connectivity. Coordinates are in millimeters in the MNI coordinate system identified, along Brodmann areas, through Talairach Daemon Client (Lancaster et al., 2000).

Hemisphere asymmetry	Lobe	Region	Brodmann area	x (mm)	y (mm)	z (mm)	p	
RH-FCP								
Left > Right	Limbic	Posterior cingulate	31	−2	−53	25	0.001	
		Cingulate gyrus	31	−2	−57	29	0.001	
		Cingulate gyrus	23	−9	−23	28	0.001	
	Occipital	Cuneus	19	−6	−81	25	0.001	
		Parietal	Precuneus	19	−30	−81	37	0.002
	Precuneus		7	−27	−81	49	0.01	
Right > Left		Superior parietal lobule	7	−37	−70	56	0.001	
	Temporal	Superior temporal gyrus	39	−58	−58	25	0.014	
		Anterior	Culmen	*	6	−45	4	0.012
	Frontal	Middle frontal gyrus	8	26	19	47	0.001	
		Medial frontal gyrus	10	21	31	35	0.003	
		Superior frontal gyrus	8	23	15	46	0.001	
	Parietal	Superior parietal lobule	7	38	−65	47	0.001	
		Inferior parietal lobule	7	42	−65	43	0.001	
	Temporal	Middle temporal gyrus	21	58	−4	−21	0.037	
		Inferior temporal gyrus	20	54	−7	−21	0.003	
		Superior temporal gyrus	22	58	−57	16	0.001	
	LH-FCP							
	Left > Right	Parietal	Precuneus	7	−2	−61	63	0.001
			Sub-	*	−13	−17	8	0.002
lobar			Thalamus	−10	−18	5	0.002	
Thalamus			Mammillary body	−13	−26	12	0.009	
			Pulvinar					

* No Brodmann area identified.

3.2. Functional asymmetries

3.2.1. Rightward asymmetries of the DMN

Regions of the DMN exhibiting greater functional connectivity in the right hemisphere (rightward functional asymmetries) were only observed in the right-handed group in the MTG, medFG, superior frontal gyrus (SFG), middle frontal gyrus (midFG), and inferior parietal lobule (Fig. 1A and Table 1).

3.2.2. Leftward asymmetries of the DMN

Greater functional connectivity in the left hemisphere (leftward functional asymmetries) was observed across both groups. Coordinates of local minima are shown in Table 1, and the corresponding spatial maps are shown in Fig. 1A. The RH group exhibited greater leftward functional connectivity in the PCG, cingulate gyrus, cuneus, precuneus, superior temporal gyrus (STG), and superior parietal lobule. The LH group exhibited leftward asymmetries in the PCG, thalamus, and precuneus (Fig. 1A).

3.3. Structural asymmetries of the DMN

Table 2 shows the coordinates of local minima for regions of the DMN of each group presenting hemispheric asymmetries in grey matter volume. Greater grey matter volume in the right hemisphere (rightward structural asymmetry) was observed in the posterior portion of the posterior cingulate and precuneus in both groups (Fig. 1B). The RH group also exhibited rightward asymmetries in inferior parietal regions and the STG, while leftward asymmetries were observed in the anterior portion of the PCG. In the LH group the thalamus presented leftward asymmetries in grey matter volume (Table 2).

In addition, Fig. 2 shows the functional and structural asymmetries of the RH group. MidFG and medFG exhibited rightward functional asymmetries, whereas leftward structural asymmetries are present in these same regions. Functional and structural leftward asymmetries overlap in the anterior portion of the PCG while no overlapping was observed in the anterior region, although leftward functional asymmetries are present across both anterior and posterior portions of the PCG (Fig. 1A). In temporal regions,

overlapping of functional and structural asymmetries occurs in both hemispheres. Leftward structural and functional asymmetries are present in posterior portions of MTG, while rightward structural and functional asymmetries occur in anterior portions MTG and STG (Fig. 2).

4. Discussion

Findings in the present study support the idea that functional connectivity and grey matter volume within the default mode network are not equally distributed between hemispheres. Using ICA and dual-regression for functional connectivity and voxel-based morphometry for assessing grey matter volume, we explored two different data sets and identified hemispheric asymmetries within the DMN in right- and left-handed subjects.

4.1. Rightward asymmetries

Greater functional connectivity in the right hemisphere was only observed in the RH group. The MTG/ITG and mid/medFG had the most extensive rightward functional asymmetry (Fig. 1A). Tian et al. (2011) also reported rightward asymmetries for the ITG and STG of small world network properties. Other studies (Luders et al., 2006; Watkins et al., 2001) report rightward asymmetries of structural properties such as grey matter volume and cortical thickness for these regions, similar to the data shown here (Table 2). However, in contrast to the rightward asymmetry in functional connectivity found here in the middle and medial frontal gyri, Luders et al. (2006) described leftward asymmetry in cortical thickness for the middle and medial frontal gyri, evidence that structural asymmetry does not necessarily imply asymmetry in functional connectivity.

While functional activity measures in attention and resting conditions are different, brain activity within the DMN decreases during most attention-demanding tasks (Buckner, Andrews-Hanna, & Schacter, 2008), suggesting a strong correlation with fluctuations in attention (Hayden, Smith, & Platt, 2009; Weissman, Roberts, Visscher, & Woldorff, 2006). Previous studies have shown that rightward dominance of right-handers in temporal regions is more prominent than that of left-handers when using a

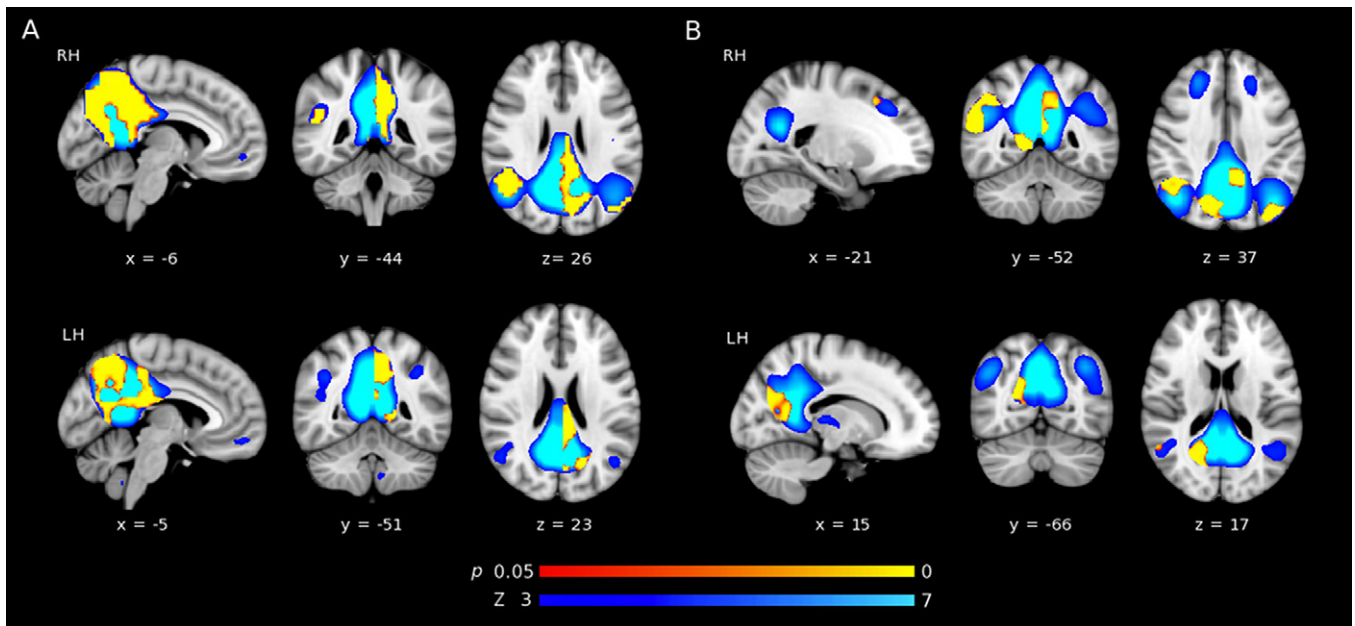


Fig. 1. Functional and structural asymmetries of the DMN. The default mode network for each group is presented in blue. RH: right handed; LH: left handed. (A) Hemispheric asymmetries of functional connectivity. (B) Hemispheric asymmetries in grey matter volume. Both functional and structural asymmetries are projected in red-yellow ($p < 0.05$, corrected). Greater leftward connectivity/grey matter volume is represented by clusters in the left hemisphere. Greater rightward connectivity/grey matter volume is represented by clusters in the right hemisphere. Images are projected in radiological convention. Coordinates are in mm in the MNI standard space. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2

Coordinates of local minima of p (corrected) for regions of the DMN showing hemispheric asymmetries in grey matter volume for the RH and LH groups. Left > Right: leftward asymmetry of grey matter volume. Right > Left: rightward asymmetry of grey matter volume. Coordinates are in millimeters in the MNI coordinate system; Brodmann areas were identified using Talairach Daemon Client (Lancaster et al., 2000).

Hemisphere asymmetry	Lobe	Region	Brodmann area	x (mm)	y (mm)	z (mm)	p	
RH-FCP								
Left > Right	Anterior	Culmen	*	−27	−38	−17	0.001	
	Frontal	Superior frontal gyrus	8	−19	22	43	0.006	
	Limbic	Posterior cingulate	31	−2	−57	25	0.001	
		Posterior cingulate	29	−2	−56	13	0.001	
		Anterior cingulate	32	−2	41	0	0.003	
	Occipital	Superior occipital gyrus	19	−34	−81	31	0.001	
	Parietal	Superior parietal lobule	7	−32	−76	51	0.001	
		Precuneus	19	−30	−82	39	0.001	
		Precuneus	31	−8	−47	31	0.001	
		Precuneus	7	−2	−78	51	0.038	
	Right > Left	Frontal	Medial frontal gyrus	11	8	53	−14	0.001
			Paracentral lobule	5	7	−43	57	0.045
		Limbic	Cingulate gyrus	23	6	−13	29	0.021
Cingulate gyrus			24	5	−17	35	0.05	
Occipital		Precuneus	31	22	−73	29	0.001	
		Cuneus	18	18	−77	29	0.001	
		Middle temporal gyrus	19	53	−64	14	0.001	
Parietal		Precuneus	7	7	−73	35	0.001	
		Precuneus	31	25	−69	29	0.001	
		Inferior parietal lobule	40	49	−54	40	0.001	
Temporal		Middle temporal gyrus	39	49	−65	15	0.001	
LH-FCP								
Left > Right		Anterior	Culmen	*	−26	−38	−17	0.003
	Limbic	Posterior cingulate	31	−2	−57	24	0.017	
		Posterior cingulate	30	−2	−49	21	0.025	
	Sub-lobar	Thalamus	Pulvinar	−8	−27	10	0.041	
Right > Left	Limbic	Posterior cingulate	31	27	−62	17	0.001	
		Posterior cingulate	30	19	−55	14	0.001	
	Occipital	Cuneus	18	18	−71	21	0.001	
	Parietal	Precuneus	31	25	−62	23	0.001	
		Inferior parietal	40	43	−51	43	0.017	
	Temporal	Superior temporal gyrus	22	55	−54	17	0.011	

* No Brodmann area identified.

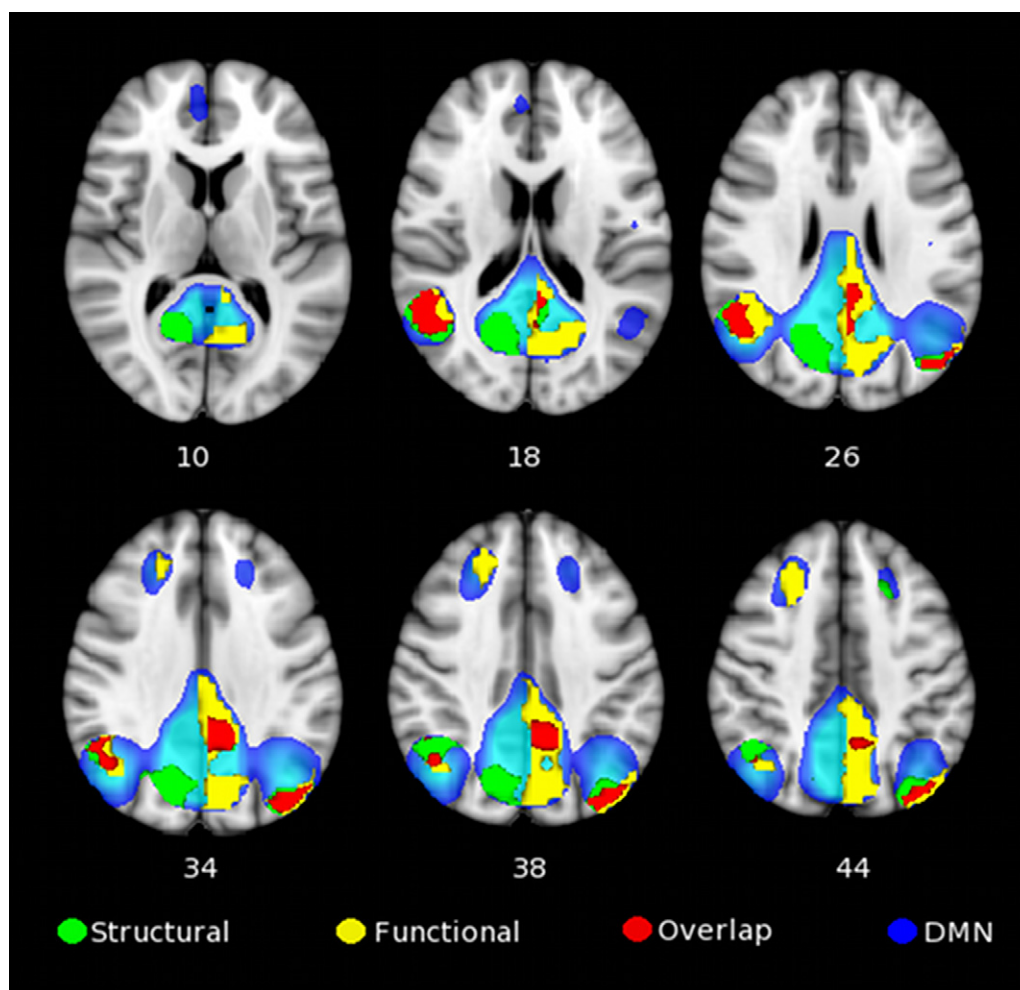


Fig. 2. Functional and structural asymmetries within the DMN of the RH group. The DMN is shown in blue, structural asymmetries in green, functional asymmetries in yellow, and overlapping of structural and functional asymmetries in red. Rightward asymmetries are represented by clusters in the right hemisphere. Leftward asymmetries are represented by clusters in left hemisphere. The image is in radiological convention projected over the MNI152 standard brain. Coordinates of axial slices are in millimeters in the MNI coordinate system. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

face-processing task (Badzakova-Trajkov, Häberling, Roberts, & Corballis, 2010; Bourne, 2008). Furthermore, rightward functional asymmetries observed in the middle frontal gyrus were also found in these regions during the landmark test for spatial attention (Çiçek, Deouell, & Knight, 2009) and face-processing tasks (Badzakova-Trajkov et al., 2010). Notably, this region showed inverse structural asymmetry in the right-handed group (Fig. 2), as also reported by Luders et al. (2006).

To determine which regions are connected to the right hemisphere, seed-based correlation analysis, performed using seeds in both temporal and frontal clusters (Fig. S1), showed the most prominent rightward functional asymmetry in the RH group (Fig. 1A). These seeds are highly connected to all regions of the DMN. Interestingly, the frontal seed exhibited a significant bilateral correlation in frontal regions but not in temporal regions (Fig. S1), suggesting functional asymmetry of connectivity patterns between seeds of the DMN, which was also reported by Yan et al. (2009).

Sample size is much larger in the right-handed than in the left-handed group, which could explain why there were more rightward functional asymmetries observed in the RH-FCP group. In contrast to the rightward structural asymmetries found in the PCG and precuneus in both groups (Fig. 1B), rightward functional asymmetries in the PCG, cuneus, and precuneus were only observed in the RH-FCP group (Fig. 1A), even though they all extend and are restricted to regions near the longitudinal fissure (5 mm), which could

contribute to signal contamination between hemispheres (Yan et al., 2009).

4.2. Leftward asymmetries

Leftward functional asymmetries were observed in both groups, while only the RH-FCP group presented leftward asymmetries in grey matter volume (Fig. 1B and Table 2). Greater functional connectivity in the left hemisphere was found in the MFG, CG, SOG, infPL, and precuneus for the right-handed group. Of these, leftward functional asymmetries have been reported in small world network properties for the MFG and CG (Tian et al., 2011). Leftward asymmetries in cortical thickness have been reported in MFG, CG, medFG, and infPL (Luders et al., 2006). Interestingly, the same study also found clusters of significant rightward asymmetries on the lateral surface in the posterior inferior temporal lobe.

Using rsfMRI, Liu et al. (2009) reported rightward asymmetries of functional connectivity in the visual cortex and occipital-parietal regions. The same study stated that regions “along the cortical midline” are the “most left-lateralized” regions, and they also exhibited leftward asymmetry in the present study (Table 1). Greater leftward functional connectivity and grey matter volume was observed in thalamic nuclei for the LH-FCP group (Tables 1 and 2). To our knowledge, no previous study has described asymmetry in functional connectivity properties of the thalamus using neuroimaging

techniques. In contrast to asymmetries found in temporal and frontal areas in the RH group, functional asymmetries in the LH group extended neither to frontal nor to temporal areas, even though the DMN component for this group did cover these regions (Fig. 1). It was found that the right-handed group presented more areas showing asymmetry than the left-handed group. Language lateralization is expressed differently depending on hand preference (Häberling, Badzakova-Trajkov, & Corballis, 2011; Pujol, Deus, Losilla, & Capdevila, 1999; Szaflarski et al., 2002). Nevertheless, these differences must be interpreted with caution since sample size in the RH-FCP group is larger than that of the LH-FCP group; thus, the absence of asymmetries in the left-handed group could be an effect of this constraint. What appears to be more important is that both groups exhibited leftward functional asymmetries in ventral and dorsal regions of the PCG and rightward structural asymmetries in the ventral portion (Fig. 1). There might be a level of consistency in this particular asymmetry, which has been observed using FCD on a 900-person data set from healthy subjects (Tomasi & Volkow, 2011).

4.3. Relation between structural and functional asymmetry

There is strong evidence supporting the idea that functional connectivity reflects structural connectivity (Deco, Jirsa, & McIntosh, 2011; Greicius, Supekar, Menon, & Dougherty, 2009) and as pointed out earlier, many of the regions showing asymmetry in the present study have also been reported to have structural and functional asymmetry (Luders et al., 2006; Swanson et al., 2011; Watkins et al., 2001). For example, leftward functional asymmetries for the PCG were reported here and by Tian et al. (2011), whereas structural asymmetries in grey matter volume and whole-brain network organization were greater in the left than in the right PCG (Iturria-Medina et al., 2011; Paus et al., 1996).

Data obtained in the present study suggest that functional asymmetries are not always determined or reflected by structural asymmetries. Fig. 2 shows the extension of functional and structural asymmetries of the RH-FCP group, where midFG and medFG exhibited rightward functional asymmetries, but leftward structural asymmetries were also present. Luders and colleagues (Luders et al., 2006) also showed leftward structural asymmetries for these regions, while another study described rightward functional asymmetry for the midFG (Swanson et al., 2011).

Overlapping of functional and structural asymmetries was observed in the anterior but not in the posterior portion of the PCG (Figs. 1 and 2). Although the PCG is often treated as a whole (homogenous), its subregions show different patterns of functional connectivity (Margulies et al., 2009), and it has been proposed to be made up of a dorsal (anterior) and a ventral (posterior) region (Vogt, Vogt, & Laureys, 2006) which appear to be functionally distinct (Leech, Kamourieh, Beckmann, & Sharp, 2011). This might explain why overlapping between structural and functional asymmetry was observed only in the dorsal region (Fig. 2). The same property could explain the segregation of structural asymmetry in temporal regions.

The middle temporal and superior temporal gyri also presented structural and functional asymmetries in the present and previous studies (Toga & Thompson, 2003) even though the direction of these asymmetries is not fully consistent. Some studies report leftward structural asymmetries in these regions (Toga & Thompson, 2003) while others report rightward asymmetries (Luders et al., 2006; Watkins et al., 2001). Tian et al. (2011) reported rightward functional asymmetries in these same regions. In this study, rightward structural and functional asymmetries were found in the anterior portion of the MTG/STG and leftward structural and functional asymmetries in the posterior portion of the MTG.

According to an interesting recent study by Tomasi and Volkow (2011), PCG exhibits leftward FCD while other regions such as the middle frontal, temporal, and frontal regions and the precuneus exhibit rightward FCD. These results are comparable to the functional asymmetries found here, as the PCG exhibited leftward asymmetries whereas rightward asymmetries were observed in frontal and temporal regions (Fig. 1 and Table 1). However, the structural asymmetries we observed differ from those reported earlier (Tomasi, 2009) since the posterior cingulate/precuneus showed leftward asymmetries in dorsal regions in the RH group and rightward asymmetries in ventral regions for both groups. Additionally, the midFG of the RH group presented rightward asymmetries in its anterior and leftward asymmetries in its posterior portion (Fig. 1).

In order to quantify laterality across groups, the numbers of voxels of the DMN, of functional asymmetries, and of grey matter volume asymmetries were calculated in both groups (Table S1). Although the DMN spanned both hemispheres, functional and structural asymmetries were not equally distributed between them (Table S1). For functional asymmetries, the percentage of significant voxels was greater in the left hemisphere. Structural asymmetries were the opposite, as more voxels were present in the right hemisphere. Similar asymmetry scores have been obtained by analyzing asymmetries in specific regions with different techniques (Liu et al., 2009; Luders et al., 2006; Tian et al., 2011; Tomasi & Volkow, 2011; Watkins et al., 2001). These results are limited to regions within the DMN. Luders et al. (2006) found that overall cortical thickness exhibits rightward asymmetry if only a few cortical points are sampled. Interestingly, this asymmetry is reversed if more cortical points are considered. Future studies using seeds along the DMN could help to clarify this asymmetry.

4.4. Consistent asymmetries of the PCG and precuneus

The only regions that consistently showed asymmetry across groups were the PCG and precuneus, which showed greater functional connectivity in the left hemisphere (Fig. 2 and Table 1) and greater grey matter volume in the right hemisphere (Fig. 1B and Table 2). Using meta-analysis from data of the 1000 Functional Connectomes Project (Biswal et al., 2010) to compare a large set of brain regions, Tomasi and Volkow (2010) found that the posterior cingulate/precuneus exhibits the greatest local functional connectivity density (lFCD) and is “the most prominent hub” of the human brain.

The degree of brain lateralization in motor and language functions in left-handed subjects has been reported to be different from that in right-handed subjects (Kim et al., 1993; Szaflarski et al., 2002). Moreover, it has been found that left-handed subjects have a larger *corpus callosum* (Witelson, 1985). In the present study, we found fewer asymmetries in left-handed than in right-handed subjects for both functional connectivity and grey matter volume (Fig. 1A and B). This observation could be attributed to a larger *corpus callosum* in left-handers (Habib et al., 1991; Witelson, 1985; Witelson & Goldsmith, 1991) if considering an excitatory model in which the *corpus callosum* integrates information from both hemispheres (Gazzaniga, 2000) and greater lateralization suggests lower callosal connectivity (Häberling et al., 2011). However, this idea is only tentative since some studies report no differences (Preuss et al., 2002; Steinmetz et al., 1992) or larger callosal areas in right-handers (Westerhausen et al., 2004).

Asymmetries in these regions could be used as biomarkers for psychiatric diseases. Swanson et al. (2011) found through resting state fMRI that functional asymmetries within the DMN are different in patients with schizophrenia from those in controls, describing leftward asymmetries in the cingulate gyrus/precuneus

for controls but rightward asymmetries for these regions in patients with schizophrenia. Future studies are necessary to clarify differences in structural brain asymmetry between controls and patients, and could reveal the nature of these asymmetries.

5. Conclusion

In summary, the present study of two groups of healthy subjects provides evidence that the default mode is unequally distributed between hemispheres, both functionally and structurally. Although some differences varied across groups, leftward functional asymmetry of the posterior cingulate/precuneus was the most consistent result in both groups, indicating a left dominance of functional connectivity in this specific region for both left- and right-handed subjects. Grey matter volume was greater in the left posterior portion of the posterior cingulate and precuneus across all groups. The RH group (largest data set) showed overlapping of structural and functional asymmetry in the anterior portion of the posterior cingulate and leftward structural but rightward functional asymmetry in the middle and medial frontal gyri. These findings provide insight into the functional and structural hemispheric asymmetry of the DMN.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2012.02.014.

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