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Altered resting-state cerebellar-cerebral functional connectivity in obsessive-compulsive disorder

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Original Article

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Abstract

Background. The role of the cerebellum in obsessive-compulsive disorder (OCD) has drawn increasing attention. However, the functional connectivity between the cerebellum and the cerebral cortex has not been investigated in OCD, nor has the relationship between such functional connectivity and clinical symptoms.

Methods. A total of 27 patients with OCD and 21 healthy controls (HCs) matched on age, sex and education underwent magnetic resonance imaging (MRI). Seed-based connectivity analyses were performed to examine differences in cerebellar-cerebral connectivity in patients with OCD compared with HCs. Associations between functional connectivity and clinical features in OCD were analyzed.

Results. Compared with HCs, OCD patients showed significantly decreased cerebellar-cerebral functional connectivity in executive control and emotion processing networks. Within the OCD group, decreased functional connectivity in an executive network spanning the right cerebellar Crus I and the inferior parietal lobule was positively correlated with symptom severity, and decreased connectivity in an emotion processing network spanning the left cerebellar lobule VI and the lingual gyrus was negatively correlated with illness duration.

Conclusions. Altered functional connectivity between the cerebellum and cerebral networks involved in cognitive-affective processing in patients with OCD provides further evidence for the involvement of the cerebellum in the pathophysiology of OCD, and is consistent with impairment in executive control and emotion regulation in this condition.

Introduction

Obsessive-compulsive disorder (OCD) is characterized by intrusive thoughts (obsessions) and repetitive behaviors (compulsions), has a lifetime prevalence of 2–3% in the general population, and is associated with substantial morbidity (Ruscio *et al.*, 2010). It is also a chronic disabling mental disorder, seriously affecting the patient's personal life, and resulting in heavy economic burdens on families and society.

Neurophysiological studies have reported a number of cognitive dysfunction in patients with OCD, including impairment in memory, attention, planning, response inhibition and decision-making (Benzina *et al.*, 2016). And a growing body of neuroimaging studies have indicated that altered activation in a broad range of brain networks may underlie cognitive impairment and clinical symptoms in OCD (Nakao *et al.*, 2014; Heinzel *et al.*, 2017). Resting-state functional magnetic resonance imaging (rs-fMRI) studies detecting intrinsic activity fluctuations have identified a number of well-defined networks, including the default-mode network (DMN), executive control network (ECN), salience network (SN; Goulden *et al.*, 2014), and etc. The DMN includes several brain regions, such as medial prefrontal cortex (mPFC), precuneus, posterior cingulate cortex (PCC) and bilateral inferior parietal lobule (Raichle and Snyder, 2007), involved in cognitive functions, including intrinsic stimulus-independent thoughts (Gilbert *et al.*, 2007), autobiographical memory, and monitoring of internal and external environment (Buckner *et al.*, 2008). The ECN, often characterized as a task-positive network, mainly encompasses dorso-lateral prefrontal cortex, posterior parietal cortex, angular gyrus and occipital cortex, and is associated with the performance of cognitively demanding tasks (Sridharan *et al.*, 2008). A growing number of studies have reported that patients with OCD exhibit altered functional connectivity within and between the DMN and ECN (Peng *et al.*, 2014; Chen *et al.*, 2016; Fan *et al.*, 2017), which may be associated with impairment of monitoring and goal-directed behavior (Fink *et al.*, 2017; Vaghi *et al.*, 2017). In addition, neuroimaging studies have revealed abnormal activation and connectivity in motor network and frontal-limbic circuits in patients with OCD (Mantovani *et al.*, 2013; de

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Vries *et al*., 2017), associated with inhibition deficits and dysregulation of emotion (Heinzel *et al*., 2017; Thorsen *et al*., 2018) in this condition.

Despite these important findings, previous studies have not yet systematically explored the role of the cerebellum in OCD. Cerebellum is traditionally considered to participate in motor coordination and physical balance (Schmahmann, 2004), while evidence from recent animal and human studies has indicated that the cerebellum has reciprocal connections with prefrontal and parietal cortices (Schmahmann and Pandya, 1989; Middleton and Strick, 2000; Kelly and Strick, 2003; Ramnani *et al*., 2006), and plays a pivotal role in cognitive and affective processes (Schmahmann, 2004). Growing evidence from resting-state functional connectivity (rsFC) studies have indicated that separate regions of the cerebellum are connected to distinct cerebral areas, forming a complex topography function (Habas *et al*., 2009; Krienen and Buckner, 2009). Segregated cerebral-cerebellar loops may mediate executive control, effective, default-mode, and sensorimotor function (Habas *et al*., 2009; Krienen and Buckner, 2009). Recent studies have indicated that altered cerebro-cerebellar functional connectivity is associated with several psychiatric disorders, including autism spectrum disorder (Khan *et al*., 2015), schizophrenia (Guo *et al*., 2015), and major depressive disorder (MDD; Guo *et al*., 2013). Moreover, altered functional connectivity between the cerebellum and the cognitive and affective cortex are correlated with the severity of symptom in MDD (Alalade *et al*., 2011) and cognitive impairment in seasonal affective disorder (Yuan *et al*., 2017).

There has, however, been relatively little attention to cerebellar-cerebral functional connectivity in OCD. This is an important question given the growing evidence from brain imaging studies for a role of the cerebellum in OCD. A number of publications have indicated alterations in cerebellar structure (Pujol *et al*., 2004; Nakao *et al*., 2005; Nabeyama *et al*., 2008; de wit *et al*., 2014; Narayanaswamy *et al*., 2016) or function (Nabeyama *et al*., 2008; Ping, 2013; Nakao *et al*., 2014) in this condition, including decreased right cerebellar tonsil activation (Nabeyama *et al*., 2008), reduced cerebellar volume (Narayanaswamy *et al*., 2016), increased bilateral cerebellar region homogeneity in resting-state and the inverse correlation with the severity of compulsion in patients with OCD (Ping, 2013). Given the cognitive impairment, dysregulation of emotion and behavioral dysfunction (Heinzel *et al*., 2017; Thorsen *et al*., 2018), combined with alterations in a broad range of brain networks in OCD (Fan *et al*., 2017; Posner *et al*., 2017), we therefore compared cerebellar-cerebral functional connectivity, with a focus on executive control, effective, default-mode, and sensorimotor networks in OCD patients and healthy controls (HCs), using seeds in the cerebellum that have been suggested to be involved in multiple functions (Habas *et al*., 2009; Krienen and Buckner, 2009). We hypothesized (1) that OCD patients would exhibit disrupted functional connectivity in cerebellar-cerebral networks that mediate executive control, effective regulation, default-mode, and sensorimotor function and (2) that altered cerebellar-cerebral functional connectivity would be associated with clinical symptoms.

Materials and methods

Subjects

Twenty-seven right-handed adult patients with OCD were recruited from the Shanghai Mental Health Center, Shanghai, China, between June 2016 and April 2017. All patients were diagnosed by a psychiatrist according to DSM-IV criteria. Of the 27 OCD patients, 14 were drug-naïve and 13 were medication-free (patients who discontinued medication for at least 8 weeks were considered medication-free), the medication-free patients mainly had received treatment with selective serotonin reuptake inhibitors, and had to stop the medication by themselves for different reasons, with the obsessive-compulsive symptom still exists or relapse when the study is recruited. There are no any significant differences in age, gender, education level, Y-BOCS score, illness duration and mean frame-wise displacement between the drug-naïve and the medication-free patients (see Table 1 in Supplement). The exclusion criteria for the OCD group included any axis I psychiatric disorder comorbidity. Twenty-one HCs were recruited from the community, and matched for age, gender, handedness, and education, individuals who had any psychiatric history or family history were excluded. Additional exclusion criteria for all participants were a history of drug or alcohol abuse, craniocerebral trauma, serious physical illness, pregnancy, and contraindications to MRI. Individuals younger than 18 years or older than 65 years were also excluded.

Clinical measures

The severity of OCD symptoms was assessed using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman *et al*., 1989). To be eligible for the study, patients were required to have a Y-BOCS total score of $\geqslant$16. Current symptoms of depression and anxiety were assessed using the Beck Depression Inventory-second edition (BDI-II; Beck *et al*., 1996) and the Beck Anxiety Inventory (BAI; Steer *et al*., 1993), respectively. All participants were screened with the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan *et al*., 1998) to ascertain that there was no history of a DSM-IV psychiatric disorder.

Image acquisition

MRI scans were obtained with a 3.0 T Verio scanner (Siemens, Erlangen, Germany) with a 32-channel phased-array head coil. During the MRI scans, all participants were instructed to keep their eyes closed, to relax but not fall asleep, and to lie still without moving. Three-dimensional T1-weighted images were acquired by employing a 3D-MPRAGE sequence with the following parameters: time repetition (TR) = 2300 ms, time echo (TE) = 3.5 ms, flip angle = 9°, matrix size = 64 × 64, field of view (FOV) = 256 mm, 192 sagittal slices, slice thickness = 1 mm, acquisition voxel size = 1 × 1 × 1 mm^3. After structural MRI scannings, resting-state fMRI scans were acquired with the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 220 mm, flip angle = 77°, matrix size = 64 × 64, voxel size = 3.0 × 3.0 × 3.0 mm^3, 50 axial slices with a slice thickness of 3 mm and no slice gap, the fMRI scanning lasted for 480 seconds, and 240 volumes were obtained.

Data processing

MRI data analysis was carried out using the standard pipeline integrating SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and REST (http://restfmri.net/forum/REST_V1.8) as implemented in Data Processing & Analysis for Brain Imaging (DPABI_v2.3) (Yan *et al*., 2016). For image preprocessing, the

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first 10 volumes were removed for steady-state magnetization. The remaining 230 volumes were corrected for slice timing and realigned for head motion correction. Then the participants' structural images were manually co-registered and realigned, and subsequently co-registered to the mean functional image, and segmented as grey matter, white matter, and cerebrospinal fluid. The head motion of all participants during resting-state fMRI acquisition was examined, no participants had more than 1.5° of maximal rotation and 1.5 mm of maximal translation. Six head motion parameters, the average signals from cerebrospinal fluid and white matter were regressed in first-level analysis, we also calculated the mean frame-wise displacement (FD) of each participant (Power *et al*., 2012) and took it as a confounding variable in subsequent analysis (Yan *et al*., 2013; eMethods in the Supplement). Next, all functional data were normalized to Montreal Neurological Institute (MNI) space and the processed images were spatially smoothed with a 4 mm full width at the half maximum Gaussian kernel. Further preprocessing included removing linear trends and temporal band-pass filtering (0.01–0.08 Hz) to reduce the effects of low-frequency drift and high-frequency physiologic noise.

To identify cerebellar-cerebral functional networks, seed-based correlation analyses were carried out by using regions of interest (ROIs) in the cerebellum. Previous studies (Habas *et al*., 2009; Krienen and Buckner, 2009) have found that cerebellum seeds are able to identify cerebellar-cerebral executive control, default-mode, affective-limbic, and motor networks, and we used these seeds here (Table 1) (Krienen and Buckner, 2009). A 6 mm radius sphere was drawn from each center point as an ROI. Pearson correlation coefficients were computed between the seeds and the voxels of the whole brain to create the correlation maps for each seed and each participant. Finally, the correlation maps were z-transformed with Fisher's r-to-z transformation to improve the Gaussianity of their distribution.

Statistical analysis

We compared distributions of age, gender and years of education across the groups, using *t* tests and Chi-square tests, as appropriate. To verify the results of previous studies on the cerebellar topologies of different networks in HC group (Habas *et al*., 2009; Krienen and Buckner, 2009), and to further explore the spatial topography of cerebellar-cerebral functional connectivity in OCD group, one-sample *t* tests were conducted to explore the spatial topography of cerebellar-cerebral functional connectivity in HC and OCD group, separately. Multiple comparisons for the one-sample *t* tests were corrected by Monto Carlo stimulations with a combined individual voxel threshold at $p < 0.001$ and the required cluster size corresponded to the Alphasim correction of $p < 0.05$ (cluster size >50 voxels) (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf), calculated using DPABI (Yan *et al*., 2016). We then conducted a two-sample *t* test to compare differences in cerebellar-cerebral functional connectivity in OCD group relative to HCs, using an explicit mask made by DPABI (Yan *et al*., 2016; eMethods in Supplement for details). The significance level was set at the individual voxel $p < 0.005$ with Alphasim cluster correction of $p < 0.05$ (cluster size >90 voxels).

Mean *z* scores were extracted from connected cerebral regions which showed significant differences in the OCD group relative to the HC group, and correlation analyses were conducted to examine the relation between mean z values and severity of OCD symptoms, with significance level set at $p < 0.05$.

Post-hoc analysis was performed on brain regions showing significant differences in functional connectivity between patients and controls. We used G × Power to calculate Cohen's *d*, which was applied to determine the robustness of findings (Cohen, 1977). Effect sizes were considered as small with d value below 0.2, medium with *d* value between 0.2 and 0.5, and large with *d* value above 0.8.

Results

Subjects

Demographic and clinical characteristics of the participants are listed in Table 2. There was no significant difference between the OCD group and the control group in age, gender or years of education. The mean (S.D.) Y-BOCS total score for the OCD group was 28.6 (S.D. = 4.3), and depression and anxiety scores were significantly higher in the OCD group than in the control group (two sample *t* test, both $p < 0.001$).

Cerebellar-cerebral functional connectivity in HC group

In the HCs group, we found that cerebellar seeds had functional connectivity with distributed cerebral areas (Fig. 1). When we used a more conservative threshold of $p < 0.0001$ (with Alphasim correction of $p < 0.05$), good specificity for cerebral-cerebellar functional connectivity was seen (Fig. 2). We found significant connectivity in (1) an executive network (including middle frontal cortex, inferior parietal cortex, temporal cortex, and thalamus; Figure 2); (2) an effective regulation network (including inferior parietal cortex, superior frontal gyrus, middle frontal gyrus, caudate and precuneus) (Fig. 2); (3) the DMN (including mPFC, PCC, precuneus and bilateral parietal lobe; Fig. 2); and (4) a sensorimotor network (including supplementary motor area, parietal lobe, lingual gyrus and occipital lobe) (Fig. 2).

In the OCD group, we also found significant functional connectivity in multiple cerebellar-cerebral network, and the OCD group showed similar cerebellar-cerebral connectivity patterns with the HC group (Fig. 2 and eResults in the Supplement).

Cerebellar-cerebral functional connectivity in OCD group relative to HC group

Relative to HCs, patients with OCD showed significantly decreased functional connectivity in cerebellar-cerebral networks mediating executive, affective-limbic and motor functions (Table 3).

First, for the executive network, patients with OCD had reduced functional connectivity between (1) the bilateral Crus I_{Exec1} and the fusiform, lingual gyrus, temporal lobe, occipital lobe, inferior parietal lobule and postcentral gyrus, (2) the bilateral Crus II_{Exec2} and the superior occipital gyrus, lingual gyrus and parahippocampal gyrus, and (3) the right Lobule VI_{Exec3} and bilateral inferior temporal gyrus and right inferior parietal gyrus (Fig. 3).

Second, for the effective network, patients with OCD showed decreased functional connectivity between the right lobule VI_{Aff} and parahippocampal gyrus and middle temporal gyrus, between the left lobule VI_{Aff} and lingual gyrus, and between the $Vermis_{Limbic}$ and the fusiform gyrus (Fig. 3).

Third, for the sensorimotor network, patients with OCD had reduced functional connectivity between the right lobule V_{Mot} and the superior frontal gyrus (Fig. 3).

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Table 1. Cerebellar seeds and coordinates grouped by network

Cerebellar network	Cerebellar seed	Side	code	MNI (*x*,*y*,*z*)
Executive network	Crus I_{Exec1}	L	roi1	−12, −78, −28
	Crus I_{Exec1}	R	roi2	12, −78, −28
	Crus II_{Exec2}	L	roi3	−36, −70, −46
	Crus II_{Exec2}	R	roi4	36, −68, −44
	Lobule VI_{Exec3}	L	roi5	−36, −52, −34
	Lobule VI_{Exec3}	R	roi6	36, −52, −34
Default-mode network	Crus I_{DMN}	L	roi7	−32, −76, −34
	Crus I_{DMN}	R	roi8	34, −80, −36
Affective-limbic network	Lobule VI_{Aff}	R	roi9	26, −64, −34
	Lobule VI_{Aff}	L	roi10	−26, −64, −34
	$Vermis_{Limbic}$	L	roi11	−4, −80, −34
Motor network	Lobule V_{Mot}	R	roi12	22, −52, −22
	Lobule V_{Mot}	L	roi13	−20, −50, −24

R, right, L, left. Exec, executive; DMN, default-mode network; Aff, affective; Mot, motor.

Table 2. Participant demographic and clinical features

Variables mean (s.d.)	OCD group ($n = 27$)	HC group ($n = 21$)	t/χ^2	p Values
Age, years	29.22(8.10)	33.57(7.24)	−1.96	0.056
Sex (M/F)	16/11	12/9	0.144	0.886
Education, years	13.63(2.78)	12.95(3.10)	0.798	0.436
Mean FD	0.10(0.03)	0.08(0.04)	1.91	0.058
BDI-II scores	23.81(11.64)	3.33(3.26)	8,71	<0.001
BAI scores	17.48(9.74)	2.29(3.15)	7.61	<0.001
Y-BOCS				
Total score	28.56(4.29)	N/A	–	–
Obsession subscale score	14.70(2.25)	N/A	–	–
Compulsion subscale score	13.85(2.52)	N/A	–	–
Age of onset	21.52(5.41)	N/A	–	–
Duration of illness, years	8.21(7.55)	N/A	–	–

FD, frame-wise displacement; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; BDI-II, Beck Depression Inventory-second edition; BAI, Beck Anxiety Inventory.

Potential confounders

Decreased cerebellar-cerebral functional connectivity in executive, affective-limbic and sensorimotor networks in OCD remained significant after adjusting for age and head motion. In addition, we also found decreased cerebellar functional connectivity with cingulate and thalamus, and for the DMN, patients with OCD had reduced cerebellar functional connectivity with temporal gyrus (eResults and eTable 2 in the Supplement).

Correlation between cerebellar-cerebral FC and clinical features of OCD

Within the OCD group, connectivity of the right Crus I_{Exec1}-inferior parietal lobule was positively correlated with symptom severity of OCD measured by Y-BOCS score ($r = 0.422$, $p = 0.028$ uncorrected;) (Fig. 4a), further analysis showed that the main contribution was from the compulsive subscale score ($r = 0.427$, $p = 0.026$ uncorrected); furthermore, within OCD group, connectivity of the left lobule VI_{Aff}-lingual gyrus coupling was negatively correlated with illness duration ($r = -0.631$, $p < 0.001$ uncorrected; $p = 0.04$ Bonferroni corrected) (Fig. 4b).

Discussion

To the best of our knowledge, this study is the first to explore resting-state cerebellar-cerebral functional connectivity in OCD. We found decreased cerebellar-cerebral functional connectivity in OCD including in executive, default-mode, affective-limbic,

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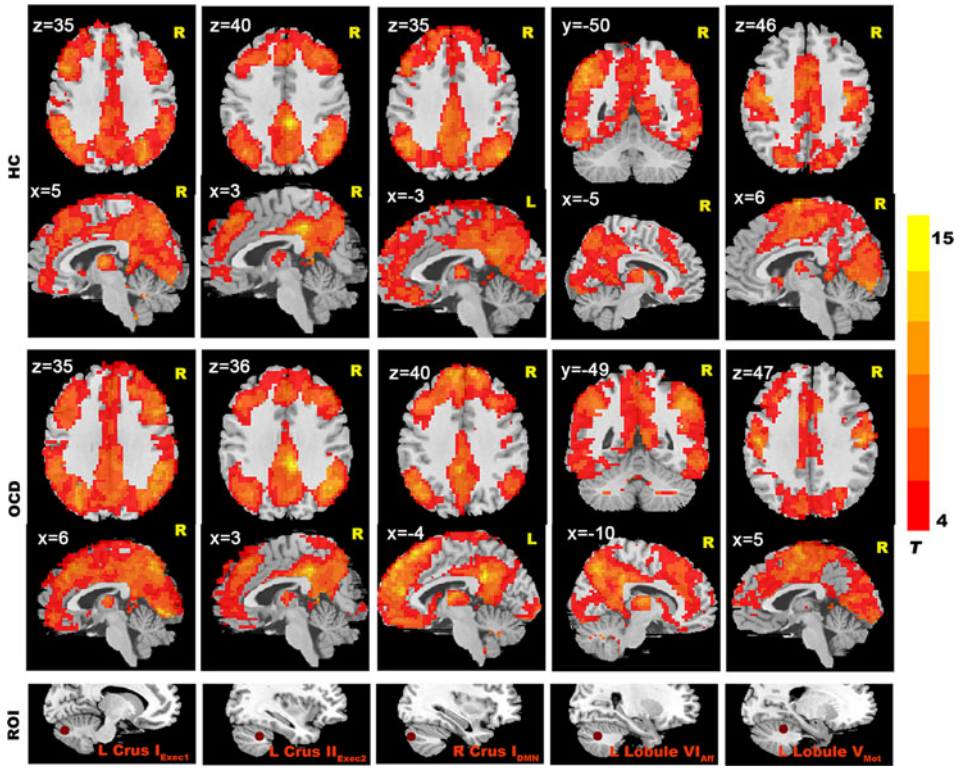


Fig. 1. Resting-state cerebellar-cerebral functional connectivity in the OCD group *vs*. HC group ($p < 0.001$).

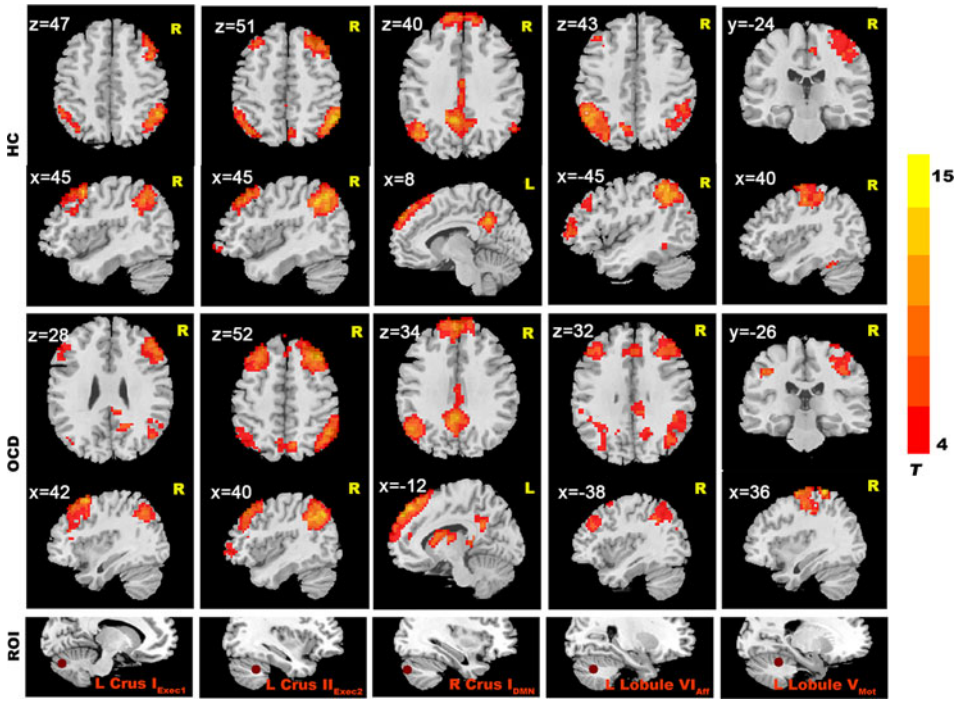


Fig. 2. Resting-state cerebellar-cerebral functional connectivity in the OCD group *vs*. the HC group ($p < 0.0001$). The seed regions shown here include: left Crus I_{Exec1}, left Crus II_{Exec2}, right Crus I_{DMN}, left Lobule VI_{Aff}, left Lobule V_{Mot}.

and sensorimotor networks. Furthermore, within the OCD group, functional connectivity in an executive network spanning the right Crus I_{Exec1} and the inferior parietal lobule was positively correlated with OCD symptom severity, and functional connectivity in an affective-limbic network spanning the left lobule VI_{Aff} and lingual gyrus was negatively correlated with illness duration, consistent with involvement of these networks in the pathophysiology of OCD (Chen *et al*., 2016; de Vries *et al*., 2017).

The present study demonstrating that segregated cerebellar-cerebral connectivity exists both in HCs and OCD patients provides a partial replication of previous studies (Habas *et al*., 2009; Krienen and Buckner, 2009). This work is in turn consistent

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Table 3. Brain regions showing decreased cerebellar-cerebral FC in the OCD group compared with the HC group

Cerebellar seeds	Brain regions	side	Voxel	MNI (*x*, *y*, *z*)	*T* values	Cohen's d
Executive network						
L Crus I_{Exec1}	Fusiform	L	96	−36, −54, −16	−4.4165	1.28
	Lingual gyrus	R	285	3, −72, 0	−4.5064	1.22
	Middle occipital gyrus	L	66	−48, −63, −12	−4.5094	1.21
	Middle temporal gyrus	R	79	42, −69, 9	−4.5343	1.12
	Superior parietal lobule	L	244	−24, −48, 60	−4.9649	1.12
	Postcentral gyrus	R	79	30, −30, 73	−3.9604	1.12
R Crus I_{Exec1}	Inferior temporal gyrus	R	64	54, 3, −36	−3.9991	1.12
	Fusiform	L	58	−30, −60 ,−9	−3.8345	1.13
	Fusiform	R	165	36, −54, −21	−3.943	1.25
	Precuneus	L	53	−6, −45, 57	−4.1569	1.04
	Inferior parietal lobule	R	52	39, −42, 57	−3.8924	1.12
L Crus II_{Exec2}	Calcarine	R	779	9, −66, 18	−4.5337	1.36
	Superior occipital gyrus	R	86	15, −45, −9	−4.4969	1.34
R Crus II_{Exec2}	Parahippocampal gyrus	R	492	18, −42, −9	−6.2699	1.70
	Lingual gyrus	L	152	−24, −45, −6	−5.9356	1.70
	Superior occipital gyrus	R	89	24, −78, 39	−4.6214	1.30
R $LobuleVI_{Exec3}$	Inferior temporal gyrus	R	99	48, −48, −9	−4.5275	1.37
	Inferior temporal gyrus	L	79	−48, −51, −9	−5.1342	1.40
	Inferior parietal gyrus	R	54	57, −36, 45	−4.4879	1.13
Affective-limbic network						
R Lobule VI_{Aff}	Middle temporal gyrus	R	40	48, −45, −12	−5.0271	1.44
	Parahippocampal gyrus	R	48	30, −42, −6	−4.0029	1.21
L Lobule VI_{Aff}	Lingual gyrus	R	64	15, −48, −9	−4.7725	1.27
$Vermis_{Limbic}$	Lingual gyrus	L	67	−21, −75, −12	−4.023	0.75
	Fusiform	R	100	36, −75, −18	−4.1261	1.15
Motor network						
R Lobule V_{Mot}	Superior frontal gyrus	R	59	33, 54, 30	−5.0498	1.29

Exec, executive control network; DMN, default-mode network; Aff, affective; Mot, motor network.

with the increased recognition of the involvement of the cerebellum in emotional and cognitive processes mediated by a broad range of cerebellar-cerebral networks (Schmahmann, 2004; Stoodley and Schmahmann, 2010). Findings of altered cerebellar-cerebral functional connectivity in OCD patients may well underlie cognitive and affective dysfunctions in this condition.

Decreased connectivity of the cerebellum-cerebral executive network in OCD

We found lower functional connectivity of the cerebellum with a cerebral executive network in OCD. Previous work has reported that the executive network is strongly involved in higher cognitive function, including attention control, planning and decision-making (Chamberlain *et al.*, 2006; Sylvester *et al.*, 2012; Dong *et al.*, 2015). Functional abnormality of this network has been reported in patients with OCD (Chen *et al.*, 2016), which may lead to a dysfunctional strategies for coping with threat and uncertainty (Gottlich *et al.*, 2014), related to the clinical symptoms of OCD, such as excessive monitoring of intrusive thoughts and behavior. Peterburs and Desmond (2016) indicated that the cerebellum contributes to performance monitoring, a set of cognitive and affective functions underlying adaptive behavior, and altered functional connectivity of the cerebellum-cerebral executive network has associated with anxiety vulnerability (Caulfield *et al.*, 2016). Thus lower the cerebellar-cerebral ECN connectivity may reflect abnormal external monitoring, with excessive attention to unrelated external stimulation, which subsequently evokes excessive anxiety in OCD, it may explain why patients must exert great effort to resist the obsessive–compulsive urges. Furthermore, the right Crus I_{Exec1}-inferior parietal lobule coupling was positively correlated with symptom severity of OCD (mainly compulsive symptom). Parietal cortex is an important part of the executive network, and is involved in attention and response inhibition (Dong *et al.*, 2015), we hypothesize that decreased functional connectivity between the cerebellum and inferior

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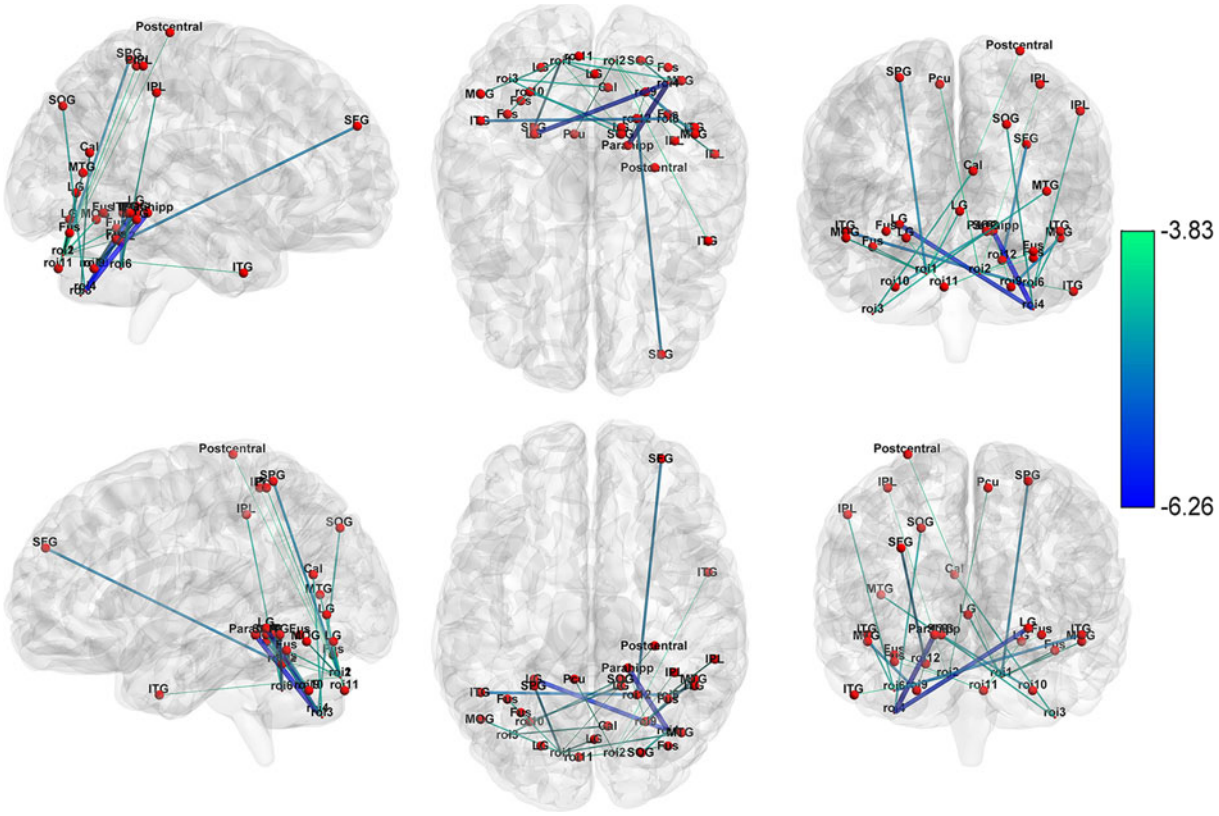


Fig. 3. Decreased cerebral-cerebellar functional connectivity in patients with OCD relative to HCs. The widths of the line are proportional to the *t* values. MTG = Middle Temporal Gyrus; ITG = Inferior Temporal Gyrus; LG = Lingual Gyrus; Parahippo = Parahippocampal Gyrus; Fus = Fusiform; SFG = Superior Frontal Gyrus; Pcu = Precuneus; IPL = Inferior Parietal Lobule; SOG = Superior Occipital Gyrus.

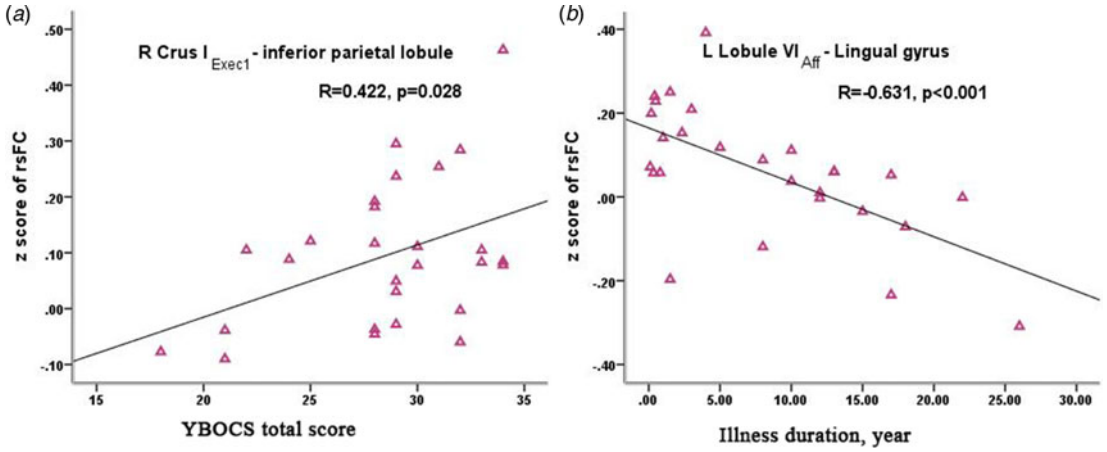


Fig. 4. Correlation between the altered cerebellar-cerebral functional connectivity with clinical features of OCD: (a) significant positive correlation of decreased right Crus I_{Exec1}-inferior parietal lobule connectivity with the severity of obsessive-compulsive symptoms; (b) significant negative correlation of decreased left lobule VI_{Aff}–lingual gyrus connectivity with illness duration. Note: rsFC = resting-state functional connectivity; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; L = left; R = right.

parietal lobule may underlie inhibitory impairment, resulting in excessive repetitive behavior in OCD.

Decreased connectivity of the cerebellum-cerebral sensorimotor network in OCD

In addition, compared with HCs, patients with OCD showed significantly decreased functional connectivity between the cerebellum and sensory cortex (including superior occipital gyrus, inferior occipital gyrus, and inferior temporal gyrus). This may reflect aberrant information transition between these brain regions, associated with excessive sensitivity to external stimulation (Andreasen and Pierson, 2008). Neurophysiological studies in OCD have revealed that abnormal activation of temporal gyrus is associated with dysfunctions in early inhibitory control processes and difficulties inhibiting task-irrelevant

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information (Wolff *et al.*, 2017). Thus altered connectivity between the cerebellum and temporal gyrus might result in failure to suppress irrelevant information, associated with the rigid and repetitive thoughts in OCD.

In addition, there was decreased functional connectivity between the sensorimotor area of the cerebellum and the superior frontal gyrus in OCD patients relative to HCs in this study. Cerebellar activation has been shown to contribute to decreased activation of the sensorimotor cortex during self-produced tactile stimulation (Blakemore *et al.*, 1999). In line with cerebellar involvement in sensory prediction (Jutta *et al.*, 2016), altered cerebellar-cerebral connectivity in the sensorimotor network in OCD might be consistent with alterations in visuospatial processing and perception in this disorder (Wolff *et al.*, 2017; Geller *et al.*, 2018).

We also found the decreased functional connectivity of left lobule VI_{Aff}-lingual gyrus coupling in patients with OCD, which was negatively correlated with illness duration. Neuroimaging studies have pointed to the role of lingual gyrus in processing emotional related visual stimuli (Lane *et al.*, 1999). In light of the functional role of the lingual gyrus, we hypothesis that our observation relates to the phenomenology of OCD, whereby specific visual stimuli, such as messy scenes or images that may induce contamination or check related behaviors. Furthermore, the correlation of cerebellar-lingual gyrus coupling with the illness duration is perhaps consistent with previous work indicating that thickness and surface area of lingual gyrus are negatively correlated with the illness severity in OCD (Venkatasubramanian *et al.*, 2012).

Decreased connectivity of the cerebellum-cerebral affective-limbic network in OCD

We also found the decreased functional connectivity between the cerebellum and emotion processing (limbic) regions (including parahippocampal gyrus and cingulate gyrus) in OCD patients compared with HCs. The limbic system is involved in social cognition and emotional regulation, the parahippocampal gyrus is supposed to involved in episodic memory, and the cingulate gyrus participates in the regulation of emotion and social cognition (Campos *et al.*, 2016). A meta-analysis concludes that the involvement of the cerebellum in social cognition depends on its functional connectivity with the cerebrum (Van Overwalle *et al.*, 2015). Moreover, cerebellar stimulation can alter limbic function and elicit behaviors like grooming (Reis *et al.*, 1973), thus we hypotheses that decreased connectivity between the cerebellum and limbic system might underlie the phenomenology and dysregulation of emotion and cognition in OCD (Paul *et al.*, 2016).

Decreased connectivity of the cerebellum-cerebral DMN in OCD

Additionally, we found decreased functional connectivity between the cerebellum and the DMN (including precuneus, cingulate gyrus, and superior temporal gyrus; eTable2 in Supplement). The DMN has been supposed to play an important role in self-referential, internal-directed attention (Gilbert *et al.*, 2007), while the executive network participates in external-stimuli related attention (Sridharan *et al.*, 2008; Sylvester *et al.*, 2012). Cognitive behavior therapy may improve the reduced negative relationship between the DMN and the executive network revealed by previous research (Stern *et al.*, 2012), suggesting that there are competitive relationships between these two networks. Our findings of decreased connectivity between cerebellum and both DMN and executive networks might underlie the difficult to 'switch off' when attention was needed to direct to external stimuli in a cognitive task, which in turn may lead to difficulties in separating from internally generated intrusive thoughts, and the thought-action fusion, that is, associated with obsessive symptom.

The present study reported altered cerebellar-cerebral connectivity in a broad of different networks in patients with OCD relative to HCs. However, we failed to identify any differences in cerebellar-striatum or cerebellar-amygdala connectivity in OCD. There are several possible reasons: on the one hand, the reproducibility of neuroimaging findings may decrease due to intrinsically low statistical power of the relatively small sample size; on the other hand, this study used the whole-brain voxel-wise analysis to compare group difference of the cerebellar-cerebral connectivity, increased number of multiple comparisons may mask the results of brain regions that contain few voxels. The question of cerebellum connectivity with striatum and amygdala in OCD should be further explored in future studies, with a more specific assumption and larger sample sizes.

A number of limitations of our study deserve emphasis. First, our sample size was relatively small, which may have limited our ability to find additional differences across groups, and increase the instability of the results. Second, due to the lack of objective measures of cognitive function in the present study, definitive conclusions about the relationship between functional connectivity and cognitive dysfunction cannot be drawn. Further work using neuropsychological testing and task-based fMRI is needed to confirm the hypotheses formulated here. Third, the above results and discussion are based on data processed without global signal regression, because the global signal may remove true blood oxygen dependence level (BOLD) signal and potentially alter group differences in functional connectivity (Saad *et al.*, 2012). Finally, we did not apply a statistical correction for the number of separate tests (13 ROIs), given that this was an exploratory study.

Conclusion

In conclusion, our study reports altered functional connectivity between the cerebellum and distributed cerebral regions in patients with OCD. These data prompt the hypothesis that a range of cortical-cerebellar networks may be involved in the pathophysiology of OCD, and provides a new direction for the study of OCD. However, the exact role of cerebellar-cerebral networks in the pathogenesis and development of OCD are not yet fully delineated. Future research, including neuropsychological testing, and focused on changes of functional connectivity in cerebellum-cerebral networks during treatment may be useful in further expanding this model of OCD, and in determining whether it has clinical utility.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718001915

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Declaration of interest. None.

Ethical standards. The authors note that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Alalade E, Denny K, Potter G, Steffens D, and Wang LH (2011) Altered cerebellar-cerebral functional connectivity in geriatric depression. *PLoS ONE* **6**, e20035.

Andreasen NC and Pierson R (2008) The role of the cerebellum in schizophrenia. *Biological Psychiatry* **64**, 81–88.

Beck AT, Steer RA, Ball R and Ranieri W (1996) Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *Journal of Personality Assessment* **67**, 588–597.

Benzina N, Mallet L, Burguiere E, N'Diaye K and Pelissolo A (2016) Cognitive dysfunction in obsessive-compulsive disorder. *Current Psychiatry Reports* **18**, 80.

Blakemore S-J, Frith CD and Wolpert DW (1999) Spatiotemporal prediction modulates the perception of self-produced stimuli. *Journal of Cognitive Neuroscience* **11**, 551–555.

Buckner RL, Andrews-Hanna JR and Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences* **1124**, 1–38.

Campos C, Santos S, Gagen E, Machado S, Rocha S, Kurtz MM and Rocha NB (2016) Neuroplastic changes following social cognition training in schizophrenia: a systematic review. *Neuropsychology Review* **26**, 310–328.

Caulfield MD, Zhu DC, McAuley JD and Servatius RJ (2016) Individual differences in resting-state functional connectivity with the executive network: support for a cerebellar role in anxiety vulnerability. *Brain Structure and Function* **221**, 3081–3093.

Chamberlain SR, Fineberg NA, Blackwell AD, Robbins TW and Sahakian BJ (2006) Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *American Journal of Psychiatry* **163**, 1282–1284.

Chen YH, Meng X, Hu Q, Cui HS, Ding YZ, Kang L, Juhas M, Greenshaw AJ, Zhao AM, Wang YH, Cui GC and Li P (2016) Altered resting-state functional organization within the central executive network in obsessive-compulsive disorder. *Psychiatry and Clinical Neuroscience* **70**, 448–456.

Cohen (1977) *Statistical Power Analysis for the Behavioral Sciences*, Rev. ed. Hillsdale, NJ, England: Lawrence Erlbaum Associates, Inc.

de Vries FE, de Wit SJ, van den Heuvel OA, Veltman DJ, Cath DC, van Balkom AJLM and van der Werf YD (2017) Cognitive control networks in OCD: a resting-state connectivity study in unmedicated patients with obsessive-compulsive disorder and their unaffected relatives. *World Journal of Biological Psychiatry* **18**, 1–13.

de wit J S, Alonso P and Schweren L (2014) Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. *American Journal of Psychiatry* **171**, 340–349.

Dong G, Lin X and Potenza MN (2015) Decreased functional connectivity in an executive control network is related to impaired executive function in internet gaming disorder. *Progress in Neuropsychopharmacology & Biological Psychiatry* **57**, 76–85.

Fan J, Zhong MT, Gan J, Liu WT, Niu CY, Liao HY, Zhang HC, Yi JY, Chan RCK, Tan CL and Zhu XZ (2017) Altered connectivity within and between the default mode, central executive, and salience networks in obsessive-compulsive disorder. *Journal of Affective Disorder* **223**, 106–114.

Fink J, Hendrikx F, Stierle C, Stengler K, Jahn I and Exner C (2017) The impact of attentional and emotional demands on memory performance in obsessive-compulsive disorder. *Journal of Anxiety Disorder* **50**, 60–68.

Geller DA, Abramovitch A, Mittelman A, Stark A, Ramsey K, Cooperman A, Baer L and Stewart SE (2018) Neurocognitive function in paediatric obsessive-compulsive disorder. *World Journal of Biological Psychiatry* **19**, 142–151.

Gilbert SJ, Dumontheil I, Simons JS, Frith CD and Burgess PW (2007) Comment on "wandering minds: the default network and stimulus-independent thought". *Science* **317**, 43.

Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR and Charney DS (1989) The Yale-Brown obsessive compulsive scale. II. Validity. *Archives of Gene Psychiatry* **46**, 1012–1016.

Gottlich M, Kramer UM, Kordon A, Hohagen F and Zurowski B (2014) Decreased limbic and increased fronto-parietal connectivity in unmedicated patients with obsessive-compulsive disorder. *Human Brain Mapping* **35**, 5617–5632.

Goulden N, Khusnulina A, Davis NJ, Bracewell RM, Bokde AL, McNulty JP and Mullins PG (2014) The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. *Neuroimage* **99**, 180–190.

Guo WB, Liu F, Xue ZM, Gao KM, Liu ZN, Xiao CQ, Chen HF and Zhao JP (2013) Abnormal resting-state cerebellar-cerebral functional connectivity in treatment-resistant depression and treatment sensitive depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **44**, 51–57.

Guo W, Liu F, Zhang Z, …, Zhao JP (2015) Increased cerebellar functional connectivity with the default-mode network in unaffected siblings of schizophrenia patients at rest. *Schizophrenia Bulletin* **41**, 1317–1325.

Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V and Greicius MD (2009) Distinct cerebellar contributions to intrinsic connectivity networks. *Journal of Neuroscience* **29**, 8586–8594.

Heinzel S, Kaufmann C, Grützmann R, Hummel R, Klawohn J, Riesel A, Bey K, Lennertz L, Wagner M and Kathmann N (2017) Neural correlates of working memory deficits and associations to response inhibition in obsessive compulsive disorder. *Neuroimage Clinical* **17**, 426–434.

Kelly RM and Strick PL (2003) Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *Journal of Neuroscience* **23**, 8432–8444.

Khan AJ, Nair A and Keown CL (2015) Cerebro-cerebellar resting-state functional connectivity in children and adolescents with autism spectrum disorder. *Biological Psychiatry* **78**, 625–634.

Krienen FM and Buckner RL (2009) Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. *Cerebral Cortex* **19**, 2485–2497.

Lane RD, Chua PM and Dolan RJ (1999) Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. *Neuropsychologia* **37**, 989–997.

Mantovani A, Rossi S, Bassi BD, Simpson HB, Fallon BA and Lisanby SH (2013) Modulation of motor cortex excitability in obsessive-compulsive disorder: an exploratory study on the relations of neurophysiology measures with clinical outcome. *Psychiatry Research* **210**, 1026–1032.

Middleton Strick PL (2000) Cerebellar projections to the prefrontal cortex of the primate. *Journal of Neuroscience* **21**, 700–712.

Nabeyama M, Nakagawa A, Yoshiura T, Nakao T, Nakatani E, Togao O, Yoshizato C, Yoshioka K, Mayumi T and Kanba S (2008) Functional MRI study of brain activation alterations in patients with obsessive-compulsive disorder after symptom improvement. *Psychiatry Research* **163**, 236–247.

Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, Kudoh A, Tada K, Yoshioka K, Kawamoto M, Togao O and Kanba S (2005) Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study. *Biological Psychiatry* **57**, 901–910.

Nakao T, Okada K and Kanba S (2014) Neurobiological model of obsessive-compulsive disorder: evidence from recent neuropsychological and neuroimaging findings. *Psychiatry and Clinical Neuroscience* **68**, 587–605.

Narayanaswamy JC, Jose D, Kalmady SV, Agarwal SM, Venkatasubramanian G and Janardhan Reddy Y. C. (2016) Cerebellar volume deficits in medication-naive obsessive compulsive disorder. *Psychiatry Research* **254**, 164–168.

Paul S, Simon D, Endrass T and Kathmann N (2016) Altered emotion regulation in obsessive-compulsive disorder as evidenced by the late positive potential. *Psychological Medicine* **46**, 137–147.

https://doi.org/10.1017/S0033291718001915 Published online by Cambridge University Press

Peng ZW, Xu T and He QH (2014) Default network connectivity as a vulnerability marker for obsessive compulsive disorder. *Psychological Medicine* **44**, 1475–1484.

Peterburs J and Desmond JE (2016) The role of the human cerebellum in performance monitoring. *Current Opinion in Neurobiology* **40**, 38–44.

Ping L (2013) Abnormal spontaneous neural activity in obsessive-compulsive disorder: a resting-state functional magnetic resonance imaging study. *PLoS ONE* **8**, e63262.

Posner J, Song I, Lee S, Rodriguez CI, Moore H, Marsh R and Blair Simpson H (2017) Increased functional connectivity between the default mode and salience networks in unmedicated adults with obsessive-compulsive disorder. *Human Brain Mapping* **38**, 678–687.

Power JD, Barnes KA, Snyder AZ, Schlaggar BL and Petersen SE (2012) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* **59**, 2142–2154.

Pujol J, Soriano-Mas C and Alonso P (2004) Mapping structural brain alterations in obsessive-compulsive disorder. *Archives of Gene Psychiatry* **61**, 720–730.

Raichle ME and Snyder AZ (2007) A default mode of brain function: a brief history of an evolving idea. *NeuroImage* **37**, 1083–1090.

Ramnani N, Behrens TEJ, Johansen-Berg H, Richter MC, Pinsk MA, Andersson JLR, Rudebeck P, Ciccarelli O, Richter W, Thompsen AJ, Gross CG, Robsen MD, Kastner S and Matthews PM (2006) The evolution of prefrontal inputs to the cortico-pontine system: diffusion imaging evidence from macaque monkeys and humans. *Cerebral Cortex* **16**, 811–818.

Reis DJ, Doba N and Nathan MA (1973) Predatory attack, grooming, and consummatory behaviors evoked by electrical stimulation of cat cerebellar nuclei. *Science* **182**, 845–847.

Ruscio AM, Stein DJ, Chiu WT and Kessler RC (2010) The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication. *Molecular Psychiatry* **15**, 53–63.

Saad ZS, Gotts SJ, Murphy K, Chen G, Jo HJ, Martin A and Cox RW (2012) Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. *Brain Connect* **2**, 25–32.

Schmahmann JD (2004) Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *Journal of Neuropsychiatry and Clinical Neuroscience* **16**, 367–378.

Schmahmann JD and Pandya DN (1989) Anatomical investigation of projections to the basis pontis from posterior parietal association cortices in rhesus monkey. *Journal of Comparative Neurology* **289**, 53–73.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R and Dunbar GC (1998) The Mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, **59**(Suppl 20), 22–33; quiz 34–57.

Sridharan D, Levitin DJ and Menon V (2008) A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceeding of the National Academy of Sciences of the United States of America* **105**, 12569–12574.

Steer RA, Rissmiller DJ, Ranieri WF and Beck AT (1993) Structure of the computer-assisted Beck Anxiety Inventory with psychiatric inpatients. *Journal of Personality Assessment* **60**, 532–542.

Stern E R, Fitzgerald KD, Welsh RC, Abelson JL and Taylor SF (2012) Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. *PLoS ONE* **7**, e36356.

Stoodley CJ and Schmahmann JD (2010) Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex* **46**, 831–844.

Sylvester CM, Corbetta M, Raichle ME, Rodebaugh TL, Schlaggar BL, Sheline YI, Zorumski CF and Lenze EJ (2012) Functional network dysfunction in anxiety and anxiety disorders. *Trends in Neurosciences* **35**, 527–535.

Thorsen AL, Hagland P, Radua J, Mataix-Cols D, Kvale G, Hansen B and van den Heuvel OA (2018) Emotional processing in obsessive-compulsive disorder: a systematic review and meta-analysis of 25 functional neuroimaging studies. *Biological Psychiatry Cognitive Neuroscience Neuroimaging* **3**, 563–571.

Vaghi MM, Hampshire A, Fineberg NA, Kaser M, Brühl AB, Sahakian BJ, Chamberlain SR and Robbins TW (2017) Hypoactivation and dysconnectivity of a frontostriatal circuit during goal-directed planning as an endophenotype for obsessive-compulsive disorder. *Biological Psychiatry Cognitive Neuroscience Neuroimaging* **2**, 655–663.

Van Overwalle F, D'aes T and Mariën P (2015) Social cognition and the cerebellum: a meta-analytic connectivity analysis. *Human Brain Mapping* **36**, 5137–5154.

Venkatasubramanian G, Zutshi A, Jindal S, Srikanth SG, Kovoor JM, Kumar JK and Janardhan Reddy YC (2012) Comprehensive evaluation of cortical structure abnormalities in drug-naive, adult patients with obsessive-compulsive disorder: a surface-based morphometry study. *Journal of Psychiatry Research* **46**, 1161–1168.

Wolff N, Buse J, Tost J, Roessner V and Beste C (2017) Modulations of cognitive flexibility in obsessive compulsive disorder reflect dysfunctions of perceptual categorization. *Journal of Child Psychology and Psychiatry* **8**, 939–949.

Yan CG, Cheung B and Kelly C (2013) A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage* **76**, 183–201.

Yan CG, Wang XD, Zuo XN and Zang YF (2016) DPABI: data processing & analysis for (resting-state) brain imaging. *Neuroinformatics*, **14**, 339–351.

Yuan ML, Meng YJ, Zhang Y, Nie XJ, Ren ZJ, Zhu HR, Li YC, Lui S, Gong QY, Qiu CJ, and Zhang W (2017) Cerebellar neural circuits involving executive control network predict response to group cognitive behavior therapy in social anxiety disorder. 16, 673–682.

https://doi.org/10.1017/S0033291718001915 Published online by Cambridge University Press