

Medial frontal and dorsal cortical morphometric abnormalities are related to obsessive-compulsive disorder

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ABSTRACT

Whole-brain voxel-based morphometry (VBM) studies provide support for orbitofrontal, medial frontal as well as for dorsal cortical volumetric alteration in obsessive-compulsive disorder (OCD). However, there is still a need to replicate *a priori* unpredicted findings and to elucidate white matter volumetric abnormalities and relationships between grey (GM) and white (WM) matter volume and clinical characteristics of OCD. We compared GM and WM volume in a group of 14 patients with OCD and 15 healthy controls using a 3 T MRI scanner and an optimized VBM protocol. Regression analysis was used to examine relationships between GM and WM volume and clinical variables. In OCD we have found total WM volume reduction and marked mediofrontal, right temporo-parieto-occipital, right precentral, left middle temporal, left cerebellar and bilateral pons and mesencephalon GM volume reduction in the voxel-based analysis ($p \leq 0.05$, FDR corrected, extent threshold 100 voxels). Regression analysis indicated a positive relationship between left orbitofrontal GM volume and severity of obsessive-compulsive symptoms and a negative relationship between symptom severity and GM volume in supramarginal gyri. Earlier age of OCD onset and longer illness duration were associated with smaller left occipital GM and right parietal WM and with greater left medial frontal GM and left frontal WM ($p \leq 0.001$, uncorrected, extent threshold 50 voxels). Our results confirm volumetric abnormalities in the medial frontal and dorsal cortical areas in OCD. The relationships between OCD and clinical variables provide further evidence that frontal, parietal and occipital structures play a role in the disorder.

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Obsessive-compulsive disorder (OCD) has traditionally been linked with a dysfunction in fronto-striatal circuits including orbitofrontal and anterior cingulate cortex (ACC) [2]. However, a recent review and meta-analysis [22] integrating findings from various methodological approaches has led to a conclusion that this view is not sufficient to explain the neurobiological basis of OCD and suggested a more comprehensive model including two relatively independent fronto-striatal networks: the widely accepted orbitofronto-striatal loop subserving affective processes and the dorsolateral prefronto-striatal loop that also involves the parietal cortex and is implicated in spatial and attentional functions.

Also morphometric analyses provide support for the more widely distributed abnormalities in OCD. The region of interest

(ROI) studies that include only a limited number of brain regions based on *a priori* hypotheses reported most consistently reduced grey matter (GM) volume in orbitofrontal cortex and other limbic structures belonging to the orbitofronto-striatal loop [22]. On the other hand, the relatively new and automated approach of voxel-based morphometry (VBM) [4], allowing whole brain analysis, extended the findings to dorsal brain areas, such as the dorsolateral prefrontal [6,12,37] and parietal [37,16,36,21] cortex. Moreover, there are reports on cerebellar [16,21,28], insular [16,21,28] and temporal [16,21,39] alterations of GM volume in OCD. In VBM, T1-weighted images are segmented into GM, WM and cerebrospinal fluid (CSF) and normalized to a brain template. Spatial normalization expands and contracts some brain regions. Therefore, a modulation step (i.e. multiplying voxel values by the Jacobian determinants derived from the spatial normalization) is often used to restore the original volume information. The results of modulated VBM are usually interpreted as markers of volume changes and in most recent publications are simply labeled as volumes [20], although they actually reflect modulated density [15]

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Table 1
Demographic, clinical and brain volumetric data in patients with OCD and healthy control subjects.

Characteristics	OCD patients		Control subjects		Analysis	
	(n = 14)		(n = 15)		Test statistics	p
	Mean	SD	Mean	SD		
Demographic						
Age (years)	28.6	6.1	28.7	6.5	$t = -0.04$, d.f. = 27	0.969
Sex (men:women)	5:9	NA	6:9	NA	$\chi^2 = 0.06$, d.f. = 2	0.812
Education (3 levels)	2:10:2	NA	0:6:9	NA	$\chi^2 = 7.43$, d.f. = 3	0.024
Clinical						
Y-BOCS score	16.4	7.0	NA	NA	NA	NA
Obsession subscore	8.1	2.9	NA	NA	NA	NA
Compulsion subscore	8.2	4.5	NA	NA	NA	NA
Age of OCD onset (years)	13.9	6.6	NA	NA	NA	NA
Duration of illness (years)	15.6	8.3	NA	NA	NA	NA
Brain volumes						
Grey matter (ml)	701.9	82.97	726.6	49.98	$t = 0.98$, d.f. = 27	0.336
White matter (ml)	463.5	63.06	505.4	39.56	$t = 2.16$, d.f. = 27	0.040
Cerebrospinal fluid (ml)	361.4	95.45	415.1	135.8	$t = 1.22$, d.f. = 27	0.232
Total brain (ml)	1527	197.5	1647	180.2	$t = 1.72$, d.f. = 27	0.098

SD – standard deviation; NA – not applicable/not applied; d.f. – degrees of freedom; ml – millilitres

or absolute amounts of grey/white matter [3] and the units are arbitrary. Although VBM has been criticized for its basic principle of brain normalization, inaccurate localization due to image registration and smoothing or for statistical approaches assuming normal distribution of the data, VBM has proven useful in characterizing subtle changes in brain structure in a variety of diseases associated with neurological and psychiatric dysfunction [20].

Most morphometric studies in OCD were applied to GM abnormalities, whereas only a handful of them assessed white matter (WM) volume. However, WM may play a critical role in OCD pathophysiology as documented by the clinical effect of neurosurgery and deep brain stimulation [24,14]. Pujol et al. [28] did not find any differences in WM volume between OCD and healthy control subjects, whereas Duran et al. [8] reported smaller total WM volume, two other studies found WM volume reduction in frontal regions [5,37] and one also in the right parietal lobe [5]. In addition, little is known about the relationship between brain tissue volume and the clinical characteristics of OCD and its course. Understanding the relationships between brain tissue and clinical variables may be of interest for the development of new therapeutic methods. Most attention has been focused on the relationship between GM volume and symptom severity [6,12,37,36,28,39,5,34] however results are inconsistent.

The aim of our study was firstly to contribute to the validation of morphometric findings in OCD which is needed especially in *a priori* unpredicted regions and in WM. Secondly, we aimed to investigate relationships between GM, WM volume, severity of symptoms, and course of illness. Based on previous research, we hypothesized volumetric abnormalities would be found in the medial frontal cortex as well as in other regions belonging to one of the two fronto-striatal loops proposed by Menzies et al. [22]. We predicted that GM and WM volume in these areas will be related to clinical characteristics such as symptom severity, age of onset and duration of illness.

Fifteen right-handed patients diagnosed with OCD by two psychiatrists according to ICD-10 [38] and DSM-IV [1] criteria were included in the study. One patient had to be excluded due to accidental finding of glioma. We analyzed data from 14 OCD patients and 15 right-handed healthy controls (Table 1). At the time of study, four patients were drug-free, eight were using SSRI medication, one patient was treated with a combination of SSRI and mirtazapine and one with venlafaxine. Medication status was stable for at least one month. Duration of medication use was classified into five categories: 1–3 months (one patient), 3–6 months (one patient), 6–12 months (two patients), 12–24 months (three patients) and more

than 24 months (three patients). Clinical symptoms were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [13] on the day of magnetic resonance (MRI) examination. The study was approved by the Local Ethical Committee and all subjects signed informed consent.

Patients and controls underwent a MRI examination on a 3 T Siemens Trio scanner with a standard 12-channel head coil using the following protocol: T1-weighted (T1W) 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) with voxel size of 1 mm × 1 mm × 1 mm, 160 sagittal slices, echo time (TE) of 4.63 ms, repetition time (TR) of 2300 ms, flip angle of 10°, and field of view (FOV) of 256 mm.

Structural MRI analysis was performed using an optimized VBM protocol in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>) implemented in MATLAB 7.3 (Math Works, Natick Massachusetts, USA). Briefly, each 3D volume of T1W images was segmented into GM, WM, and CSF. Spatial normalization parameters were estimated by matching GM tissue with the standard GM template provided by SPM5. The normalization parameters were applied to the original T1W images. Optimally normalized T1W images were then segmented into GM, WM, and CSF segments, modulated by Jacobian determinants and smoothed by a Gaussian kernel of 10 mm full width at half maximum (FWHM).

Between-group comparisons of GM, WM and CSF volume were performed by independent sample *t*-tests. Regression analysis was used to investigate the relationship between GM and WM volume and age of OCD onset, duration of illness and Y-BOCS score. For all analyses, total brain volume was used as a nuisance covariate [27], age was also taken into account as covariate for age of OCD onset and illness duration. The FDR (false discovery rate) corrected $p \leq 0.05$ with the extent threshold consisting of 50 or 100 voxels per cluster was accepted as significant for regression and inter-group analysis, respectively. However, in the second step we also considered uncorrected voxel-level $p \leq 0.001$ in clusters containing more than 50 voxels as being significant and reported them with regard to their overlap with the inter-group results. Demographic data between groups were compared using the *t*-test (age) or chi-square test (sex and education) and intercorrelations between clinical variables as well as correlation between brain volume and the length of medication use were computed using Spearman's correlation. The significance threshold for demographic and clinical data was set at $p \leq 0.05$.

The demographic and clinical data are summarized in Table 1. The two groups did not differ in age, sex and handedness. The

Table 2
GM volume reduction in OCD patients compared to controls. The table shows up to 3 local maxima more than 8.0 mm apart and reports only clusters containing more than 100 voxels ($p \leq 0.05$, FDR corrected). Voxels significant after FWE correction are in bold. Coordinates refer to standard stereotactic space [35].

Cluster-level			Voxel-level					Coordinates	Localization
<i>p</i> (cor)	No. of voxels	<i>p</i> (unc)	<i>p</i> (FWE-cor)	<i>p</i> (FDR-cor)	<i>t</i> -value	equiv. <i>Z</i>	<i>p</i> (unc)	<i>x y z</i> (mm)	
0.287	108	0.025	0.003	0.006	7.65	5.44	0.000	32 –72 2	R lingual gyrus (BA 19)
0.009	303	0.001	0.027	0.009	6.61	4.98	0.000	–10 46 32	L medial and superior frontal gyrus – medial part (BA 9, 10)
			0.046	0.009	6.35	4.85	0.000	–16 54 6	
			0.445	0.010	5.11	4.19	0.000	–14 50 22	
0.000	1486	0.000	0.031	0.009	6.55	4.95	0.000	12 34 4	Anterior cingulate (BA 24)
			0.080	0.009	6.07	4.71	0.000	6 24 0	
			0.342	0.010	5.27	4.28	0.000	–4 22 2	
0.001	467	0.000	0.035	0.009	6.49	4.92	0.000	50 –80 30	R superior occipital gyrus (BA 19)
			0.048	0.009	6.32	4.84	0.000	50 –64 52	R inferior parietal lobule (BA 40)
			0.088	0.009	6.02	4.69	0.000	68 –54 16	R superior temporal gyrus (BA 22)
0.000	692	0.000	0.045	0.009	6.35	4.85	0.000	–48 –18 –20	L middle temporal gyrus (BA 21)
			0.531	0.011	4.98	4.11	0.000	–58 –28 –14	
			0.543	0.011	4.96	4.10	0.000	–40 –40 –8	
0.006	329	0.000	0.123	0.009	5.84	4.60	0.000	16 54 8	R medial and superior frontal gyrus – medial part (BA 8, 9, 10)
			0.608	0.011	4.87	4.05	0.000	12 46 34	
			0.957	0.017	4.26	3.66	0.000	14 50 24	
0.104	161	0.008	0.195	0.009	5.59	4.46	0.000	46 –2 22	R precentral gyrus (BA 6)
			0.739	0.013	4.69	3.94	0.000	48 –16 26	
0.000	1488	0.000	0.209	0.009	5.56	4.44	0.000	14 –16 –10	Pons and mesencephalon
			0.219	0.009	5.53	4.43	0.000	–12 –14 –10	
			0.246	0.009	5.46	4.39	0.000	8 –22 –6	
0.014	273	0.001	0.361	0.010	5.24	4.26	0.000	42 –26 –14	R fusiform gyrus (BA 20)
			0.667	0.012	4.79	4.00	0.000	48 –20 –20	
			0.987	0.019	4.09	3.54	0.000	42 –6 –24	
0.118	154	0.009	0.410	0.010	5.16	4.22	0.000	–18 –58 –38	L cerebellum
			0.525	0.011	4.99	4.12	0.000	–18 –48 –36	
			0.999	0.024	3.81	3.35	0.000	–26 –52 –40	
0.005	342	0.000	0.709	0.012	4.74	3.96	0.000	46 2 –8	R superior temporal gyrus (BA 38)
			0.870	0.014	4.48	3.80	0.000	46 16 –8	
			0.938	0.016	4.32	3.70	0.000	40 12 –18	

Abbreviations: FWE – family-wise error, FDR – false discovery rate, BA – Brodmann area, L – left, R – right, GM – grey matter, *p* – *p*-value, *Z* – *z*-score, cor – corrected, unc – uncorrected.

education level was higher in controls compared with patients ($p = 0.024$). The mean Y-BOCS score in patients was 16.4, indicating marked psychopathology. Y-BOCS score and illness duration were not correlated with each other, however a relationship was found between Y-BOCS score and age of OCD onset ($r = -0.63$, $p = 0.015$) as well as between illness duration and age of onset ($r = -0.59$, $p = 0.026$).

OCD patients and control subjects did not differ in total brain volume, grey matter (although patients had smaller grey matter volume, the difference did not reach statistical significance – see Table 1) and cerebrospinal fluid volume, total white matter volume was smaller in OCD (Table 1). Compared with controls, OCD patients showed a reduction in GM volume in the bilateral medial frontal cortex, anterior cingulate and temporal cortex, in the right precentral, parietal and occipital regions, left cerebellum and bilateral cerebral pons and mesencephalon (Table 2, Fig. 1). The positive findings in medial frontal, right parietal, right occipital and left temporal cortex remained significant even after more rigorous FWE (family-wise error) correction. A comparison of the medicated OCD subgroup ($N = 10$) with controls showed the same pattern of decreased GM in OCD patients. Although at the adopted threshold the results showed decreased gray matter only in the bilateral anterior cingulate (BA 24), mesencephalon, left hippocampus, right parahippocampal gyrus and left cerebellum; at the FDR corrected level, without extent threshold, grey matter in the patient group was reduced in the bilateral medial frontal cortex, insula, lateral temporal and occipital cortex, right precentral and inferior parietal region and left lingual gyrus as well. Duration of medication use was not related to GM, WM and total brain volume ($r = 0.10$, $p = 0.789$; $r = 0.41$, $p = 0.241$; $r = 0.39$, $p = 0.265$). No increases in GM volume and no abnormalities in WM volume were observed in

OCD compared with controls at the *a priori* adopted significance threshold.

Regression analyses revealed at the less rigorous significance threshold a positive relationship between left orbitofrontal (inferior frontal gyrus, BA 11) GM volume and Y-BOCS score and a negative relationship between Y-BOCS score and GM volume in supramarginal gyri. Age of onset and illness duration were inversely related to the same GM and WM structures. Earlier age of OCD onset and longer illness duration were associated with smaller left inferior and middle occipital GM (BA 18, 19) and right parietal WM and with greater left medial frontal GM (BA 8, 9) and left frontal WM. None of the results were significant on a FDR corrected level.

Our results provide support for both hypotheses showing volumetric abnormalities in the brain regions involved in OCD pathophysiology [22] and the relationship between brain structure and clinical variables. Marked reduction of GM volume in OCD localized in the medial frontal cortex supports the traditional orbitofronto-striatal hypothesis [22]. However, volumetric abnormalities in other cortical areas and the relationships between parietal and occipital GM or WM and clinical variables provide further evidence that brain regions involved in OCD pathophysiology are not confined to orbitofronto-striatal circuits.

The medial frontal cortex including the ACC subregion plays a key role in performance monitoring and error detection processes which are overactive in OCD and may trigger one of the most prominent OCD symptoms, a feeling that something is wrong [9]. ACC in OCD patients has been shown to be hyperactive under various conditions – during performance monitoring [10], symptom provocation [29] and also at rest [32]. A possible explanation of the relationship between its functional and structural alteration pro-

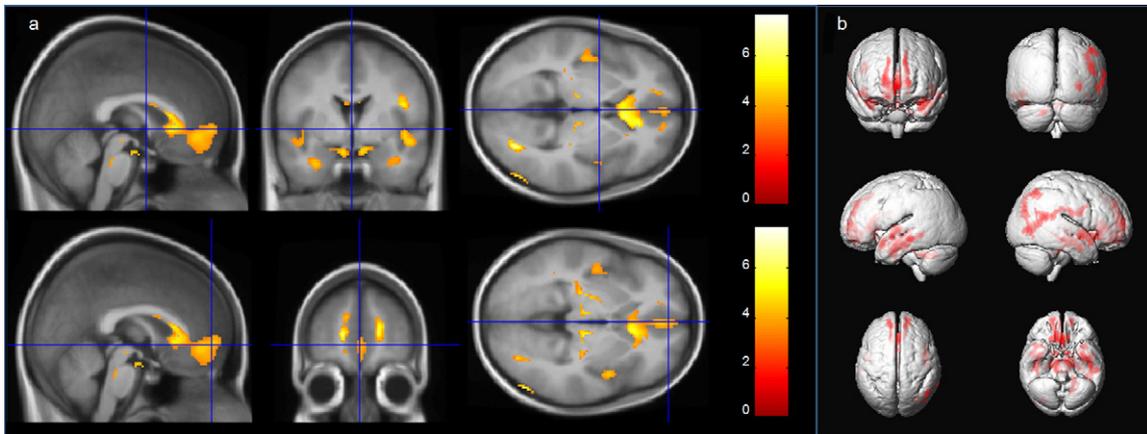


Fig. 1. GM volume changes in OCD patients compared to controls. The figure displays regions reduced in GM in OCD ($p \leq 0.05$, FDR corrected, extent threshold 100 voxels). Images are sliced according to the following coordinates $x y z$ in the standard stereotaxic space [35] (a): 0, 0, 0 (upper image); 7, 54, 4 (lower image). A study-specific template was used for the three-dimensional display (b).

vides a combined functional and spectroscopic study supporting the hypothesis that the hyperactivity is to compensate decreased neuronal density or viability [40]. Alternatively, it is possible that ACC hyperactivity leads to neurotoxic changes resulting in brain tissue volume reduction. Our findings suggest that morphometric alterations in OCD involve more broadly distributed areas of the medial frontal cortex. Consistently with a previous VBM study [11], we have found a reduction in GM volume in the bilateral medial frontal and medial superior frontal gyrus. In contrast to a majority of morphometric studies, there were no volumetric alterations in the orbitofrontal cortex in our OCD sample, however, we found a relationship between GM volume in a part of the left orbitofrontal cortex and Y-BOCS score. Moreover, orbitofrontal cortex is closely interconnected with ACC [7] and both structures contribute to the same fronto-striatal circuit [22].

Volumetric alteration of the large temporo-parieto-occipital region is in line with current studies showing the importance of dorsal cortical regions in OCD [22] and a deficit in visuospatial tasks in OCD patients [26]. The rapidly growing body of evidence points especially to parietal abnormalities in OCD [23]. Concurrently, the results of our regression analyses support the hypothesis that not only frontal but also parietal brain tissue volumes are related to clinical variables in OCD. In agreement with previous PET and SPECT studies reporting a negative correlation between OCD symptom severity and right [18,17] or bilateral [25] parietal region, right temporo-parietal junction and left supramarginal gyrus [19], we found a negative relationship between symptom severity and GM volume in supramarginal gyri. Our findings of the relationships between age of onset and illness duration and frontal and parietal WM abnormalities correspond with prior reports on frontal and parietal WM volume and integrity in OCD [37,5,23,33]. Interestingly, two candidate genes (MOG – myelin oligodendrocyte glycoprotein gene and OLIG2 – gene for oligodendrocyte lineage transcription factor 2) related to WM have been associated with this disorder [41,31].

Volumetric changes in the occipital cortex and their relationship with clinical variables in OCD were not included in our expectations. However, results of several previous studies suggest that the occipital cortex may play an important role in OCD [34,33,30]. Our findings of reduced GM volume in the right occipital cortex and the relationship between GM volume in the left occipital cortex and age of OCD onset and illness duration support the hypothesis of occipital contribution to OCD.

Considering the role of basal ganglia in OCD, it is surprising that there were no differences between OCD patients and controls in

this region. However, only about half of the VBM studies reported abnormal basal ganglia volume in OCD. A possible explanation may lie in the heterogeneity within the disorder. For example, an OCD subtype belonging to pediatric autoimmune neuropsychiatric disorders with streptococcal infections affecting basal ganglia [2] may show differential results in this structure.

Several limitations of this study should be acknowledged. Small sample size, differences in education level between groups, use of psychotropic medication and previous treatment might have influenced the results. The results of regression analysis should be interpreted with caution, especially due to the small sample size. However, our findings are in line with current literature evidence suggesting the implication of the medial frontal and parietal cortex in OCD and provide further support for the importance of the occipital cortex in this disorder.

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