Supplemental Methods

1.1 Data acquisition, symptom dimensions, medication use and co-morbidity

All participants were screened for DSM-IV Axis I disorders with a standardized structured interview (either with the English version (1, 2) or the native language translated versions in Dutch (translated by M.A.C. van Groenestijn, G.W. Akkerhuis, R.W. Kupka, N. Schneider & W.A. Nolen, 1998, Swets Test Publishers, Lisse, the Netherlands), Japanese (translated by T. Kitamura, T. Tomita, S. Okano and A. Kikuchi, edited by S. Takahashi, 2003, Nippon Hyoron Sha Co. Ltd., Tokyo, Japan), Korean (3), Portuguese (4), or Spanish (5) version). OCD symptom severity and symptom dimensions were assessed with the Yale-Brown Obsessive-Compulsive Scale (YBOCS) severity scale and symptom checklist (either with the English version (6) or with the native language translated versions in Dutch (translated by W.A. Arrindell and F.A. Albersnagel and P. van Oppen, 1990), Japanese (7), Korean (8), Portuguese (translated by FR Asbahr, F. Lotufo Neto, G.X. Turecki, J.A. Del Porto, L.R. Rodríguez, M. Baruzzi, M.A. Lima, and V. Gentil, 1992) or Spanish (9) version). The presence of five previously identified symptom dimensions (10) designated as “aggressive/checking”, “contamination/cleaning”, “symmetry/ordering”, “sexual/religious obsessions”, and “hoarding” was thus assessed. A dimension was considered to be present if the patient reported either current or lifetime history of at least one symptom included in the dimension.

Of the 176 patients receiving medication at the time of MRI scanning, 66 were on SSRI monotherapy, 54 used 2 or more SSRI’s, 11 used clomipramine, 25 used an antidepressant (SSRI or clomipramine) and additionally antipsychotics, 7 used other types of medication, and of 13 subjects the specific medication was unknown. Medication-free participants (N=222, N=14 missing data) were at least 4 weeks off medication, with the exception of 1 participant from the Kyoto sample that was 1 week off medication, and of 14 participants of the London samples (4 of London I; 10 of the London II sample) of which the time off medication was not recorded.

Forty-six percent of OCD patients fulfilled criteria for one or more lifetime co-morbid diagnosis. These were: bipolar I (1%) and II (1.3%) disorder, major depressive disorder (26.0%), dysthymia (8.6%), alcohol abuse/dependence (2.2%), substance abuse/dependence (3.2%), any tic disorder (11.2%), attention-deficit hyperactivity disorder (0.6%), trichotillomania (5.5%), panic disorder with (3.0%) and without (2.8%) agoraphobia, social phobia (18.0%), specific phobia (10.5%), post-traumatic stress disorder (4.0%), generalized anxiety disorder (11.4%), somatisation disorder (1.2%), hypochondriasis (1.5%), anorexia (1.5%) and bulimia (1.1%) nervosa, binge eating disorder (1.8%), anxiety disorder not otherwise specified, anxiety disorder related to substance use (0.7%), pain disorder (0.8%), psychotic episode (0.3%), body dysmorphic disorder (3.9%), intermittent explosive disorder (4.1%), and other impulse control disorders (pathological gambling (0.5%), impulsive shopping (3.2%), hypersexuality (1.4%)).

In the control group, 1.7% had one or more lifetime psychiatric axis I diagnosis. These were major depressive disorder (1.1%), social phobia (0.4%), specific phobia (0.8%), and generalized anxiety disorder (0.4%).

1.2 Data quality control

Prior to data processing all scans were visually inspected and scans of participants with gross brain pathology (N=7) or with artifacts or poor image quality hampering image segmentation (N=31) were excluded (Table 2). In parallel to visual quality checking an automated quality check was performed that used covariance analysis on the sample homogeneity of segmented gray and white matter images (vbm8 toolbox (11)). This extra quality

check, did not lead to exclusion of participants other than those excluded by visual inspection, however. SPM8 and the vbm8 toolbox were used under Matlab R2007b (The Mathworks Inc., Natick, MA, USA).

Supplemental Results

1.1 Post-hoc analysis of regional brain volume between OCD patients and healthy controls in the matched analysis

To ensure that the observed group differences were not confounded by age or educational level, we performed a post-hoc analysis in demographically matched samples (N=645, see Supplemental Tables S2 and S3) after excluding participants based on the frequency spectra of age and educational level per group per site. The resulting sample of OCD patients (N=329) and controls (N=316) were matched on age, gender, educational level, handedness and ethnicity overall and separately per site (all p>.05; data not shown). In the matched analysis total gray matter [mean±SD, OCD: 704ml±64; controls: 701ml±67; t(df=643)=-.6, p=.57] and white matter [OCD: 514±49; controls: 512ml±53; t(df=643)=1.4; p=.16] did not differ between the groups.

1.2 Post-hoc analysis of effects of scan site and clinical variability on group-interaction findings

To ascertain that specific sites did not drive group-interaction results, we performed a factorial analysis of covariance (ANCOVA) over gray matter and white matter images with diagnosis (2 levels) and sites (6 levels) as between-subjects factors and age, gender, total gray matter or white matter volume and educational level as nuisance covariates. Diagnosis-by-site interactions (F-contrast thresholded at p<.001 uncorrected with minimum cluster-extent (k_e)=100) were observed in posterior insular (gray matter: x/y/z=[33/-15/0], k_e=271, Z=4.16, BA13), lateral prefrontal (gray matter: x/y/z=[35/38/27], BA9/10, k_e=319, Z=3.92; x/y/z=[54/17/23], BA44/45, k_e =141, Z=3.37; white matter: x/y/z=[23/45/21], k_e =140, z=4.07), superior temporal (gray matter: x/y/z=[54/-20/9], BA41, k_e=167, Z=3.45) and occipital (white matter: x/y/z=[-20/-86/7]; k_e=574, Z=4.49) regions. These regions did not overlap with regions showing significant group-interactions.

In this same factorial model we performed Jack-knife sensitivity analyses by iteratively leaving one site out and reanalyzing group differences in the subsample of OCD patients versus controls of the remaining sites This showed lower dorsomedial prefrontal cortex and inferior frontal gyrus/anterior insula gray matter volume in all re-analyses at Z>3.1, higher cerebellum gray matter volume in all re-analyses at Z>2.1, and lower frontal white matter in all re-analyses at Z>3.1. Further, inspection of parameter estimate plots of the peak-voxel of group interaction findings also indicated homogeneous effects across all sites (data not shown).

Additionally, the possible clinical confounder of current medication use was added as a nuisance covariate to the main group comparison between OCD patients (N=412) and controls (N=368); this did not affect the results.

1.3 Within-group linear (age-proper) and non-linear (age-squared) effects of age

In both groups age correlated positively and linearly with gray matter volume (i.e., a relative preservation of regional volume – as compared to global brain volume loss - with increasing age) in bilateral hippocampal-amygdalar complex, parahippocampal gyrus, cerebellum, the left thalamus and occipital cortex, and with bilateral posterior frontal white matter volume (data not shown). In patients, additionally, age correlated positively and linearly with volume of right thalamus, bilateral hypothalamus, and bilateral brainstem/pons. Negative linear correlations with

age (a relative accelerated decrease in regional volume with increasing age), in both groups, were observed in bilateral frontal cortex (widespread) and inferior parietal cortex, and bilateral thalamus and bilateral dorsal anterior frontal white matter. In controls only, age correlated negatively and linearly with volume of bilateral putamen / caudate nucleus and right insula, and bilateral occipital white matter. In patients only, age correlated inversely linearly with volume of bilateral posterior cingulate cortex and left temporal cortex.

Age-squared correlated positively with frontal gray matter volume (OCD patients only). Age-squared correlated negatively with parts of bilateral amygdala gray matter volume (controls only) and bilateral parahippocampal gyrus gray matter volume (patients only). Age-squared correlated positively with occipital white matter volume in both groups, whereas it correlated negatively with bilateral frontal white matter showed in patients only (detailed information on within-group aging effects are available from the authors).

1.4 Post-hoc hierarchical multiple linear regression analysis on medication status

Using MarsBar (http://marsbar.sourceforge.net/) we first extracted the mean volume of the middle frontal gyrus (x/y/z=-27/14/60] gray matter, operculum/insular [x/y/z=-44/-3/7] gray matter and dorsal frontal [x/y/z=-11/-26/69] white matter in 1mm radius spheres around the peak voxels per subject. We then performed hierarchical multiple linear regression analyses in SPSS with middle frontal gray matter, opercular/insular gray matter and dorsal frontal white matter volume as respective dependent variables. After stepwise entering and controlling for scan sequence (1), age/total gray matter (or white matter) volume (2), gender/education (3), and YBOCS total severity score (4), current medication status (medication-negative=0, positive=1) was entered into the models.

Results showed that medication use only significantly influenced middle frontal gyrus gray matter [model R-square change=.007, F-change(df=1,359)=6.1; beta(95% confidence interval)=-.009(-.016- -.002); t(df=1)=-2.46, p=.014], but not opercular/insular gray matter [model R-square change=.002, F-change(df=1,359)=2.3; beta(95% confidence interval)=-0.007(-.002-.016); t(df=1)=1.52, p=.13] or frontal white matter [model R-square change=.001, F-change(df=1,359)=.6; beta(95% confidence interval)=-.007(-.025 - .010); t(df=1)=-.80, p=.42].

1.5 Co-morbidity analysis

1.5.1 Co-morbid anxiety disorders

Of 273 patients there was information on the presence of a co-morbid anxiety disorder (i.e. panic disorder, social phobia, specific phobia, post-traumatic stress-disorder, general anxiety disorder or anxiety disorder not otherwise specified) currently or lifetime. Of the OCD patients, 83 had a lifetime diagnosis of co-morbid anxiety disorders, and in most of these patients (N=75) it was currently present as well. We therefore only present the lifetime co-morbid anxiety disorder analysis given the great overlap with the current co-morbid anxiety disorder group. We thus assessed the effect of co-morbid anxiety disorders on regional gray matter and white matter volume, by comparing patients with a lifetime (N=83) co-morbid anxiety disorder diagnosis with those without (N=190) in separate general linear models per tissue segment. Age, gender, educational level, scan sequence and total gray matter (or white matter) were included as covariates of no interest. Patients with current or lifetime comorbid anxiety disorders were matched on age, gender, total gray matter and white matter volume, YBOCS total severity and educational level with patients without comorbid anxiety (all p>.05), but not on ethnicity (chi-square=>26, p<.001). See Supplemental Table S5 for imaging results.

1.5.2 Co-morbid major depressive disorder

Of 388 patients we had information on the presence of current or past co-morbid diagnosis of major depressive disorder (MDD). To assess the effect of MDD on regional gray matter and

white matter volume we compared patients with current (N=46) or lifetime (N=101) MDD with those who did not have a lifetime diagnosis of MDD (N=287) in separate general linear models per comparison and tissue segment. Age, gender, educational level, scan sequence and total gray matter or white matter volume were added to the models as covariates of no interest. Compared with the lifetime negative group, patients with lifetime MDD were older (t=3.9 (df= 386), p<.001, mean age of 35 years vs. 30 years), had lower total gray matter volume (t=-2.7, p=.01), different gender ratios (Chi-square=15, P<.001; male/female: N=34/N=67 vs. N=161/N=126), and different ethnicity (Chi-square=22.9, p<.001), but similar educational level and YBOCS total severity score (p>.05). Patients with current MDD had lower total gray matter (t=-2.3, p=.02) and white matter volume (t=-2.1, p=.04), had significantly different gender ratios (Chi-square=10.5, p=.001; male/female N=14/N=32 vs. N=161/N=126), different ethnicity (Chi-square=19.4, p<.001), but similar age, educational level and YBOCS severity (p>.05). See Supplemental Table S5 for imaging results.

1.5.3 Post-hoc hierarchical multiple linear regression analysis on co-morbid major depression and anxiety disorder status

We used stepwise hierarchical multiple linear regression to ascertain that observed co-morbidity results (Supplemental Table S5) were truly related to co-morbid diagnosis rather than demographic and/or clinical variability between the groups. Using MarsBar (http://marsbar.sourceforge.net/) we first extracted the mean volume of 1mm radius spheres around all gray and white matter main group-interaction peak voxels Supplemental Table S5. We then performed hierarchical multiple linear regression analyses in SPSS with these volumes as respective dependent variables. After stepwise entering and controlling for scan sequence (1), age/total gray matter (or white matter) volume (2), gender/education (3), and YBOCS total severity score (4), lifetime or current co-morbid depression or lifetime co-morbid anxiety-disorder (absent=0, present=1) was entered into the models.

All but 3 results of the co-morbid anxiety analysis remained significant: left cerebellum ([x/y/z=-44/-75/-23]; model R-square change=.015, F-change(df=1,265)=9.0; beta(95% confidence interval)=-0.016(.006-.027); t(df=1)=2.99, p=.003]), tempero-occipital ([x/y/z=35/-74/18]; model R-square change=.063, F-change(df=1,3265)=25.8; beta(95% confidence interval)=-0.032(-.045--.020); t(df=1)=-5.08, p<.001), superior frontal ([x/y/z=-20/-3/57], model R-square change=.034, F-change(df=1,265)=17.11; beta(95% confidence interval)=-.021(-.031--.011); t(df=1)=-4.14, p<.001), mid-cingulum ([x/y/z=-9/-33/47], model R-square change=.013, F-change(df=1,265)=6.36; beta(95% confidence interval)=-.017(-.030--.004); t(df=1)=-2.52, p=.012]), and the insula ([x/y/z=-42/8/0], model R-square change=.021, F-change(df=1,265)=15.62; beta(95% confidence interval)=-.018(-.027--.009); t(df=1)=-3.95, p<.001]) remained significant. The findings in superior temporal gray matter ([x/y/z=36/14/-29]; model R-square change=.000, F-change(df=1,265)=.022; beta(95% confidence interval)=-.001(-.011-.009); t(df=1)=-.15, p=.883]), supplementary motor area ([x/y/z=-8/9/44]], model R-square change=.003, F-change(df=1,265)=1.96; beta(95% confidence interval)=-.007(-.016-.003); t(df=1)=-1.40, p=.16]), and frontal white matter ([x/y/z=-12/6/47]], model R-square change=.002, F-change(df=1,265)=1.41; beta(95% confidence interval)=-.007(-.018-.004); t(df=1)=-1.19, p=.24]), however, did not remain significant after controlling for demographic and clinical variability (see Supplemental Table S5).

All results from the co-morbid depression analysis remained significant: frontal white matter ([x/y/z=-21/-9/57]], model R-square change=.013, F-change(df=1,325)=6.71; beta(95% confidence interval)=-.022(-.038--.005); t(df=1)=-2.59, p=.10]), frontal gray matter ([x/y/z=-26/18/59]], model R-square change=.021, F-change(df=1,325)=15.38; beta(95% confidence interval)=-.020(-.031--.010); t(df=1)=-3.92, p<.001]), and supplementary motor area ([x/y/z=11/-3/63]], model R-square change=.016, F-change(df=1,380)=8.41; beta(95% confidence interval)=-.016(-.027--.005); t(df=1)=-2.90, p=.004]).

1.6 The effects of OCD symptom dimensions on regional brain volume

Of 331 OCD patients there was information on the lifetime presence or absence of all 5 OCD-subdimensions (checking/aggression, contamination/cleaning, sexual/religious, hoarding, symmetry/ordering). To assess the effect of OCD-subdimension on regional gray matter and white matter volume we made a separate general linear model per tissue segment with age, education, YBOCS total severity score, scanning sequence/site, total gray matter or white matter volume, and gender as covariates of-no-interest, and the presence (1) or absence (0) of the 5 subdimensions as covariates of interest. The contrasts [1] and [-1] per subdimension regressor then indicated, respectively, higher (positive; [1]) or lower (negative: [-1]) regional brain volume if the subdimension was present. See Supplemental Table S4 for results.

TABLE S1. Scan Sequences Used at Each Center

		Type of 1.5 T MRI scanner		MRI scan sequence parameters						
OBIC Center	N	Vendor	Model	Sequence	TR (ms)	TE (ms)	FA (º)	Orientation	Matrix size	Voxel size
Amsterdam	102*	Siemens	Sonata	MPRAGE	2700.0	4.0	8	Coronal	256 x 160 x 160	1.00 x 1.00 x1.50
Barcelona	188	General Electric	Signa Excite	3DSPGR	11.8	4.2	15	Axial	256 x 256 x 130	1.17 x 1.17 x 1.20
Kyoto	132	Phillips	Gyroscan Intera	MPRAGE	9.9	5.8	8	Sagittal	256 x 256 x 130	0.98 x 0.98 x 1.50
London I	40*	General Electric	Signa	3D SPGR	14.8	1.7	20	Axial	256 x 256 x 124	0.94 x 0.94 x 1.50
London II	37	General Electric	Signa HDx	3D SPGR	10.8	5.0	18	Axial	256 x 256 x 146	1.09 x 1.09 x 1.10
Sao Paulo I	75	General Electric	Signa	3D SPGR	10.5	4.2	15	Axial	256 x 256 x 248	0.94 x 0.94 x 0.80
Sao Paulo II	22*	Phillips	Gyroscan S15-ACS	FFE T1	30	9	30	Axial	256 x 256 x 134-170	0.94 x 0.94 x 1.20
Seoul I	86*	General Electric	Signa	SPGR	14.4	5.5	20	Sagittal	256 x 256 x 124	0.82 x 0.82 x 1.50
Seoul II	98	Siemens	Magnetom Avanto	MPRAGE	1160.0	4.8	15	Axial	416 x 512 x 160-208	0.45 x 0.45 x 0.90

Matrix size (in voxels; a x b x c; c=number of slices); Voxel size (in mm; a x b x c; a x b=in-plane resolution, c=slice thickness); N, number of scans included in analysis; TR, repetition time; TE, echo time; FA, flip angle.
*Previously published in voxel-based morphometry studies and included in the various meta-analysis (N=250; In order of presentation in table: see references (12-16)). Data of the remaining N=530 participants have not been published before.

TABLE S2. Gray Matter and white matter volume differences Between matched samples of OCD Patients (N=329) and Controls (N=316)

Region	Side	BA	k_e	Coordinates			Z	P_{FWE}
				x	y	z		
Gray Matter								
Controls > OCD patients								
IFG / AI	L	47/13/45	1789	-44	17	-3	5.15	0.01
				-45	-3	3	3.14	
dmPFC / anterior cingulate cortex / pre-SMA	R/L	32/9/ 8/24/6	2469	0	8	45	4.23	0.006
				2	26	38	4.14	
				-2	47	23	4.06	
OCD patients > controls								
Cerebellum, left fusiform gyrus	L / R	NA/ 37	2980	-12	-54	-26	4.32	0.05
				18	-59	-29	3.99	
				-24	-59	-14	3.88	
Fusiform gyrus	L	20	193	-38	-32	-20	3.95	0.47
				-42	-36	-29	3.18	
Fusiform gyrus	R	20	279	38	-32	-20	3.95	0.25
				41	-45	-26	3.20	
White Matter								
Controls > OCD patients								
Frontal white matter	L	Medial	1302	-11	33	27	5.16	0.01
				-12	39	20	5.09	
	R	Medial	1541	14	39	20	3.94	0.02
				27	20	14	3.69	
				20	54	15	3.60	
	L	Inferior	900	-32	27	4	3.90	0.11
				-29	17	12	3.74	
	L	Posterior medial	159	-9	11	48	3.64	0.44
	L	Orbitofrontal	481	-20	47	-14	3.59	0.28
				-14	38	-12	3.45	
OCD patients > controls: ns								

Analysis of covariance thresholded at p<.001 uncorrected and a minimum cluster-extent (ke) of 100 voxels. Results are corrected for age, gender, educational level, total gray matter or white matter volume and scan sequence. BA, Brodmann area; L, left; R, right; IFG, inferior frontal gyrus; AI, anterior insula, dmPFC, dorsomedial prefrontal cortex; pre-SMA, pre-supplementary motor area; ns, not significant. Coordinates (x/y/z) are in MNI standard space. p_{FWE}, whole-brain cluster-corrected and non-stationarity corrected p-value.

TABLE S3. Group-by-Age Interactions on Regional Brain Volume in the Demographically Matched Sample of OCD Patients (N=329) and Controls (N=316)

	Side	BA	k_e	Coordinates			Z	P_{FWE}
				x	y	z		
Gray Matter								
Relative volume preservation with aging in OCD patients vs. controls								
Linear								
Putamen, insula	R	13/NA	1568	32	5	-11	4.02	0.04
				33	11	-2	3.82	
				42	5	-8	3.75	
Nucleus accumbens	L	NA	188	-11	3	-14	3.41	0.71
				-11	12	-6	3.26	
Non-linear								
IFG/MFG/OFC	L	46/10/47	392	-45	50	6	3.76	0.46
				-39	39	-8	3.67	
OFC	L	10	206	-20	56	-8	3.60	0.71
Relative accelerated volume loss with aging in OCD patients vs. controls								
Linear								
ITG	L	20	252	-62	-39	-23	4.08	0.57
MTG	R	21	171	62	-27	-11	3.60	0.39
				56	-36	-8	3.58	
Non-linear								
Fusiform gyrus	L	37	519	-47	-63	-21	4.47	.20
White Matter								
Relative volume preservation with aging in OCD patients vs. controls								
Linear	*ns*							
Non-linear								
Frontal white matter	L	Anterior	217	-21	51	4	3.97	0.35
	L	Inferior	164	-33	30	0	3.75	0.48
	R	Inferior	154	24	32	-14	3.31	0.49
Relative accelerated volume loss with aging in OCD patients vs. controls								
Linear / Non-linear	*ns*							

Group-by-age interaction analysis thresholded at p<.001 uncorrected and a minimum cluster-extent (ke) of 100 voxels. Table shows local maxima more than 8.0mm apart. Results are corrected for gender, educational level, total gray matter or white matter volume and scan sequence. BA, Brodmann area; L, left; R, right; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; OFC, orbitofrontal cortex; MTG, middle temporal gyrus; IFT, inferior temporal gyrus; ns, not significant. Coordinates (x/y/z) are in MNI standard space. p_{FWE}, whole-brain cluster-corrected and non-stationarity corrected p-value,

TABLE S4. Effect of Clinical Variables* and Medication Status on Gray and White Matter Volume Within OCD Patients

	Side	BA	k_e	Coordinates [a]			Z	P_{FWE}
				x	y	z		
Using medication at time of scan (med+, N=176; med- N=222)**								
Gray matter								
Med+>med-								
Rolandic operculum extending to posterior insula	L	6	246	-44	-3	7	3.85	0.49[a]
Med->med+								
Middle frontal gyrus	L	6/8	150	-27	14	60	3.77	0.48
White matter								
Med+>med-	*ns*							
Med->med+								
Frontal white matter	L	Posterior	114	-11	-26	69	3.37	0.66[a]
Symptom dimensions (N=331)								
Gray matter								
Aggr/check pos								
Lingual gyrus	R	18	242	12	-75	0	4.09	0.34
Aggr/check neg								
Superior parietal cortex	L	7	156	-33	-50	63	4.04	0.76
Cont/clean pos/neg	*ns*							
Hoarding pos	*ns*							
Hoarding neg								
Cerebellum	R	NA	219	41	-63	-24	3.36	0.83
Sex/reli pos								
Middle temporal gyrus	L	21	240	-56	-24	-3	3.55	0.64
Sex/reli neg	*ns*							
Sym/order pos	*ns*							
Sym/order neg								
Fusiform gyrus	L	20	654	39	-24	-33	3.94	0.33
White matter								
Aggr/check pos	*ns*							
Aggr/check neg								
Parietal white matter	L	Superior	119	-20	-38	66	3.83	0.53
Cont/clean pos/neg	*ns*							
Hoarding pos/neg	*ns*							
Sex/reli pos/neg	*ns*							
Sym/order pos/neg	*ns*							

Analysis of covariance thresholded at p<.001 uncorrected and a minimum cluster-extent (ke) of 100 voxels. Table shows local maxima more than 8.0mm apart. Results are corrected for age, gender, educational level, total gray matter or white matter volume and scan sequence, and YBOCS severity (symptom dimension analysis only). BA, Brodmann area; L, left; R, right; ns, not significant; pos, positive [1]; neg, negative [-1] contrast. Subdimensions: Aggr/check, aggression/checking; Cont/clean,

contamination/cleaning; Sex/reli, sexual/religious; Sym/order, symmetry/ordering. Coordinates (x/y/z) are in MNI standard space. p_{FWE}, whole-brain cluster-corrected and non-stationarity corrected p-value.

*** Note: Regression with YBOCS total severity score (N=380), disease duration (N=391) and age of onset (N=391) did not yield any significant results.**

**** Note:** patients with (+, POS) and without (-, NEG) current medication use differ significantly on age (p=.013; POS(mean age=33.2 years)>NEG(mean age=30.9years)), educational level (p<.001; NEG(mean=14.3years)>POS(mean=12.9years)), ethnicity (p=.04), total white matter (p=.04; NEG(mean=518.5 ml)>POS(mean=508.1ml), YBOCS severity (p<.001; POS(mean =26.2 points)>NEG(mean=23.8 points)), age-of-onset (p=.001; POS(mean=21.8years)>NEG(mean=18.7years)). Tested with independent t-tests (age, age-of-onset, total white matter, YBOCS severity score) or Chi-square (ethnicity).

[a]Result not significant after stepwise controlling for demographic and clinical variability between the groups (See supplemental results 1.5.3).

.

TABLE S5. Effect of Comorbid Anxiety and Depression on Gray and White Matter Volume Within OCD Patients

	Side	BA	k_e	Coordinates [a] x	y	z	Z	P_{FWE}
***Lifetime* co-morbid anxiety disorder (Anx+; N=83; Anx-; N=190)**								
Gray matter								
Anx+ > Anx-								
Cerebellum	L	NA	1897	-44	-75	-23	4.65	0.03
				-50	-78	-11	3.29	
				-45	-84	-3	3.28	
Superior temporal pole	R	38	194	36	14	-29	3.53	0.57[a]
Anx- > Anx+								
Tempero-occipital	R		819	35	-74	18	5.33	0.05
Superior frontal gyrus	L	6	274	-20	-3	57	4.29	0.28
Cingulum (mid)	L	31	297	-9	-33	47	3.74	0.64
Insula	L	13	170	-42	8	0	3.71	0.63
Supplementary motor area	L	6	1116	-8	9	44	3.63	0.08[a]
				-9	11	56	3.59	
				0	9	54	3.55	
White matter								
Anx+ > Anx-	*ns*							
Anx- > Anx+								
Frontal white matter	L	-	256	-12	6	47	4.12	0.17[a]
***Current* co-morbid major depressive disorder (Depr+, N=46; Depr-, N=287)**								
Gray matter								
Depr+ > Depr-	*ns*							
Depr- > Depr+								
Middle and superior frontal gyrus	L	6	425	-26	18	59	3.91	0.19
				-18	5	57	3.85	
				-27	0	60	3.81	
White matter								
Depr+ > Depr-	*ns*							
Depr- > Depr+								
Frontal white matter	L	NA	182	-21	-9	57	4.07	0.40
***Lifetime* co-morbid major depressive disorder (Depr+, N=101; Depr-, N=287)**								
Gray matter								
Depr+ > Depr-	*ns*							
Depr- > Depr+								
Supplementary motor area	R	6	235	11	-3	63	3.88	0.57
White matter								
Depr+ > Depr-	*ns*							
Depr- > Depr+	*ns*							

Analysis of covariance thresholded at p<.001 uncorrected and a minimum cluster-extent (ke) of 100 voxels. Table shows local maxima more than 8.0mm apart. Results are corrected for age, gender, educational level, total gray matter or white matter volume and scan sequence in the model. BA, Brodmann area; L, left; R, right; ns, not significant. Coordinates (x/y/z) are in MNI standard space. p_{FWE}, whole-brain cluster-corrected and non-stationarity corrected p-value.

[a]Result not significant after stepwise controlling for demographic and clinical variability between the groups.

References

1. Sheehan DV, Lecrubier Y, Sheehan KH: 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. J Clin Psychiatry 1998; 59(Suppl 20:22; quiz 34-57)
2. First M, Gibbon M, Williams J: Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID I/P). New York, NY, Biometrics Research, New York State Psychiatric Institute, 2002
3. Hahn O, Ahn J, Song S, Cho M, Kim J, JN B, Cho S, Jeong B, Suh D, Hahm B, Lee D, Park J, Hong J: Development of Korean version of structured clinical interview schedule for DSM-IV axis I disorder: interrater reliability. J. Korean Neuropsychiatr. 2000; 39(2):362-72
4. Del-Ben C, Vilela J, Crippa J, Hallak J, Labate C, Zuardi A: Reliability of the Structured Clinical Interview for DSM-IV – Clinical Version translated into Portuguese. Rev. Bras. Psiquiatr. 2001; 23(3):156-9
5. First M, Spitzer R, Gibbon M, Williams J: Guía del usuario para la entrevista clínica estructurada para los trastornos del eje I del DSM-IV® SCID-1, Ed. Elsevier-Masson, 1999
6. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS: The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989; 46(11):1006-11
7. Nakajima T, Nakamura M, Taga C, Yamagami S, Kiriike N, Nagata T, Saitoh M, Kinoshita T, Okajima Y, Hanada M, et al.: Reliability and validity of the Japanese version of the Yale-Brown Obsessive-Compulsive Scale. Psychiatry Clin Neurosci 1995; 49(2):121-6
8. Huh M, Shim G, Byun M, Kim S, Kim E, Jang J, Shin M, Kwon J: The impact of personality traits on ratings of obsessive-compulsive symptoms. Psychiatry Investig. in press
9. Vega-Dienstmaier JM, Sal YRHJ, Mazzotti Suarez G, Vidal H, Guimas B, Adrianzen C, Vivar R: [Validation of a version in Spanish of the Yale-Brown Obsessive-Compulsive Scale]. Actas Esp Psiquiatr 2002; 30(1):30-5
10. Mataix-Cols D: Deconstructing obsessive-compulsive disorder: a multidimensional perspective. Curr Opin Psychiatry 2006; 19(1):84-9
11. Kurth F, Luders E, Gaser C: VBM 8 Toolbox Manual, 2010
12. van den Heuvel OA, Remijnse PL, Mataix-Cols D, Vrenken H, Groenewegen HJ, Uylings HB, van Balkom AJ, Veltman DJ: The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. Brain 2009; 132(Pt 4):853-68
13. Gilbert AR, Mataix-Cols D, Almeida JR, Lawrence N, Nutche J, Diwadkar V, Keshavan MS, Phillips ML: Brain structure and symptom dimension relationships in obsessive-compulsive disorder: a voxel-based morphometry study. J Affect Disord 2008; 109(1-2):117-26
14. Valente AA, Jr., Miguel EC, Castro CC, Amaro E, Jr., Duran FL, Buchpiguel CA, Chitnis X, McGuire PK, Busatto GF: Regional gray matter abnormalities in obsessive-compulsive disorder: a voxel-based morphometry study. Biol Psychiatry 2005; 58(6):479-87
15. Yoo SY, Roh MS, Choi JS, Kang DH, Ha TH, Lee JM, Kim IY, Kim SI, Kwon JS: Voxel-based morphometry study of gray matter abnormalities in obsessive-compulsive disorder. J Korean Med Sci 2008; 23(1):24-30
16. Kim JJ, Lee MC, Kim J, Kim IY, Kim SI, Han MH, Chang KH, Kwon JS: Grey matter abnormalities in obsessive-compulsive disorder: statistical parametric mapping of segmented magnetic resonance images. Br J Psychiatry 2001; 179:330-4