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Online Supplement DS1

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DS2 Post-hoc analysis of cortical thickness between healthy controls and OCD patients in a matched sample group

To ensure that demographic variables such as age and education were not confounders in the original dataset, a post-hoc analysis was performed on participants closely matched on demographics (n=645). Participants were excluded based on frequency spectra of age and educational level per site (See De Wit et al. 2014). This resulted in a sample group of controls (n=316) and patients (n=329) that were matched on age, sex, educational level, handedness and ethnicity overall and per site (See online Tables DS1–3 for results).

Post-hoc analysis of the effects of scan sequence on group-interaction findings.

To determine that results were not affected by specific scan sequences from each site an ANCOVA was performed to investigate the interaction of scan sequence with group comparisons of cortical thickness and subcortical volumes. The ANOVA were comprised of 9 levels (one for each scan sequence) and 2 levels for diagnosis as between-subjects factors. Age, gender and level of education were added as covariates of no interest in the model. For cortical thickness there were no sequence by diagnosis interactions at $p < 0.05$ corrected for multiple comparisons with Monte-Carlo permutation testing. For subcortical structures, no sequence by diagnosis interaction was evident at $p < 0.0036$ ($p < 0.05$ Bonferroni corrected).

Table DS1 Areas of decreased cortical thickness in the matched sample of OCD patients (n=329) compared to healthy controls (n=316)

Grey matter region	Hemisphere	Mean thickness (mm)		Local maxima Z-value	p-value	Talaraich coordinates
FRONTAL		HC (SD)	OCD (SD)			
Inferior frontal	Right	2.630 (0.152)	2.583 (0.160)	-3.461	0.00005	50.6 23.5 16.3
Superior frontal	Left	3.098 (0.203)	3.045 (0.230)	-5.371	<0.00	-8.8 26.6 32.7
	Right	2.818 (0.201)	2.780 (0.209)	-2.807	0.00050	8.0 56.8 22.3
PARIETAL						
Inferior parietal	Left	2.421 (0.181)	2.370 (0.175)	-3.367	0.00008	-41.5 -63.5 26.5
TEMPORAL						
Middle temporal	Right	2.755 (0.165)	2.699 (0.167)	-3.659	0.00003	57.9 -42.4 -8.2

Results are shown at $p < 0.05$ corrected for multiple comparisons with Monte-Carlo simulations. Covariates of no interest in this analysis included scan sequence, level of education, age and sex. No significant increases of cortical thickness in OCD patients compared with healthy controls were observed.

Table DS2 Subcortical regional volumes in the matched sample of OCD patients (n=329) compared to healthy controls (n=316)

Subcortical region	Hemisphere	F-value	p-value
Hippocampus	Left	7.554	0.0004
	Right	5.641	0.0013

Results of the ANOVA analysis between groups are shown here. Results are shown at $p < 0.0036$ ($p < 0.05$ Bonferroni corrected). Covariates of no interest in this analysis included scan sequence, level of education, age and sex

Table DS3 Group-by-age interaction effects for cortical thickness, in matched sample of OCD patients (n=329) and healthy controls (n=316)

Grey matter region	Hemisphere	Surface area (mm^2)	Local maxima Z-value	p-value	Talaraich coordinates
Relative cortical thinning with aging in OCD patients vs. controls					
Linear					
Inferior parietal	Left	953.72	2.957	0.0031	-38.3 -67.1 36.5
Non-linear					
Inferior parietal	Left	1723.93	3.197	0.0014	-38.2 -63.7 45.6
Superior parietal	Right	1027.55	2.355	0.0185	14.3 -79.1 37.0

Results are shown at $p < 0.05$ corrected for multiple comparisons with Monte-Carlo simulations. Covariates of no interest in this analysis included scan sequence, level of education, age and sex.

DS3 Comparison of OCD patients with healthy controls after excluding patients on medication, and with lifetime co-morbid anxiety and major depressive disorder

In order to investigate the comparison of OCD patients with healthy controls in the absence of confounding variables such as medication use and co-morbid anxiety and depression, a secondary analysis comparing cortical thickness and subcortical volumes between groups was conducted where 1) patients on medication, 2) patients with lifetime co-morbid anxiety, 3) patients with lifetime co-morbid depression were excluded in turn. Cortical thickness was compared with a GLM ANCOVA model in Freesurfer's glm_fit and subcortical volumes were analysed in SPSS 20.0 with the same model. Age, sex, level of education and scan sequence was included as covariates of no interest. The results of these analyses are presented in Tables DS4-7. There were no significant differences in subcortical volumes between controls and OCD patients when excluding patients with lifetime co-morbid anxiety disorder, as well as patients on medication.

Table DS4 Comparison of cortical thickness between OCD patients (N=222) and healthy controls (N=368) after exclusion of patients on medication

Grey matter region	Hemis phere	Local maxima Z- value	p-value	Talairach coordinates
HC > OCD				
Superior	Left	4.222	< 0.0001	-9.7 4.4
Inferior	Right	5.680	< 0.0001	51.7 23.0
Precentral	Right	3.771	0.0002	27.0 -18.0
Posterior	Right	5.639	< 0.0001	6.1 -12.2
Middle	Left	6.470	< 0.0001	-57.6 -42.1 -
	Right	5.840	< 0.0001	59.5 -45.3 -

Results are shown at p< 0.05 corrected for multiple comparisons with Monte Carlo simulations. Covariates of no interest include age, sex, scan sequence and level of education.

Table DS5 Comparison of cortical thickness between OCD patients (N=190) and healthy controls (N=368) after exclusion of patients with lifetime co-morbid anxiety disorder

Grey matter region	Hemis phere	Local maxima Z- value	p-value	Talaraich coordinates
HC > OCD				
Insula	Right	8.205	<	34.4 -16.5
Caudal middle	Right	3.530	0.000	36.7 4.1
Paracentral	Left	10.419	<	-6.5 -21.1
Pericalcarine	Right	12.531	<	12.3 -86.3 4.5

Results are shown at p < 0.05 corrected for multiple comparisons with Monte Carlo simulations. Covariates of no interest include age, sex, scan sequence and level of education.

Table DS6 Comparison of cortical thickness between OCD patients (N=287) and healthy controls (N=368) after exclusion of patients with lifetime co-morbid major depressive disorder

Grey matter region	Hemis phere	Local maxima Z- value	p-value	Talaraich coordinates
HC > OCD				
Superior frontal	Left	4.576	<	-8.5 26.1
Inferior frontal	Left	2.869	0.004	-32.1 29.1 3.8
	Right	3.516	0.000	49.1 25.0
Rostral middle	Left	2.823	0.004	-31.2 46.7 6.3
Medial	Right	3.240	0.001	8.3 51.6 -
Lateral occipital	Left	4.115	<	-15.5 -90.2

Results are shown at p < 0.05 corrected for multiple comparisons with Monte Carlo simulations. Covariates of no interest include age, sex, scan sequence and level of education.

Table DS7 Comparison of subcortical volumes between OCD patients and healthy controls after exclusion of patients with lifetime co-morbid anxiety disorder

Subcortical	Hemisphere	F-value	p-value
HC > OCD			
Hippocampus	Left	7.677	< 0.001
	Right	5.057	0.002

Results of the ANOVA analysis between groups are shown here. Results are shown at p <0.0036 (p < 0.05 Bonferroni corrected). Covariates of no interest in this analysis included scan sequence, level of education, age and sex

DS4 Post-hoc hierarchical multiple linear regression analysis on medication status

The mean cortical thickness and subcortical volume of regions that showed significant differences within OCD patients based on medication use were extracted from Freesurfer for analysis in SPSS 20.0. The cortical regions included the left lateral orbitofrontal, insula, superior temporal, inferior temporal, bilateral lateral occipital and right superior frontal and middle temporal gyri. Subcortical regions included bilateral caudate, putamen, hippocampus, amygdala and accumbens, as well as left pallidum. Stepwise multiple linear regression analyses were then performed on each region by stepwise entering scan sequence, age, sex, education, YBOCS total score and medication status (present = 1, absent = 0) into the model.

The following regions remained significant for medication status: **left lateral occipital** (*model R-square change=0.065; F-change=24.645; beta 95% confidence interval=-0.256; t=-4.964; p<0.001*), **left lateral orbitofrontal** (*model R-square change=0.048; F- change=27.576; beta 95% confidence interval=-0.225; t=-5.251; p<0.001*), **left superior temporal** (*model R-square change=0.014; F-change=6.050; beta 95% confidence interval=- 0.118; t=-2.460; p=0.014*), **right lateral occipital** (*model R-square change=0.074; F- change=28.264; beta 95% confidence interval=-0.273; t=-5.316; p<0.001*), **right superior frontal** (*model R-square change=0.010; F-change=5.582; beta 95% confidence interval=- 0.101; t=-2.363; p=0.19*) and **right middle temporal** (*model R-square change=0.018; F- change=7.318; beta 95% confidence interval=0.137; t=2.705; p=0.007*).

The following regions did not remain significant after stepwise regression and controlling for demographic and clinical variability: left insula and left inferior temporal gyri.

Table DS8 Effect of medication use on cortical thickness in OCD patients.

Medication use in patients (med+ n=176; med- n=222)							
	Grey matter region	**Hemisphere**	**Mean thickness**		**Local maxima Z-value**	**p-value**	**Talairach coordinates**
			- med (SD)	+ med (SD)			
- med > + med	Lateral occipital	Left	2.015 (0.213)	1.875 (0.164)	20.020	< 0.0001	-9.7 -98.7 7.6
	Lateral orbitofrontal		2.573 (0.190)	2.430 (0.185)	10.267	< 0.0001	-26.6 32.2 -9.1
	Insula[a]		2.580 (0.192)	2.439 (0.197)	6.477	< 0.0001	-28.6 16.3 8.0
	Superior temporal		3.073 (0.202)	2.953 (0.236)	3.264	0.0011	-46.6 -2.3 -14.9
	Lateral occipital	Right	1.899 (0.167)	1.861 (0.157)	19.136	< 0.0001	11.3 -97.0 12.8
	Superior frontal		2.658 (0.214)	2.506 (0.222)	7.036	< 0.0001	15.5 44.2 4.6
	Middle temporal		2.857 (0.177)	2.803 (0.185)	3.092	0.0020	61.8 -36.0 -3.6
+ med > - med	Inferior temporal[a]	Left	2.442 (0.189)	2.506 (0.173)	-4.424	< 0.0001	-42.0 -60.2 -1.4

Results are shown at $p < 0.05$ corrected for multiple comparisons with Monte-Carlo simulations. Covariates of no interest in this analysis included scan sequence, level of education, age and sex. Abbreviations: - med: not on medication at time of scan; + med: on medication at time of scan.

[a]Indicates results that are not significant after stepwise regression controlling for demographic and clinical variability

DS5 Co-morbid anxiety analysis

There was information on co-morbid anxiety presence/absence in 273 OCD patients. These included panic disorder, social phobia, specific phobia, post-traumatic stress disorder, general anxiety disorder and anxiety disorders not otherwise specified. Lifetime diagnosis of co-morbid anxiety was available in 83 OCD patients and in 75 of these patients it was currently present as well. Because there was a large overlap of lifetime and current anxiety co-morbidity, only the lifetime (n=75) diagnoses were considered for analysis. Cortical thickness (in FreeSurfer) and subcortical volumes (in SPSS 20.0) were compared between OCD patients with (n=83) and without (n=190) a lifetime diagnosis of anxiety. Age, sex, educational level and scan sequence were included as covariates of no interest (See Table DS9 for results).

DS6 Co-morbid major depressive disorder (MDD) analysis

There was information on MDD presence/absence in 388 OCD patients. Patients with lifetime MDD (n=101) were compared with OCD patients without MDD (n=287) on measures of cortical thickness and subcortical volumes. Age, sex, educational level and scan sequence were included as covariates of no interest (See Table DS9 and DS10 for results).

Table DS9 The effect of co-morbid anxiety and depression on cortical thickness within OCD patients

Grey matter region	**Hemisphere**	**Mean thickness**		**Local maxima Z-value**	**p-value**	**Talairach coordinates**
Lifetime co-morbid anxiety disorder (anx+ n=83; anx- n=190)						
		anx- (SD)	**anx+ (SD)**			
anx- > anx+						
Insula[a]	Left	2.567 (0.236)	2.445 (0.187)	6.399	< 0.0001	-28.7 19.1 10.1
Rostral middle frontal	Left	2.408 (0.200)	2.305 (0.167)	5.639	< 0.0001	-25.3 33.4 24.4
Paracentral	Left	2.505 (0.184)	2.394 (0.151)	6.383	< 0.0001	-4.0 -30.2 68.2
Pericalcarine	Left	2.070 (0.140)	1.972 (0.126)	5.065	< 0.0001	-9.2 -88.0 8.4
Inferior parietal[a]	Left	2.392 (0.193)	2.313 (0.144)	2.983	0.0029	-32.3 -76.2 26.2
Paracentral	Right	2.362 (0.159)	2.253 (0.135)	6.453	< 0.0001	5.4 -23.6 71.1
Insula	Right	2.846 (0.216)	2.732 (0.186)	4.770	< 0.0001	34.9 -15.0 18.6
anx+ > anx-						
Entorhinal	Right	3.075 (0.180)	3.222 (0.163)	-6.061	< 0.0001	28.8 1.3 -36.7
Lifetime co-morbid major depression (dep+: n=101; dep-: n=287)						
		dep- (SD)	**dep+ (SD)**			
dep+ > dep-						
Inferior frontal	Left	2.474 (0.205)	2.506 (0.240)	5.750	< 0.0001	-32.4 26.8 8.7
Superior frontal[a]	Left	2.585 (0.312)	2.607 (0.322)	3.982	0.0001	-14.1 43.0 10.9
Lateral orbitofrontal	Left	2.383 (0.190)	2.417 (0.207)	4.197	< 0.0001	-33.6 35.0 -8.3
dep- > dep+						
Entorhinal	Right	3.196 (0.154)	3.047 (0.157)	-4.204	< 0.0001	29.1 0.3 -36.0
Middle temporal	Left	2.868 (0.201)	2.756 (0.224)	-4.619	< 0.0001	-51.9 -60.5 -0.3

Results are shown at $p < 0.05$ corrected for multiple comparisons with Monte Carlo simulations. Covariates of no interest include age, sex, scan sequence and level of education.

[a]Indicates results that are not significant after stepwise regression controlling for demographic and clinical variability

Table DS10 The effect of co-morbid depression on subcortical volumes within OCD patients

Subcortical region	Hemisphere	F-value	p-value
Lifetime co-morbid major depression (dep+ n=101; dep-n=287)			
dep- > dep+			
Hippocampus[a]	Left	4.877	0.002

Results of the ANOVA analysis between groups are shown here. Results are shown at $p < 0.0036$ ($p < 0.05$ Bonferroni corrected). Covariates of no interest in this analysis included scan sequence, level of education, age and sex

[a]Indicates results that are not significant after stepwise regression controlling for demographic and clinical variability

DS7 Post-hoc hierarchical multiple linear regression analysis on co-morbid anxiety and major depression

The mean cortical thickness and subcortical volume of regions that showed significant difference between patients with co-morbid anxiety and/or MDD and patients without co-morbidity was extracted from FreeSurfer for analysis in SPSS 20.0. Stepwise multiple linear regression analyses were performed on these regions by entering scan sequence, age, sex, education, YBOCS total score and lifetime/current co-morbid anxiety disorder or lifetime/current co-morbid MDD (present =1, absent = 0) into the model.

For the co-morbid anxiety disorder analysis, the following regions remained significant after controlling for demographic and clinical variability: **left paracentral** (*model R-square change=0.045; F-change=14.481; beta 95% confidence interval=0.212; t=3.805; p<0.001*), **left pericalcarine** (*model R-square change=0.041; F-change=15.633; beta 95% confidence interval=0.202; t=3.954; p<0.001*), **left rostral middle frontal** (*model R-square change=0.053; F-change=18.393; beta 95% confidence interval=0.230; t=4.289; p<0.001*), **right entorhinal** (*model R-square change=0.086; F-change=24.199; beta 95% confidence interval=-0.293; t=-4.919; p<0.001*), **right insula** (*model R-square change=0.027; F- change=9.221; beta 95% confidence interval=0.165; t=3.037; p<0.003*) and **right paracentral** (*model R-square change=0.064; F-change=20.348; beta 95% confidence interval=0.253; t=4.511; p<0.001*).

The following regions did not remain significant after stepwise regression and controlling for demographic and clinical variability: left insula and the left inferior parietal regions.

For the lifetime diagnosis of MDD, the following regions remained significant after controlling for demographic and clinical variability: **left lateral orbitofrontal** (*model R- square change=0.015; F-change=7.890; beta 95% confidence interval=0.128; t=2.809; p=0.005*), **left middle temporal** (*model R-square change=0.030; F-change=11.640; beta 95% confidence interval=-0.178; t=-3.412; p=0.001*), **left inferior frontal** (*model R-square change=0.016; F-change=8.345; beta 95% confidence interval=0.132; t=2.889; p=0.004*), t=3.926; p<0.001) and **right entorhinal** (*model R-square change=0.064; F-change=23.656; beta 95% confidence interval=-0.253; t=-4.864; p<0.001*).

The left hippocampus and superior frontal regions did not remain significant after stepwise regression and controlling for demographic and clinical variability.

Table DS11 Demographic and clinical characteristics of the healthy controls (N=368) and OCD patient (N=412) group (as shown in de Wit et al. 2014)

Characteristic	**OCD patients**		**Healthy controls**		**Statistics**	
	Mean	**SD**	**Mean**	**SD**	**t**	**P**
Age (years)	32.1	9.6	30.2	9.3	2.9	0.004
Education level	13.7	2.8	14.6	3.1	-4.0	<0.001
YBOCS score	24.9	6.2				
Age at onset of clinical symptoms	20.1	8.7				
	N	**%**	**N**	**%**	**χ^2**	**P**
Male	202	49.0	195	53.0	1.2	0.28
Right-handed	354	85.9	330	89.7	1.0	0.65
Ethnicity					2.7	0.26
Caucasian	195	47.3	192	52.2		
Asian	171	41.5	146	39.7		
Other	6	1.5	11	3.0		
Medication use at time of scan	176	42.7	0	0.0	210.1	< 0.001
Current	149	36.2	0	0.0	210.1	< 0.001
Lifetime	213	51.7	7	1.9	253.7	< 0.001
Prepubertal OCD	51	13.0				
OCD symptom dimensions						
Aggression/checki	236	57.2				
Contamination/cle	202	49.0				
Symmetry/orderin	168	40.8				
Sexual/religious	130	31.6				
Hoarding	87	21.1				

DS8 Association of OCD symptom dimensions with cortical thickness and subcortical volume

There was information on lifetime presence/absence of OCD symptom dimensions for n=331 patients. The five dimensions were checking/aggression, contamination/cleaning, sexual/religious, hoarding and symmetry/ordering. Cortical thickness and subcortical volume were included in a general linear model with the five dimensions to investigate associations between the variables. Age, education, sex, scan sequence and total YBOCS score were included as covariates of no interest in the model. 1 for a positive association and -1 for a negative association with thickness/volume indicated the absence/presence of each dimension (See Table DS12 for results).

Table DS12 Effect of symptom severity and symptom dimensions on cortical thickness in OCD patients

	Grey matter region	**Hemisphere**	**Surface area size(mm^2)**	**Local maxima Z-value**	**p-value**	**Talaraich coordinates**
- correlation YBOCS	Lateral occipital	Left	1610.63	-5.634	< 0.0001	-13.9 -98.6 8.0
	Lateral occipital	Right	2354.92	-3.984	0.0001	11.7 -96.9 13.7
OCD symptom dimensions (n=331)						
+ correlation contam/clean	Lateral orbitofrontal	Left	2053.93	5.840	< 0.0001	-12.6 49.5 -17.2
	Precentral		1319.85	4.109	< 0.0001	-54.0 3.6 2.6
	Frontal pole	Right	1169.64	5.275	< 0.0001	8.3 62.0 -6.1
+ correlation hoarding	Inferior frontal	Left	10600.78	4.543	< 0.0001	-32.0 20.8 10.4
	Lateral occipital		1653.60	3.501	0.0005	-15.9 -94.7 -7.6
	Middle temporal		1550.72	3.256	0.0011	-42.9 -60.0 7.2
	Lateral orbitofrontal		1052.22	3.062	0.0022	-15.5 17.1 -18.9
	Superior parietal		992.99	2.417	0.0156	-17.9 -75.2 33.8
	Superior frontal	Right	2280.36	6.088	< 0.0001	14.4 38.6 8.8

	Inferior frontal		1799.27	4.965	< 0.0001	37.4 12.5 20.1
	Medial orbitofrontal		1792.09	4.012	< 0.0001	8.4 50.9 -12.0
	Cuneus		921.23	2.323	0.0202	5.7 -84.7 19.3
+ correlation sex/religious	Isthmus cingulate	Left	2054.23	4.802	< 0.0001	-10.1 -51.0 9.8
	Rostral middle frontal		6694.23	4.383	< 0.0001	-25.8 27.7 29.8
	Lateral occipital		3106.46	4.035	< 0.0001	-22.1 -92.4 -8.9
	Superior parietal	Right	2827.72	4.237	< 0.0001	19.2 -75.9 35.1
	Supramarginal		1287.03	3.183	0.0015	53.3 -29.4 42.8
	Precuneus		902.64	2.959	0.0031	8.9 -38.6 41.1
	Lateral orbitofrontal		1078.97	2.558	0.0105	27.2 27.1 -12.0
+ correlation sym/order	Precentral	Left	8299.76	5.444	< 0.0001	-28.3 -8.6 44.0
	Insula		931.44	5.263	< 0.0001	-34.2 -14.5 17.2
	Postcentral		832.66	3.822	0.0001	-14.7 -31.1 57.8
	Lingual		1557.63	3.040	0.0024	-7.1 -91.0 -3.4
	Lateral occipital	Right	2959.27	3.729	0.0002	18.4 -95.6 14.7
	Medial orbitofrontal		2250.68	3.594	0.0003	10.4 54.5 -6.9
- correlation sym/order	Superior temporal	Right	1825.34	-3.927	0.0001	44.6 -1.2 -17.9
+ correlation check/aggr	Lateral occipital	Right	1415.53	2.924	0.0035	32.7 -80.6 17.0
- correlation check/aggr	Entorhinal	Right	2098.43	-3.930	0.0001	24.8-5.4 -27.0

Results are shown at $p < 0.05$ corrected for multiple comparisons with Monte-Carlo simulations. Covariates of no interest in this analysis included scan sequence, level of education, age, sex and YBOCS severity (for the symptom dimension analysis).

Abbreviations: contam/clean: contamination/cleaning; sym/order: symmetry/order; check/aggr: checking/aggression

[a]Indicates results that are not significant after stepwise regression controlling for demographic and clinical variability