Data Supplement for Boedhoe et al., Cortical Abnormalities Associated With Pediatric and Adult Obsessive-Compulsive Disorder: Findings From the ENIGMA Obsessive-Compulsive Disorder Working Group. Am J Psychiatry (doi: 10.1176/appi.ajp.2017.17050485)

Supplementary Information and Supplementary Figures

Supplementary Section S1

Cortical Measures

Cortical surface area and thickness are distinct features of cortical morphometry that are somewhat genetically independent (1) and are driven by different neurobiological processes. The number of radial columns is thought to determine the area of the cortical surface, where the number of columns is influenced by the number of founder cells in the ventricular zone. In contrast, cortical thickness is influenced by the number of cells within a column. While development of cortical surface area may depend on input from subcortical structures, development of cortical thickness has been argued to depend more on local or intrinsic factors (2; 3). Surface area reflects early neurodevelopmental influences (4), whereas cortical thickness changes dynamically across the lifespan as a consequence of development and disease (5). Studying these properties independently will make it easier to interpret the cortical abnormalities reported in OCD in the context of the postulated neurodevelopmental basis for OCD (6).

Image Exclusion Criteria

Prior to data processing scans were visually inspected at each site locally and scans with gross brain pathology, artifacts or poor image quality hampering image segmentation were excluded. A neuroimaging researcher at each site individually examined each segmentation by three major steps following standardized ENIGMA protocols to harmonize quality control procedures across multiple sites.

First, outliers were determined by calculating the interquartile range for each of the volumes per cohort and per group (OCD patients and healthy controls). For each subject that was marked as a statistical outlier, a re-inspection of the subject's segmentation was conducted in 3D to evaluate whether it was segmented properly, and excluded if necessary. Second, cortical segmentations were overlayed directly on a subject's T1-weighted scan and snapshots from internal slices of the brain were presented on a webpage for easy checking. Third, webpages were created with external views of the segmentations from different angles of each subject. For these latter two steps, we instructed the sites to perform extensive quality checking according to a standardized manual (available on http://enigma.ini.usc.edu/protocols/imaging-protocols/) encompassing the most common segmentation errors by FreeSurfer based on our own experience of several samples across different sites and scanners.

Further, we collected study-wide statistics (means and standard deviations) as well as histogram plots in order to identify non-normally distributed data and major outliers. Lastly, the coordinating PI site (VUMC Amsterdam) checked the histograms and summary statistics of every site for possible irregularities that would indicate incorrect segmentations. Where needed, sites were asked to re-inspect suspicious irregularities.

Intracranial volume correction (ICV)

The ICV measure, sometimes referred to as total intracranial volume (TIV), refers to the estimated volume of the cranial cavity as outlined by the supratentorial dura mater or cerebral contour when dura is not clearly detectable. The consistent ICV measures during aging makes it a reliable tool for correction of head size variation across subjects in studies that rely on morphological features of the brain (7).

Because it is difficult to distinguish between skull and CSF (both dark on a T1 image), FreeSurfer exploits a relationship between the ICV and the linear transform to MNI305 space as described in Buckner et al. (8). ICV is found to correlate with the determinant of the transform matrix used to align an image with an atlas. Buckner et al. (8) demonstrate that a one-parameter scaling factor provides a reasonable TIV estimation. The eTIV measure from FreeSurfer is in good agreement with ICV reference segmentation acquired from proton density weighted images (9) and has previously been used in several studies to correct for variation in head size.

Supplementary Section S2

OCD symptom severity and symptom dimensions were assessed with the YBOCS severity scale and symptom checklist. The presence of five previously identified symptom dimensions (10; 11) designated as 1) “aggressive/checking ”, 2) “contamination/cleaning ”, 3) “symmetry/ordering”, 4)“sexual/religious obsessions”, and 5) “hoarding” was assessed. The dimensional structure of the YBOCS Checklist has been reasonably replicated and symptom dimensions are relatively independent from overall symptom severity (12). The consistency in the literature is remarkable despite the use of different instruments (YBOCS Checklist versus Obsessive-Compulsive Inventory) and methods (current versus lifetime symptoms, dichotomous versus ordinal scoring and factor versus cluster analysis e.g.). Following the approach of many previous studies (13–16), responses on the major categories were quantified by the absence and presence of the symptoms under that category, either current or lifetime. 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. The regression models existed of one symptom dimension being the covariate of interest and the other symptom dimensions being nuisance covariates (together with age, sex, site and ICV as nuisance covariates). The following samples did not assess the YBOCS symptom checklist: Cheng 1.5T I, Cheng 3T II, Koch, Walitza. Therefore, these samples were excluded from the symptom dimension analyses. A clinician administered the (C)Y-BOCS in all samples except for 1 adult site (Koch). This site trained their patients to assess the Y-BOCS via a self-report questionnaire.

Supplementary Section S3

Meta-analysis

Meta-analysis is a statistical method to combine the results of independent studies. This approach uses summary data from groups of people rather than data from individual subjects. In contrast, mega-analysis refers to a technique of performing an analysis by pooling individual subject-level data (in our case extracted measures across all sites) from the individual subjects. Some methodologists claim a mega-analysis can be superior to meta-analysis, since more detailed analyses can be performed in a mega-analysis. The comprehensive evaluation of missing data and greater flexibility in the control of confounders are significant advantages of a mega-analytical approach. On the other hand, meta-analysis allows for analyses of individual studies to account for local population substructure, relationships among subjects, study-specific covariates, and other ascertainment-related issues that may be better dealt with within each study. By using both meta- and mega-analysis, we sought to investigate whether the mega-analytic design has greater sensitivity to detect more subtle cortical brain abnormalities.

Statistical framework

We also examined differences between OCD patients and controls in cortical thickness and surface area by performing a meta-analysis. Similar to the mega-analysis, several covariates of interest were investigated using multiple linear regression models. All regression models and effect size estimates were computed at each site separately and a final Cohen's *d* effect size estimate was obtained using an inverse variance-weighted random-effect meta-analysis model in R (metaphor package, version 1.9-118). For the meta-analyses on correlation with illness severity, illness duration and age at onset effect sizes were expressed as Pearson's *r*. The final meta-analyzed partial-correlation *r* was estimated, with the same inverse variance-weighted random-effect meta-analysis model. This meta-analytical framework enabled us to combine data from multiple sites and weigh individual effect size estimates by level of precision. All meta-analysis models were fit using the restricted maximum likelihood method (REML (17)). Additionally, we used meta-regression analyses to test whether mean age of the sample and field strength of MR images explained a significant proportion of the variance in effect sizes across sites in the meta-analysis for OCD versus healthy controls (including covariates). Each moderator variable was separately included as a fixed effect predictor in a meta-regression model. A significance threshold for each moderator hypothesis was determined by false discovery rate (FDR) procedure at q=0.05.

Results

Adult OCD

The results of the adult meta-analysis are summarized in Supplementary Table S29. We did not observe any differences in cortical thickness in OCD patients compared to healthy controls after FDR correction (Supplementary Table S30a). The meta-analysis showed an overall robust effect of a lower surface area of the

transverse temporal cortex in OCD patients compared to healthy controls (Supplementary Tables S29b and S30b). Widespread effects of medication on cortical thickness in frontal and temporal regions were also detected by the meta-analysis (Supplementary Table S29a). For all other analyses, we did not find significant differences.

Pediatric OCD

The results of the pediatric meta-analysis are summarized in Supplementary Table S31. Compared to healthy control children, we did not detect surface area and cortical thickness differences in children with OCD (Supplementary Tables S32a-b). Compared to unmedicated children with OCD we found lower surface area of the right pericalcarine gyrus in the medicated children with OCD (Supplementary Table S31). The meta-analysis also revealed lower surface area of the left rostral middle frontal gyrus in the sub-group of children with OCD that had no additional anxiety disorder compared to healthy control children (Supplementary Table S31). For all other analyses, we did not find significant differences.

Results moderator analyses

Sample characteristics such as mean age and field strength did not significantly moderate effect size estimates of cortical thickness or surface area differences in adult OCD patients compared to controls (Supplementary Tables S33a-b). We found evidence of a significant moderating effect of mean age indicating greater cortical thinning of the right lateral occipital cortex (d=-0.322, p=0.001) in pediatric OCD compared to controls in samples with a higher mean age (Supplementary Table S34a). Mean age and field strength did not significantly moderate effect size estimates of surface area in pediatric OCD patients compared to controls (Supplementary Table S34b).

Discussion

The meta-analysis seemed less sensitive to subtle cortical changes than the mega-analysis both in children and adults. The adult meta-analysis failed to detect decreases in cortical thickness of the inferior parietal cortex in the main group comparison. When looking at the effect sizes, decreased cortical thickness of the inferior parietal cortex was present in adult patients with OCD compared to healthy controls, but at a less stringent significance threshold. The meta-analysis of the pediatric samples also failed to detect decreased cortical thickness of the parietal cortex after FDR correction, while the mega-analysis did. Decreased cortical thickness of the parietal cortex was, however, again present at a less stringent significance threshold. When looking at the magnitude and order of effect sizes we see the same pattern resulting from the meta- and mega-analysis, i.e. the magnitude and direction of effect of the effect sizes derived from the meta- and mega-analyses were highly similar. However, the same results did not reach significance in the meta-analysis while they did reach significance in the mega-analysis. This suggests that compared to a meta-analysis, a mega-analysis has greater statistical power to detect subtle cortical changes.

Supplementary Section S4

Mega-analysis

Influence of comorbidities on cortical thickness and surface area

Influence of a current comorbid major depressive disorder diagnosis on cortical thickness and surface area

Adult: We did not detect differences in cortical thickness in OCD patients with a current comorbid depression (N=167) compared to controls (N=1436) and when comparing patients with and without a comorbid depression directly (Supplementary Tables S12a-c). Patients without a current comorbid depression (N=1191) compared to controls showed global cortical thinning of the left and right hemisphere and regionally in the lateral OFC, rostral middle frontal gyrus, fusiform gyrus, inferior parietal cortex, precuneus bilaterally and unilaterally in the left caudal middle frontal gyrus, right medial OFC, right middle temporal gyrus and right parahippocampal gyrus (Supplementary Table S12b). Similar to the main group comparison, we found a reduction in surface area in the left transverse temporal cortex in the OCD patients without a current comorbid depression (Supplementary Table S13b). We did not detect differences in surface area in OCD patients with a comorbid depression compared to controls and when comparing with and without comorbid depression directly (Supplementary Table S13a-c).

Children: We found significant thinner cortices in the parietal lobe of pediatric OCD patients without a comorbid current depression (N=350) compared to controls (N=324) in the bilateral superior parietal cortex and inferior parietal cortex (Supplementary Table S14b) and a reduction in the surface area of the left posterior cingulate cortex (Supplementary Table S15b). None of the regions analyzed showed significant differences in cortical surface area or cortical thickness when comparing pediatric OCD patients with a comorbid current depression (N=29) to controls and when comparing those with and without a comorbid depression directly (Supplementary Tables S14a-c and S15a-c).

Influence of a current comorbid anxiety disorder on cortical thickness and surface area

Adult: We did not detect differences in cortical thickness in OCD patients with a current comorbid anxiety disorder (N=224) compared to controls (N=1436) and when comparing patients with and without a comorbid anxiety disorder directly (Supplementary Tables S16a-c). Patients without current comorbid anxiety (N=1113) compared to controls showed global cortical thinning of the left and right hemisphere and regionally in the lateral OFC, fusiform gyrus, inferior parietal cortex, precuneus bilaterally and unilaterally in the left middle temporal gyrus, right medial OFC, and right parahippocampal gyrus (Supplementary Table S16b). Similar to the main group comparison, we found a reduction in surface area in the left transverse temporal cortex in the OCD patients without a current comorbid anxiety disorder (Supplementary Table S17b). We did not detect differences in surface area in OCD patients with comorbid anxiety compared to controls and when comparing those with and without comorbid anxiety directly (Supplementary Table 17a-c).

Children: Compared to controls (N=324), pediatric patients without a current anxiety disorder (N=105) showed cortical thinning of the left inferior parietal cortex (Supplementary Table S18b). We did not

detect significant differences in cortical thickness in pediatric OCD patients with a comorbid anxiety disorder (N=68) compared to controls and when comparing those with and without comorbid anxiety (Supplementary Tables S18a-c). Similarly, no surface area differences were detected in these subgroup analyses (Supplementary Tables S19a-c).

Discussion

Cortical abnormalities were detected in the larger sub-group without comorbid anxiety or depression. The effect sizes of these small sub-groups with comorbid anxiety or depression are similar to those of the larger sub-groups without comorbid anxiety or depression. The discrepancies in significant findings are likely driven by the differences in sample size.

Cortical thickness effects associated with commonly prescribed medications in adult OCD patients

In post-hoc analyses we aimed to further examine the cortical thickness abnormalities associated with the most commonly prescribed medications in adult OCD patients. Due to the limited information available on medication classes, we were merely able to distinguish patients on antidepressants versus patients on antidepressants with adjuvant antipsychotics.

We observed significantly thinner cortices globally in adult medicated OCD patients on antidepressants (N=418) compared to controls (N=1435) (Cohen's d between -0.11 and -0.25; Supplementary Table S36a). The much smaller subgroup of adult medicated OCD patients on antidepressants with adjuvant antipsychotics (N=111) showed stronger effect sizes globally (Cohen's d between -0.23 and -0.50; Supplementary Table S36b). Note that, those patients taking antidepressants with adjuvant antipsychotics could represent a more clinically severe cohort that manifests these severe morphometric abnormalities. The direct comparison between OCD patients on antidepressants with those on antidepressants with adjuvant antipsychotics, however, did not show significant differences (Supplementary Table S36c).

Supplementary Section S5

Power analysis

We performed post hoc power analyses with G*Power Version 3.2.1. (18) to estimate the minimal effect size we were able to detect given our sample size. We calculated the minimal effect size (in a case-control comparison) to detect with 80% power at a nominal significance level (P=0.05) for a two-sided t-test assuming unequal variance.

When focusing on the adult samples (1498 OCD patients and 1436 controls) we were able to detect cortical differences as small as Cohen's d= 0.104 at a nominal significance level P-value=0.05 and 80% power (and Cohen's d=0.156 at a Bonferroni significance threshold for 70 tests P=0.05/70=7.14×10^{-4}). When

focusing on the pediatric samples (407 OCD patients and 324 controls) we were able to detect cortical differences as small as Cohen's d=0.209 at a nominal significance level P-value=0.05 and 80% power (and Cohen's d=0.316 at a Bonferroni significance threshold for 70 tests $P=7.14 \times 10^{-4}$).

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Supplementary Figures

Figure S1: Overview of research institutes participating in the ENIGMA Obsessive-Compulsive Disorder Working Group, displayed on a world map.

Figure S2: Mega-analysis effect sizes for regions that showed a significant (q<0.05) difference in cortical surface area between adult OCD patients and healthy controls. Negative effect sizes *d* (red) indicate lower cortical surface area in OCD patients compared to controls. The red circle indicates the transverse temporal cortex.

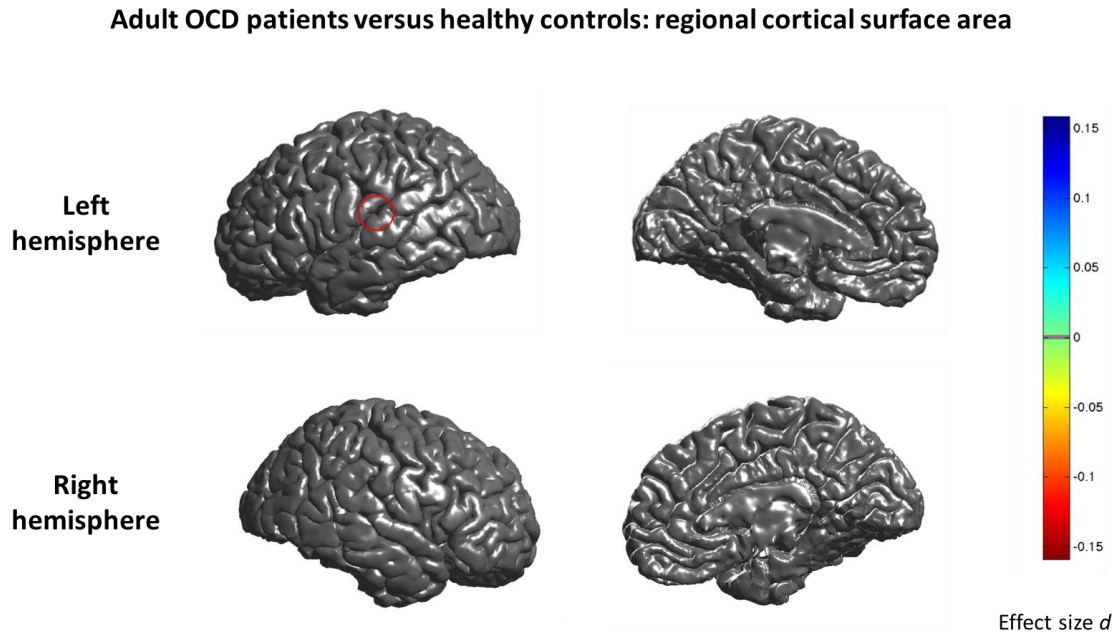

Figure S3: Mega-analysis effect sizes for regions that showed a significant (q<0.05) difference in cortical thickness between adult medicated OCD patients and adult unmedicated patients. Negative effect sizes *d* (red) indicate thinner cortices in OCD patients compared to controls.

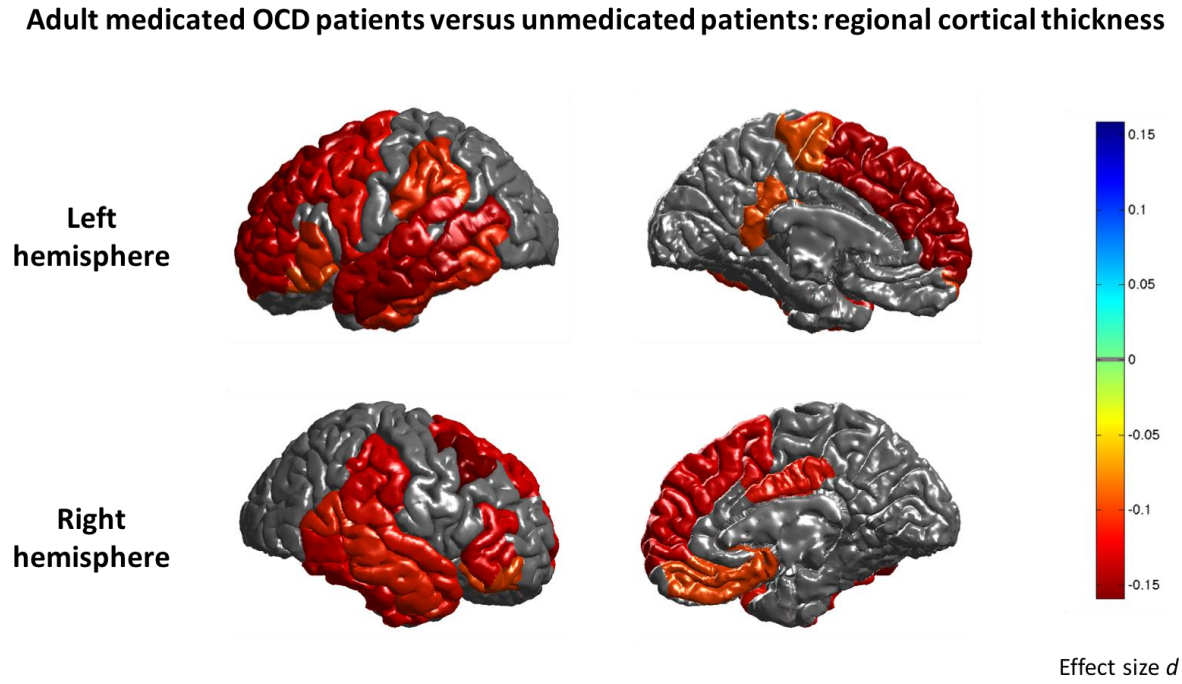

Figure S4: Mega-analysis effect sizes for regions that showed a significant (q<0.05) difference in cortical surface area between adult medicated OCD patients and healthy controls. Negative effect sizes *d* (red) indicate lower cortical surface area in OCD patients compared to controls. The red circle indicates the transverse temporal cortex.

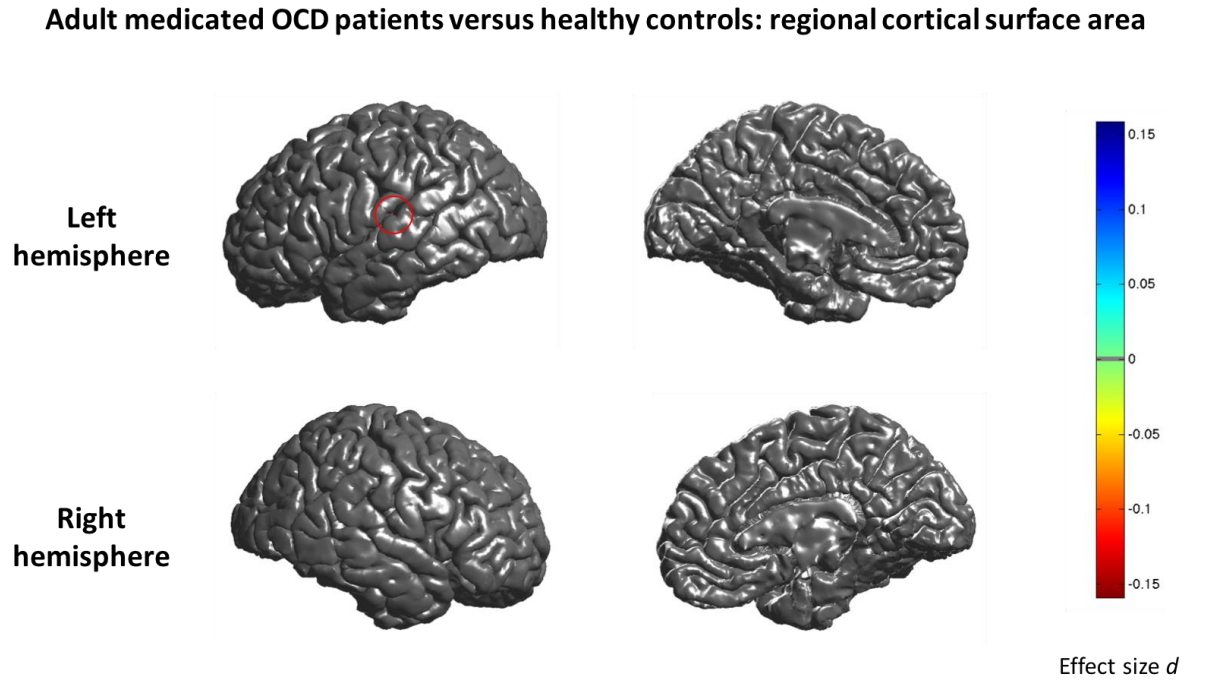

Figure S5: Mega-analysis effect sizes for regions that showed a significant (q<0.05) difference in cortical thickness between pediatric medicated OCD patients and healthy controls. Negative effect sizes *d* (red) indicate thinner cortices in OCD patients compared to controls.

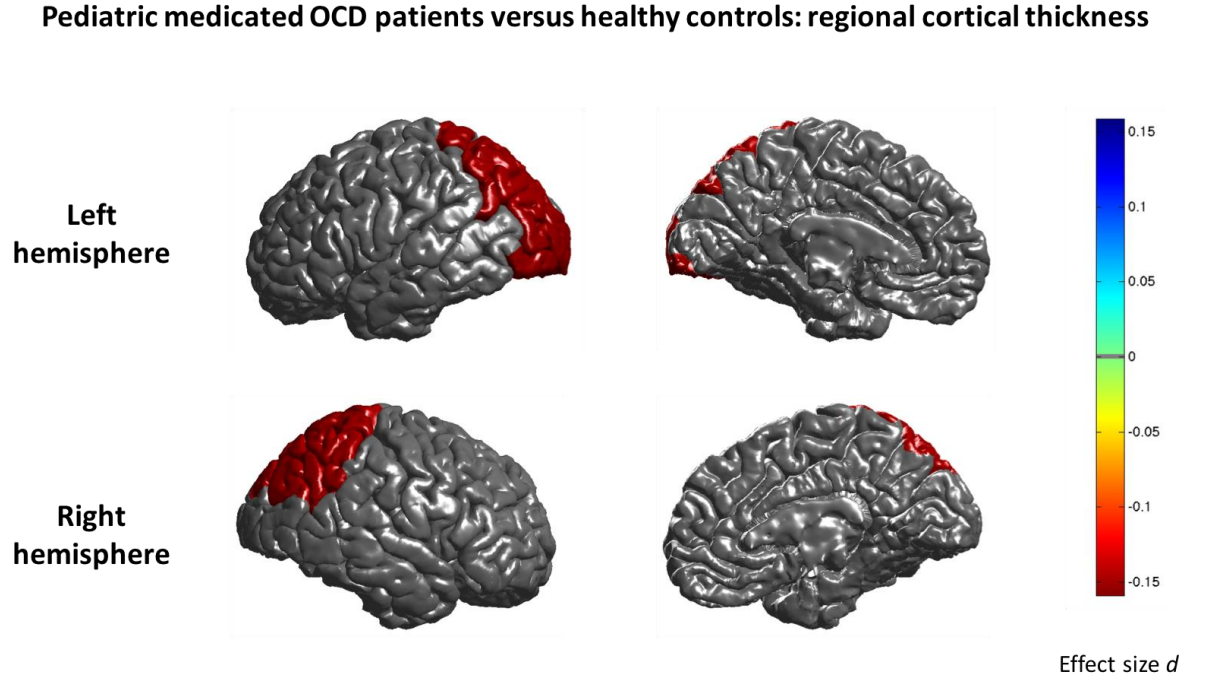

Figure S6: Mega-analysis effect sizes for regions that showed a significant (q<0.05) difference in cortical surface area between pediatric medicated OCD patients and unmedicated patients. Negative effect sizes *d* (red) indicate lower cortical surface area in medicated patients compared to unmedicated.

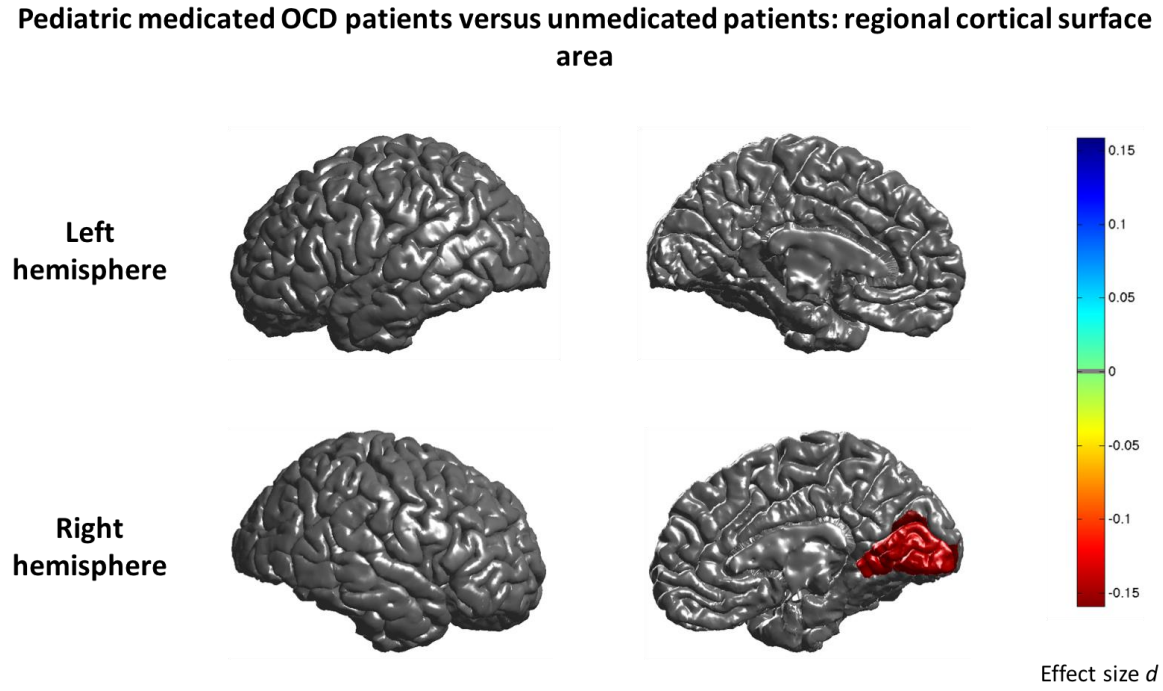

Figure S7: Mega-analysis effect sizes for regions that showed a significant (q<0.05) difference in cortical surface area between pediatric OCD patients with ordering/symmetry symptom and patients without. ~~Negative effect sizes *d* (red) indicate lower~~ cortical surface area in patients with ordering/symmetry symptoms compared to those without.

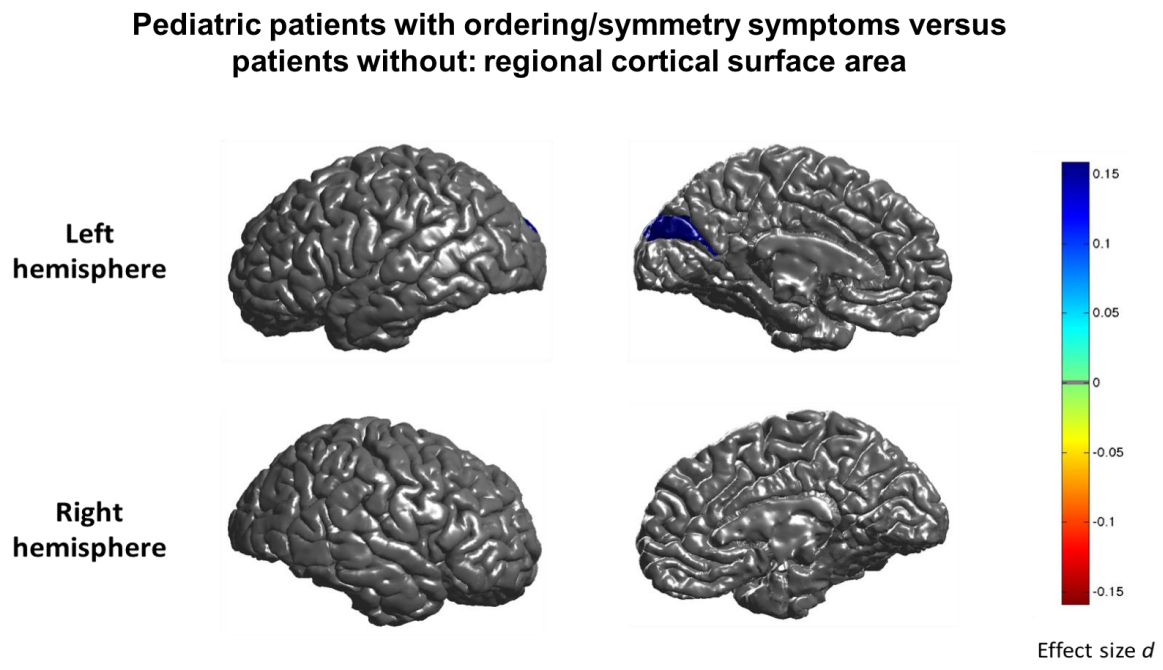

Figure S8: Mega-analysis effect sizes for regions that showed a significant (q<0.05) difference in cortical thickness between adult onset OCD patients and healthy controls. Negative effect sizes *d* (red) indicate thinner cortices in adult onset OCD patients compared to controls.

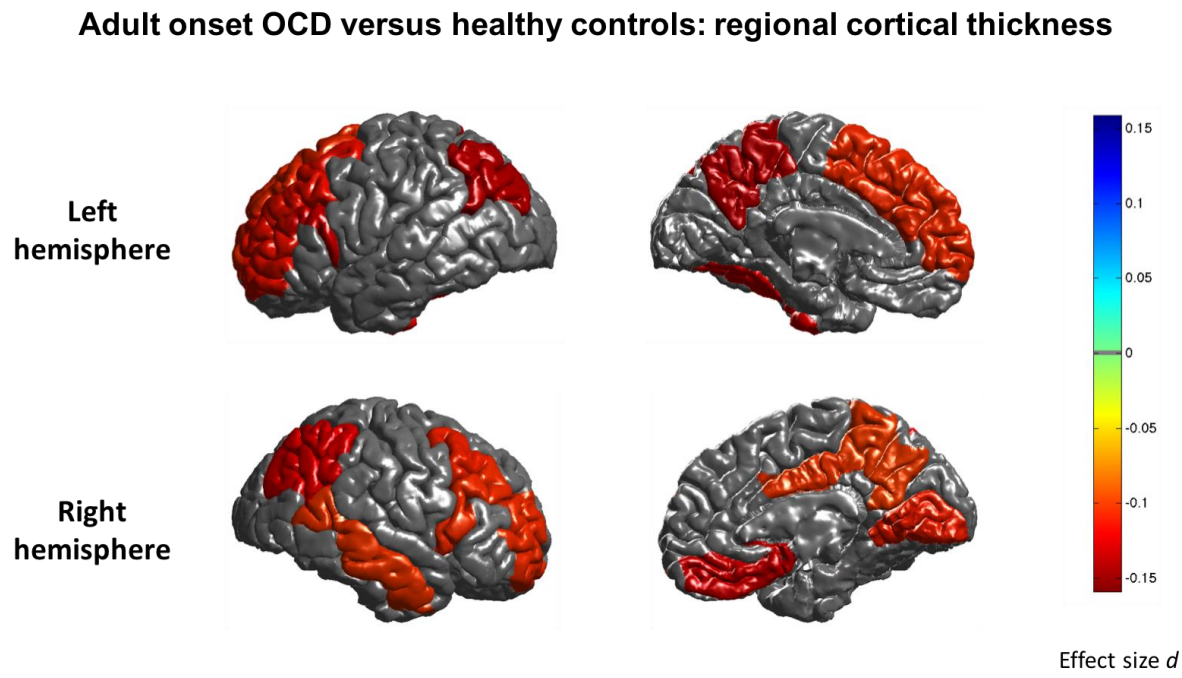

Figure S9: Mega-analysis effect sizes for regions that showed a significant (q<0.05) difference in cortical surface area between adult onset OCD patients and healthy controls. Negative effect sizes *d* (red) indicate lower cortical surface area in adult-onset OCD patients compared to controls. The red circle indicates the transverse temporal cortex.