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Distinct subcortical volume alterations in pediatric and adult OCD:

A worldwide meta- and mega-analysis

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Abstract

Objective—Structural brain imaging studies in Obsessive-Compulsive Disorder (OCD) have produced inconsistent findings. This may be partially due to limited statistical power from relatively small samples and clinical heterogeneity related to variation in disease profile and developmental stage.

Methods—To address these limitations, we conducted a meta- and mega-analysis of data from OCD sites worldwide. T_1 images from 1,830 OCD patients and 1,759 controls were analyzed, using coordinated and standardized processing, to identify subcortical brain volumes that differ in OCD patients and healthy controls. We additionally examined potential modulating effects of clinical characteristics on morphological differences in OCD patients.

Results—The meta-analysis indicated that adult patients had significantly smaller hippocampal volumes (Cohen's d=−0.13; $p=5.1x10^{-3}$, % difference −2.80) and larger pallidum volumes (d=0.16; $p=1.6x10^{-3}$, % difference 3.16) compared to adult controls. Both effects were stronger in medicated patients compared to controls (d=−0.29; $p=2.4x10^{-5}$, % difference −4.18 and d=0.29; $p=1.2x10^{-5}$, % difference 4.38, respectively). Unmedicated pediatric patients had larger thalamic volumes (d=0.38, $p=2.1x10^{-3}$) compared to pediatric controls. None of these findings were mediated by sample characteristics such as mean age or field strength. Overall the mega-analysis yielded similar results.

Conclusion—Our study indicates a different pattern of subcortical abnormalities in pediatric versus adult OCD patients. The pallidum and hippocampus seem to be of importance in adult OCD, whereas the thalamus seems to be key in pediatric OCD. This highlights the potential importance of neurodevelopmental alterations in OCD, and suggests that further research on neuroplasticity in OCD may be useful.

Introduction

Obsessive-compulsive disorder (OCD) is a neurodevelopmental disorder that affects 1–3% of the population (1; 2). In more than 50% of all OCD cases, symptoms emerge during

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childhood or adolescence (1; 3), and in more than 40% of these cases the disorder persists into adulthood (4). OCD symptoms have been associated with structural and functional brain abnormalities in the parallel cortico-striato-thalamo-cortical circuits and other related brain networks, involving fronto-parietal, fronto-limbic and cerebellar regions (5; 6).

Several studies have shown volumetric abnormalities in different deep grey matter structures, mainly the basal ganglia (7–10). Meta-analyses have repeatedly, although not consistently, reported larger volumes in the lenticular nucleus extending to the caudate (11–14). In addition, Pujol et al. (7) showed that the relative enlargement of striatal areas in OCD patients was driven by an older age of the subject and a longer disease duration, suggesting that basal ganglia alterations progress throughout the disease course, supported by the mega-analysis from the OCD Brain Imaging Consortium (OBIC) (15). These findings led to the hypothesis that preservation of basal ganglia volume resulted from neuroplastic changes due to chronic compulsivity.

Although these findings suggest ongoing neuroplasticity, a lifespan approach has seldom been used to understand the variation in structural abnormalities in OCD (5). Studying the brain characteristics of disease during childhood may minimize the potentially confounding effects of neuroplastic changes associated with chronic symptomatology and long-term treatment. Pediatric studies have been sparse and small, leaving the extant findings inconclusive and variable. For example, some studies reported increased thalamus volume in adult (16; 17) and pediatric OCD patients (18), supported by two meta-analyses (14; 19) showing larger thalamus volumes in OCD patients when pediatric and adult data were combined. In contrast, several recent meta-analyses showed no differences in thalamus volumes while combining adult and pediatric subjects (11–13). The variation across studies may partially be explained by variations in the developmental and disease stages of the subjects included.

In view of the clinical heterogeneity of OCD, relatively small samples, differences in data acquisition, data processing protocols, and statistical analyses further contribute to the inconsistent findings. Different segmentation algorithms may give variable estimates of subcortical volumes and thus their sensitivity to regionalized group differences (20). To overcome the heterogeneity in image processing and to increase sample sizes, especially regarding pediatric data, we initiated the OCD Working-Group within the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium (21).

The ENIGMA-OCD Working-Group is an international collaboration and its current aim is to identify subcortical imaging markers that differ in OCD patients and healthy controls, both in children and in adults. Therefore, we conducted a meta- and mega-analysis on structural Magnetic Resonance Imaging (MRI) data of 1,830 OCD patients and 1,759 healthy controls. The mega-analysis ensures information preservation and enables the examination of specific effects of demographic and clinical parameters. By employing meta- and mega-analysis we sought to investigate whether the mega-analytical design has greater sensitivity to detect more subtle brain abnormalities from increased statistical power.

In this study, we investigated nine regions of interest (i.e. seven subcortical grey matter regions, lateral ventricle, and total intracranial volume) in OCD patients compared to healthy controls by performing the largest meta- and mega-analysis to date. In additional exploratory analyses, we examined potential modulating effects of demographic, clinical, and methodological characteristics on subcortical brain volume in OCD. Based on previous meta- and mega-analyses, we expected subcortical brain volumes to vary across developmental stage showing differences between pediatric and adult OCD, and disease profile and stage, including co-morbidity.

Methods

Samples

The ENIGMA-OCD Working-Group includes 35 datasets from 25 international research institutes, with neuroimaging and clinical data from OCD patients and controls, including both children and adults. We considered subjects ≥18 years as adults and subjects <18 years as children. Since previous literature suggested differential effects between pediatric and adult samples, we performed separate meta- and mega-analysis for adult and pediatric data. Demographics and clinical characteristics of the participants in each center are shown in Tables 1 and 2, respectively. In total, we analyzed data from 3,589 subjects including 1,830 OCD patients (N=335 children, N=1,495 adults) and 1,759 controls (N=287 children, N=1,472 adults). All local IRBs permitted the use of extracted measures of the completely anonymized data.

Image acquisition and processing

Structural T_1-weighted MRI brain scans were acquired and analyzed locally. Images were acquired at different field strengths (i.e., 1.5T and 3T). The acquisition parameters of each sample are listed in Supplementary Table 1. The images were analyzed using the fully automated and validated segmentation software FreeSurfer v5.3. (22) following standardized protocols to harmonize analysis and quality control processes across multiple sites (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Segmentation of nine regions of interest, including seven subcortical grey matter structures, i.e., nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus, the lateral ventricle volumes (mean bilateral and right and left side separately), and total intracranial volume were visually inspected for accuracy (Supplementary Information 2).

Meta-analysis of subcortical brain volumes

We examined differences between OCD patients and controls across samples by performing a meta-analysis on the mean of the left and right hemisphere measures of each subcortical structure. The meta-analysis was based on multiple linear regression models, with the mean subcortical brain volume as the outcome measure and a binary indicator of diagnosis (0=controls, 1=patients) as the predictor of interest. All models were controlled for age, sex, and intracranial volume. Effect size estimates, adjusted for age, sex, and intracranial volume, were calculated using Cohen's d-metric computed from the t-statistic of the diagnosis indicator variable from the regression models.

To explore the influence of sex and age on between-group subcortical volume differences, we assessed the significance of diagnosis-by-sex and diagnosis-by-age interaction effects within each sample. Further, multiple linear regression models were used to investigate the within-group effects of age at onset, disease duration, disease severity (using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and the Children's Y-BOCS (23; 24) total severity score) as continuous variables. To further study the neurodevelopmental aspects of disease within the adult samples, we performed separate stratified meta-analyses comparing early-onset OCD patients (<18 years) to controls, and late-onset OCD patients (≥ 18 years) to controls. Stratified meta-analyses were also performed for medicated and non-medicated patients. Likewise separate stratified analyses were performed to investigate comorbid major depressive disorder (MDD), comorbid anxiety disorders, and OCD symptom dimensions (using the Y-BOCS symptom checklist; Supplementary Information 5 *symptom dimension analyses*).

All regression models and effect size estimates were fit at each site separately. Subsequently, a final Cohen's d-effect size estimate was obtained using an inverse variance-weighted random-effect meta-analysis model with the R package 'metaphor' (version 1.9-1[18]). The meta-analysis of disease severity, age at onset, and disease duration were exceptions. The scores on these variables were considered as continuous variables, so effect sizes are reported using Pearson's r, a partial-correlation after removing nuisance variables (age, sex, and intracranial volume). The final meta-analyzed Pearson's r was estimated following the same inverse variance-weighted random-effect meta-analysis models used for the other meta-analyses (Supplementary Information 3).

Moderator analyses

Meta-regressions were performed to examine the effects of moderator variables on meta-analysis effect sizes. We tested whether hypothesized moderating factors such as the mean age of each sample, field strength, percentage of patients taking antidepressants and percentage of patients taking antipsychotics influenced the effect size estimates of the OCD patients versus controls comparison of all subcortical volumes across samples included in the meta-analysis. Each moderator variable was separately included as a fixed effect predictor in a meta-regression model. We report uncorrected P-values with a significance threshold determined by Bonferroni correction for testing nine regions of interest ($P=0.05/9= 5.6\times10^{-3}$).

Power Analysis

Sample sizes that achieve 80% power to detect group differences given the presented effect sizes were calculated based two-sided t-tests assuming unequal variance with G*Power v3.2.1. (25). See Supplementary Information 4 for full details of the power analysis.

Mega-analysis of subcortical brain volumes

We also performed a mega-analysis by pooling all volumetric measurements. The mega-analysis of each mean ((left+right)/2) subcortical volume was performed using the following model: Brain volume= $\beta_{age}X_{age}+ \beta_{sex}X_{sex}+ \beta_{intracranial\ volume}X_{intracranial\ volume}+ \beta_{diagnosis}X_{diagnosis}+ \beta_{cohort1}X_{cohort1}+\ldots.+ \beta_{cohort35}X_{cohort35}+ \varepsilon$. Similar to the meta-analysis,

several covariates of interest were investigated using this regression model. Results were considered significant if they exceeded the Bonferroni corrected P-value threshold 5.6×10^{-3}.

Results

We included data of 25 adult cohorts and 10 pediatric cohorts. The *adult* meta- and mega-analysis contained 1,495 OCD patients and 1,472 controls and the *pediatric* meta- and mega-analysis contained 335 OCD patients and 287 controls. An overview of the number of participants included per cohort is given in Table 1. Supplementary Information 5 describes which sites were included in the analyses regarding the clinical characteristics, and what was considered a sufficient amount of data.

Meta-analysis

OCD patients versus healthy controls

Adult comparison—Results from the analysis comparing all adult OCD patients (N=1,495) to all adult controls (N=1,472) across nine regions of interest volumes are provided in Figure 1a and Table 3. Compared to controls, adult OCD patients showed significantly smaller hippocampal volume (Cohen's d [95% confidence interval]: d=−0.13 [−0.23, −0.04]; P-value= 5.08×10^{-3}, % difference −2.80) and larger pallidum volume (d= +0.16 [0.06, 0.26]; P-value= 1.60×10^{-3}, % difference 3.16). No significant diagnosis-by-sex or diagnosis-by-age interaction effect for any of the subcortical volumes was observed.

Pediatric comparison—None of the subcortical volumes was significantly different between pediatric OCD cases (N=335) and controls (N=287) after Bonferroni correction (Supplementary Table 2).

Influence of medication on subcortical volume

Adult comparisons—Compared to controls, *medicated* OCD patients (N=654) showed larger lateral ventricles (d=+0.24 [0.08, 0.41]; P-value= 2.95×10^{-3}, % difference 2.97) and a larger pallidum volume (d= +0.29 [0.16, 0.42]; P-value= 1.20×10^{-5}, % difference 4.38) as well as a smaller hippocampal volume (d=− 0.29 [−0.43, −0.16]; P-value= 2.39×10^{-5}, % difference −4.18). We did not detect any significant differences between *unmedicated* OCD patients (N=821) and healthy controls, nor between *medicated* OCD patients and *unmedicated* OCD patients. See Supplementary Table 3a–c for full meta-analytic details regarding medication influence on the adult comparisons.

Pediatric comparisons—Figure 1b and Table 4 show that the *unmedicated* pediatric OCD patients (N=159), compared with controls, had larger thalamic volume (d= +0.38 [0.14, 0.63]; P-value= 2.09×10^{-3}, % difference 3.08). Further, we found smaller nucleus accumbens volume in *medicated* pediatric OCD patients (N=170) compared with controls (d= −0.32 [−0.54, −0.09]; P-value= 5.25×10^{-3}, % difference −2.79). No significant differences were detected between *medicated* and *unmedicated* pediatric OCD patients (Supplementary Table 4a–b).

Influence of comorbid MDD on subcortical volume in adult OCD

Adult comparisons—Supplementary Table 5a–c shows that compared to controls, OCD patients with a comorbid lifetime diagnosis of depression (N=325) had smaller hippocampal volume (d=−0.27 [−0.43, −0.12]; P-value= 6.43×10^{-4}, % difference −3.41) and larger lateral ventricles (d= +0.29 [0.14, 0.44]; P-value= 1.16×10^{-4}, % difference 3.85). OCD patients without a comorbid lifetime diagnosis of MDD (N=1,041) present larger pallidum volume (d=+0.19 [0.09, 0.29]; P-value= 1.56×10^{-4}, % difference 3.78) and smaller hippocampal volume (d=−0.16 [−0.25, −0.06]; P-value= 1.04×10^{-3}, % difference −3.28). No significant subcortical volume differences were observed between OCD patients with and without a comorbid lifetime depression.

Pediatric comparisons—Too few pediatric samples had sufficient numbers of subjects with MDD to permit analyses (Supplementary Information 5).

Influence of a comorbid anxiety disorder on subcortical volume

Adult comparisons—Compared to controls, patients without a comorbid anxiety diagnosis (N=1002) showed bigger pallidum volume (d= +0.17 [0.05, 0.28]; P-value= 4.70×10^{-3}, % difference 2.83) and smaller hippocampal volume (d= −0.20 [−0.30, −0.10]; P-value= 1.51×10^{-4}, % difference −3.79). We did not detect any significant differences between OCD patients with a comorbid anxiety diagnosis (N=291) and controls. The comparison between OCD patients with and without a comorbid anxiety diagnosis showed that OCD patients with a comorbid lifetime anxiety diagnosis had larger intracranial volume (d= +0.41 [0.12, 0.70]; P-value= 5.08×10^{-3}, % difference 2.80) (Supplementary Table 6a–c).

Pediatric comparisons—Too few pediatric samples had sufficient numbers of subjects with comorbid anxiety disorders to permit analyses (Supplementary Information 5).

Influence of symptom dimensions on subcortical volume

Adult comparisons—Regression analyses within OCD patients on symptom dimensions (N=1,151) showed no association of the presence of a particular symptom dimension and volume of any of the subcortical volumes.

Pediatric comparisons—Insufficient data on the symptom dimensions was available to perform meta-analyses (Supplementary Information 5).

Influence of age of onset and disease duration on subcortical volume

Stratified analyses (Supplementary Table 7a–c) show that adult OCD patients with an early disease-onset (N=626) exhibited larger pallidum volumes (d=+0.25 [0.12, 0.38]; P-value= 2.30×10^{-4}, % difference 3.68) and that patients with a late disease-onset (N=794) exhibited smaller hippocampal volume (d=−0.18 [−0.29, −0.08]; P-value= 7.87×10^{-4}, % difference −3.36) than controls. No significant differences in subcortical brain volume were found when comparing early onset with late-onset adult OCD patients. In addition, we did not observe any significant association between age of onset nor disease duration - as continuous variables - and subcortical volumes in the *adult* (N=1420) nor *pediatric* (N=285) OCD group (Supplementary Table 8a–b and 9a–b).

Association of disease severity with subcortical volumes

We did not detect any significant associations, neither in *adult* (N=1,455) nor in *pediatric* (N=328) OCD patients, between disease severity and subcortical volumes (Supplementary Table 10 and 11).

Moderator analyses

Mean age of each sample and field strength did not moderate case-control differences in subcortical volumes in the *adult* or *pediatric* meta-analysis. The percentage of patients using an SSRI or antipsychotic medication of each adult sample did not moderate the subcortical volume differences (Supplementary 12 and 13).

Mega-analysis

Adult OCD

Results of the *adult* mega-analysis are shown in Supplementary Table 14. Overall the results of the mega-analysis yielded similar results as the meta-analysis. The case-control mega-analysis indicated a larger pallidum volume (β=0.06; P-value= 1.02×10^{-4}) and smaller hippocampal volume (β=−0.05; P-value= 4.66×10^{-4}). The pallidum (β=0.09; P-value= 5.50×10^{-7}) and hippocampus (β=−0.09; P-value= 1.99×10^{-7}) effects were more pronounced in the comparison between medicated OCD patients and controls. Early-onset patients showed larger pallidum volumes (β=0.08; P-value= 8.42×10^{-6}) than controls. Patients with a late disease-onset (β=−0.06; P-value= 8.23×10^{-5}) and patients with a comorbid depression (β=−0.07; P-value= 2.75×10^{-4}) presented smaller hippocampal volumes compared to controls.

Pediatric OCD

Results of the *pediatric* mega-analysis are shown in Supplementary Table 15. Pediatric OCD patients, compared with controls, have a larger thalamus volume (β=0.08; P-value= 5.47×10^{-3}). The thalamic effect was more pronounced in patients without a comorbid anxiety disorder (β=0.11; P-value= 9.60×10^{-4}) and in patients without a comorbid depression (β=0.09; P-value= 2.16×10^{-3}).

Discussion

This worldwide collaborative analysis identified distinct subcortical volume alterations in pediatric and adult OCD. The adult meta- and mega-analyses were consistent and results showed that, compared with controls, adult OCD patients had significantly smaller hippocampal and larger pallidum volumes. Both findings were more pronounced in the subsample of medicated OCD patients versus controls. Furthermore, the smaller hippocampal volume seemed to be driven, at least partly, by the OCD patients with comorbid depression and late disease-onset. Indeed jackknife resampling showed a robust pallidum effect and a hippocampal effect dependent on site characteristics (data not shown). The larger pallidum finding was more pronounced in the adult OCD patients with an early disease-onset. The pediatric mega-analysis showed larger thalamus in OCD based on the main group comparison, whereas the meta-analysis only showed this in unmedicated

pediatric OCD patients compared with controls. The pediatric mega-analysis also suggests that larger thalamic volume in pediatric OCD patients is specific to those without comorbid anxiety or depression. The finding of a larger thalamic volume in pediatric OCD is in line with some previous research in pediatric OCD patients (18; 26). Notably, Gilbert et al. (18) suggested a normalizing effect of pharmacological treatments on thalamic volume in pediatric OCD. The current *adult* meta- and mega-analyses did not reveal group differences in thalamic volume, consistent with the most recent meta-analyses of OCD (11–13). The only meta-analytic findings of thalamic enlargement in OCD included pediatric patients (14; 19). These results provide evidence of a clear distinction in thalamic volume across pediatric and adult OCD, and suggest that an increased thalamic volume may be an early marker of the disease, unrelated to disease severity, and may be related to altered neurodevelopment. Indeed, patients with other neurodevelopmental disorders such as Tourette's syndrome (27) and ADHD (28), also present a morphologically enlarged thalamus.

Most previous research (11; 13–15; 19) did not report volumetric differences in the hippocampal complex of OCD patients. The (para)hippocampal regions are specifically vulnerable to stress-related toxic changes (29). Greater volume loss in these regions may thus be related to chronic stress and the exaggerated emotional responsiveness seen in OCD (30). The hippocampal effect in OCD patients was more pronounced in medicated patients and seemed to be driven, at least partly, by the OCD patients with a comorbid major depression (31). These two findings are probably not independent, since patients with comorbidities are often the patients who receive medication. Further, Selles et al (32) showed that a comorbid depression is associated with a late-onset of the disease. This is in line with our finding that the hippocampal effect seemed to be driven by late-onset OCD patients. Other ENIGMA disease working-groups, such as those focusing on MDD (33), schizophrenia (34), and bipolar disorder (35), also observed smaller hippocampal volume in patients, which suggests that the hippocampal abnormalities in OCD are disease non-specific, and possibly related to chronic stress and comorbid depression.

Our results suggest a key role for the pallidum in adult OCD patients. Prior meta-analyses have reported greater lenticular (i.e., putamen and pallidum) volume in OCD patients (11–14). On the contrary patients with other anxiety disorders showed decreased lenticular nucleus volume (13). Since repetitive behaviors differentiate OCD from other anxiety disorders, the increased lenticular volume in OCD may reflect these unique symptoms (13). Our analyses also suggested that the early-onset adult OCD patients drive the pallidum effect. We, therefore, hypothesize that a larger pallidum in OCD patients could be the consequence of disease chronicity. Notably, the ENIGMA-schizophrenia (34) Working-Group also observed a larger pallidum in schizophrenia patients compared to controls. Future ENIGMA research will enable cross-diagnosis analyses to further investigate common and distinct neural substrates across psychiatric disease groups.

Our analyses could not replicate findings of increased putamen and caudate nucleus volumes observed in smaller meta-analyses (11–14). Note that, these studies used different segmentation techniques. One may argue that the technique might influence findings in case of adjacent structures such as the pallidum and putamen (36). Our current observations

suggest that subcortical alterations in adult OCD may be limited to the pallidum and hippocampus rather than widespread.

This study constitutes the largest meta- and mega-analysis of subcortical brain volumes in OCD to date. Strengths of this study include the sample size (N=3,589) and inclusion of both adults and children. Another strength is our strategy that ensured great methodological homogeneity by standardizing brain segmentation techniques and statistical models across all participating samples, which increased the power to detect small effects. A similar strategy has been used in parallel by other ENIGMA working-groups (33–35). This method generates highly significant findings and allows us to systematically investigate the effects of clinical characteristics on brain alterations in OCD patients.

This study also had limitations. First, a recent study showed effects of workstation vendor and operating system version on brain volume and cortical thickness estimates (37). Indeed the individual sites did differ in operating system and workstation vendor. Additionally, Schoemaker et al. 2016 showed that FreeSurfer tends to overestimate subcortical volumes in children (38). However, this non-systematic error probably affects patients and controls equally. Second, although we have pooled an enormous amount of data, subjects with comorbidities and subjects categorized to each specific symptom dimension especially in the pediatric datasets were still limited. However, the key variable, i.e., the CY-BOCS score, the gold standard clinical instrument in pediatric OCD research, was present in all subjects. Third, the structure labelled as “thalamus” by FreeSurfer’s segmentation algorithm may contain both white matter and grey matter. We, therefore, cannot conclude that this thalamic enlargement involves grey matter enlargement solely. Fourth, our findings indicate medication effects. It should be noted, however, that only current medication status has been taken into consideration. It is difficult to attribute the results to direct effects of the medication itself. Furthermore, the range of medications that are generally prescribed to OCD patients is very broad. Although we have tested whether different types of medication influenced our findings, we were not able to calculate relative doses of different medication types and analyze medication effects in a more fine-grained fashion due to the retrospective nature of our study. Thus we need to interpret these findings with caution.

Despite these limitations, results of this first initiative of the ENIGMA-OCD Working-Group clearly indicate a key role of the thalamus and pallidum in the pathophysiology of pediatric and adult OCD, respectively. Our findings suggest a different pattern of subcortical abnormalities in pediatric and adult OCD patients, which is in line with the developmental nature of OCD and neuroplastic changes during the course of the disease. The current study is a first step toward identifying robust brain volume alterations in OCD patients. An important next step is to apply similar methods in order to identify robust cortical imaging markers on cortical thickness and surface area measures associated with OCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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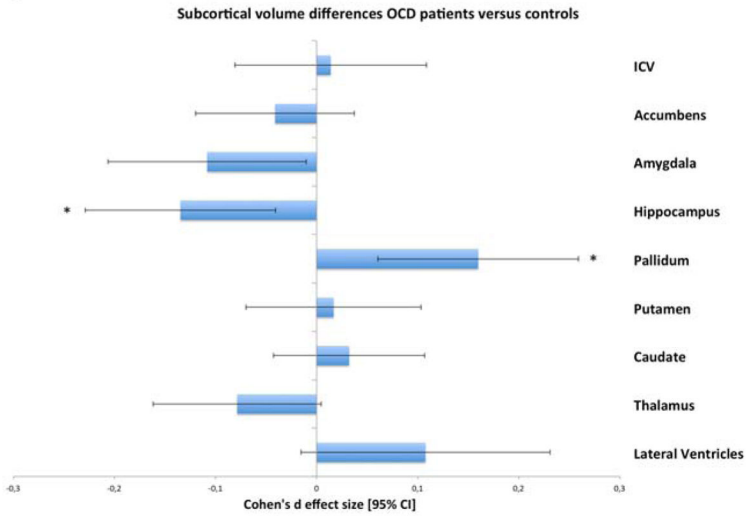
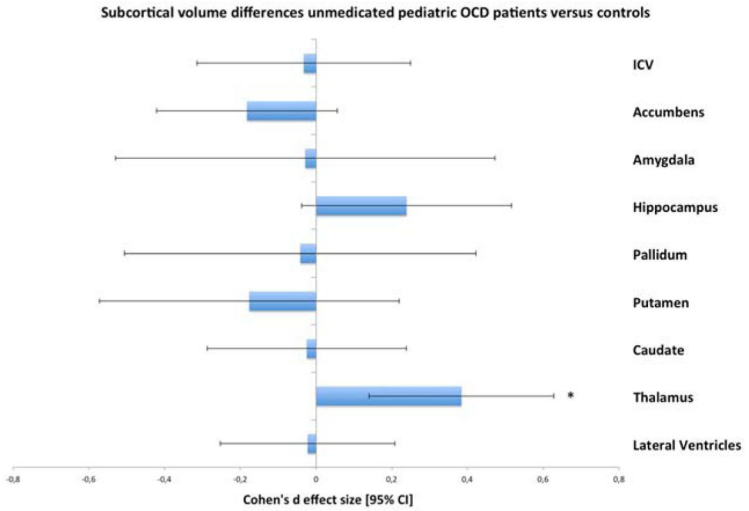
Figure 1a



* Asterisk represents a significant effect $P<5.6 \times 10^{-3}$. Abbreviations: Obsessive Compulsive Disorder (OCD), Confidence Interval (CI), Intracranial Volume (ICV).

Figure 1b



* Asterisk represents a significant effect $P<5.6 \times 10^{-3}$. Abbreviations: Obsessive Compulsive Disorder (OCD), Confidence Interval (CI), Intracranial Volume (ICV).

Figure 1.

(a) Cohen's d-effect sizes 95% CI for differences in subcortical brain volumes between adult OCD patients and healthy controls. **(b)** Cohen's d-effect sizes 95% CI for differences in subcortical brain volumes between unmedicated pediatric OCD patients and pediatric healthy controls. Effect sizes were corrected for age, sex, and intracranial volume.

Table 1

ENIGMA-OCD Working-Group Demographics (age in years), sex, and OCD patients-control breakdown for participating sites

Study #	Site PI	Site, Country	Field Strength	Age Controls		Age OCD patients		% Male Controls	% Male OCD	Total N Controls	Total N OCD	Total N
				Mean	SD	Mean	SD					
1	Benedetti	Milan, ITA	3T	34.0	12.3	35.0	10.4	73	71	62	66	128
2	Beucke	Berlin, GER	1.5T	31.9	9.5	32.4	9.7	49	50	104	92	196
3	Cheng	Kunming, CHN I	1.5T	31.4	8.0	30.6	10.2	33	38	40	24	64
4		Kunming, CHN II	3T	26.2	4.2	32.9	10.6	28	55	95	56	151
5	Denys	Amsterdam, NLD	3T	39.6	10.3	33.8	9.6	44	21	25	24	49
6	van den Heuvel	Amsterdam, NLD I	1.5T	31.6	7.7	33.5	9.2	39	30	49	54	103
7		Amsterdam, NLD II	3T	39.6	11.4	38.3	10.1	47	48	38	42	80
8	Hoexter	Sao Paulo, BRA I	1.5T	27.6	7.8	31.5	10.1	35	44	37	50	87
9	Koch	Munchen, GER	3T	30.2	9.0	31.1	9.7	40	33	75	72	147
10	Kwon	Seoul, KOR I	1.5T	24.0	3.6	24.8	5.4	56	76	104	45	149
11		Seoul, KOR II	1.5T	24.9	5.3	28.8	6.8	64	56	45	34	79
12		Seoul, KOR III	3T	26.3	6.9	26.3	6.8	61	61	89	90	179
13	Mataix-Cols	Stockholm, SWE	1.5T	36.1	11.3	38.7	10.9	36	43	33	44	77
14	Menchon	Barcelona, ESP	1.5T	33.1	10.2	34.8	9.2	45	50	66	117	183
15	Nakamae	Kyoto, JPN I	1.5T	30.3	7.8	31.7	9.3	52	49	48	82	130
16		Kyoto, JPN II	3T	30.0	7.4	33.3	9.7	48	35	42	34	76
17	Nakao	Fukuoka, JPN	3T	39.3	13.0	36.6	10.0	39	42	41	81	122
18	Reddy	Bangalore, IND I	1.5T	27.2	6.4	27.5	6.3	74	59	46	44	90
19		Bangalore, IND II	3T	26.3	5.0	29.6	8.0	62	52	156	208	364
20	Simpson	New York, USA	3T	28.3	8.0	29.6	8.0	52	52	33	33	66
21	Spalletta	Rome, ITA	3T	36.5	10.5	36.7	11.6	59	67	128	84	212
22	Stein	Cape Town, ZAF	3T	30.6	10.8	30.7	10.8	38	50	29	22	51
23	Tolin	Conneticut, USA	3T	48.0	11.9	32.1	12.0	22	67	32	27	59
24	Walitza	Zurich, CHE I	3T	32.9	9.2	31.2	7.7	28	47	18	17	35
25	Wang	Shanghai, CHN	3T	26.2	7.5	29.6	9.3	54	57	37	53	90
								adult samples combined		**1472**	**1495**	**2967**
1	Anorld	Ontario, CAN	3T	12.3	2.2	12.9	2.4	54	58	13	40	53

Study #	Site PI	Site, Country	Field Strength	Age Controls		Age OCD patients		% Male Controls	% Male OCD	Total N Controls	Total N OCD	Total N
				Mean	SD	Mean	SD					
2	Fitzgerald	Michigan, USA	3T	12.9	2.9	13.9	2.6	52	49	67	74	141
3	Gruner	Conneticut, USA	3T	14.2	2.2	14.3	2.1	52	57	23	23	46
4	Hoexter	Sao Paulo, BRA II	3T	12.0	2.4	12.6	2.5	57	61	28	28	56
5	Huyser	Amsterdam, NLD	3T	13.3	2.5	13.6	2.5	36	37	25	27	52
6	Lazaro	Barcelona, ESP I	1.5T	14.6	2.3	14.6	2.0	47	58	32	31	63
7		Barcelona, ESP II	3T	14.6	2.1	14.6	2.0	55	60	44	58	102
8	Reddy	Bangalore, IND III	3T	13.1	2.1	14.6	2.0	50	56	14	18	32
9	Soreni	Ontario, CAN	3T	11.2	3.1	13.4	2.5	52	40	21	20	41
10	Walitza	Zurich, CHE II	3T	14.6	1.3	15.7	1.4	50	81	20	16	36
								paediatric samples combined		**287**	**335**	**622**
35						**total**				**1759**	**1830**	**3589**

Abbreviations: Obsessive Compulsive Disorder (OCD), Principal Investigator (PI), Standard Deviation (SD)

Table 2

ENIGMA-OCD Working-Group Clinical characteristics of OCD patients. Percentage of OCD patients using medication, disease severity (measured with the YBOCS), age of onset of OCD, percentage of patients with a comorbid anxiety disorder, and percentage of patients with a comorbid depression are listed.

Study #	Site PI	Site, Country	% medicated OCD patients	YBOCS		Age of onset		% Comorbid lifetime anxiety	% Comorbid lifetime depression
				Mean	SD	Mean	SD		
Adult samples									
1	Benedetti	Milan, ITA	64	30.9	5.6	16.0	6.1	1.52	10.61
2	Beucke	Berlin, GER	40	20.1	7.1	17.2	7.8	11.96	18.48
3	Cheng	Kunming, CHN I	71	31.0	6.1	26.8	10.4	50.00	16.67
4		Kunming, CHN II	68	28.2	6.3	27.2	10.7	89.29	28.57
5	Denys	Amsterdam, NLD	63	26.6	6.2	18.1	6.9	4.17	41.67
6	van den Heuvel	Amsterdam, NLD I	0	22.7	6.1	14.4	7.7	22.22	33.33
7		Amsterdam, NLD II	0	21.5	6.1	15.5	6.9	40.48	52.38
8	Hoexter	Sao Paulo, BRA I	20	27.2	6.1	13.1	7.0	62.00	54.00
9	Koch	Munchen, GER	60	20.9	6.2	17.0	6.7	–	–
10	Kwon	Seoul, KOR I	24	20.2	6.0	17.4	5.2	0.00	0.00
11		Seoul, KOR II	0	23.9	6.5	18.9	6.6	0.00	2.94
12		Seoul, KOR III	2	26.5	6.5	19.0	6.4	1.11	2.22
13	Mataix-Cols	Stockholm, SWE	41	25.9	7.7	18.4	9.2	27.27	34.09
14	Menchon	Barcelona, ESP	97	25.5	5.8	21.4	8.5	20.51	18.80
15	Nakamae	Kyoto, JPN I	49	25.2	6.4	25.1	9.4	9.76	21.95
16		Kyoto, JPN II	0	22.4	6.9	25.2	9.1	8.82	20.59
17	Nakao	Fukuoka, JPN	88	22.5	5.6	24.6	9.5	–	35.80
18	Reddy	Bangalore, IND I	0	25.8	7.3	21.7	7.5	15.91	18.18
19		Bangalore, IND II	40	25.8	6.3	22.0	7.6	7.69	15.38
20	Simpson	New York, USA	0	25.5	3.7	15.0	7.0	21.21	30.30
21	Spalletta	Rome, ITA	88	23.4	8.9	18.9	10.9	9.52	9.52
22	Stein	Cape Town, ZAF	41	22.9	4.2	13.6	6.6	0.00	0.00
23	Tolin	Conneticut, USA	78	22.7	4.8	–		44.44	40.74
24	Walitza	Zurich, CHE I	59	17.1	9.9	16.7	7.8	47.06	47.06

Study #	Site PI	Site, Country	% medicated OCD patients	YBOCS		Age of onset		% Comorbid lifetime anxiety	% Comorbid lifetime depression
				Mean	SD	Mean	SD		
25	Wang	Shanghai, CHN	0	25.5	5.1	23.3	10.3	0.00	0.00
Paediatric samples									
1	Anorld	Ontario, CAN	53	20.9	7.8	8.7	2.6	25.00	17.50
2	Fitzgerald	Michigan, USA	50	18.7	7.8	9.9	3.0	50.00	6.76
3	Gruner	Conneticut, USA	52	26.9	4.5	–		43.48	39.13
4	Hoexter	Sao Paulo, BRA II	46	26.9	5.4	7.2	3.0	21.43	0.00
5	Huyser	Amsterdam, NLD	0	25.1	5.0	10.9	2.8	48.15	25.93
6	Lazaro	Barcelona, ESP I	55	22.2	6.0	12.4	2.2	16.13	3.23
7		Barcelona, ESP II	79	18.6	7.4	12.0	2.4	25.86	5.17
8	Reddy	Bangalore, IND III	83	22.6	7.3	13.1	2.1	22.22	5.56
9	Soreni	Ontario, CAN	0	22.8	4.3	–		–	–
10	Walitza	Zurich, CHE II	56	14.7	1.0	11.1	2.2	50.00	6.25

Abbreviations: Obsessive Compulsive Disorder (OCD), Principal Investigator (PI), Standard Deviation (SD), Yale Brown Obsessive Compulsive Scale (YBOCS)

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Table 3

Full meta-analytic results for each mean structure for the OCD patients versus controls comparison, controlling for age, sex, scan center, and intracranial volume. Adjusted Cohen's d is reported.

	Cohen's d (OCD–HC)	*Standard error*	95% CI			% Difference	P-value	I^2	Number of controls	Number of patients
Lateral Ventricles	0,108	0,063	−0,016	to	0,231	1,712	0,087	61,327	1466	1491
Thalamus	−0,079	0,042	−0,162	to	0,005	−1,851	0,064	12,542	1387	1375
Caudate	0,032	0,038	−0,043	to	0,107	0,844	0,399	0,003	1424	1441
Putamen	0,017	0,044	−0,070	to	0,103	0,380	0,704	16,141	1335	1365
Pallidum	**0,160**	**0,051**	**0,061**	**to**	**0,259**	**3,156**	$\mathbf{1{,}60 \times 10^{-3}}$	**32,877**	**1312**	**1336**
Hippocampus	**−0,135**	**0,048**	**−0,229**	**to**	**−0,040**	**−2,802**	$\mathbf{5{,}08 \times 10^{-3}}$	**32,692**	**1440**	**1444**
Amygdala	−0,108	0,050	−0,206	to	−0,010	−2,163	0,031	37,194	1418	1452
Accumbens	−0,041	0,040	−0,120	to	0,037	−1,025	0,305	8,384	1446	1465
ICV *	0,014	0,048	−0,081	to	0,109	0,286	0,775	35,547	1470	1493

Abbreviations: Obsessive Compulsive Disorder (OCD), Healthy Control (HC), Intracranial Volume (ICV), Confidence Interval (CI)

* Controlled for age, sex and scan center

Table 4

Full meta-analytic results for each mean structure for the pediatric unmedicated OCD patients versus pediatric controls comparison, controlling for age, sex, scan center, and intracranial volume. Adjusted Cohen's d is reported

	Cohen's d (unmedicated pediatric OCD–HC)	Standard error	95% CI			% Difference	P-value	I^2	Number of controls	Number of patients
Lateral Ventricles	−0,022	0,118	−0,253	to	0,209	−0,189	0,850	0,000	216	115
Thalamus	**0,384**	**0,125**	**0,139**	**to**	**0,628**	**3,078**	**$2{,}09 \times 10^{-3}$**	**0,000**	**201**	**103**
Caudate	−0,024	0,134	−0,288	to	0,239	−0,182	0,855	14,641	198	109
Putamen	−0,177	0,202	−0,572	to	0,219	−0,875	0,382	59,152	204	104
Pallidum	−0,042	0,237	−0,506	to	0,423	−0,176	0,860	66,561	174	87
Hippocampus	0,239	0,141	−0,038	to	0,516	1,688	0,091	22,715	210	107
Amygdala	−0,029	0,256	−0,530	to	0,473	−0,112	0,911	72,254	188	89
Accumbens	−0,183	0,122	−0,422	to	0,056	−1,500	0,134	0,004	203	111
ICV *	−0,033	0,144	−0,314	to	0,249	−0,226	0,821	29,531	219	116

Abbreviations: Obsessive Compulsive Disorder (OCD), Healthy Control (HC), Intracranial Volume (ICV), Confidence Interval (CI)

* Controlled for age, sex and scan center