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Mapping Cortical and Subcortical Asymmetry in Obsessive-Compulsive Disorder: Findings From the ENIGMA Consortium

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ABSTRACT

BACKGROUND: Lateralized dysfunction has been suggested in obsessive-compulsive disorder (OCD). However, it is currently unclear whether OCD is characterized by abnormal patterns of brain structural asymmetry. Here we carried out what is by far the largest study of brain structural asymmetry in OCD.

METHODS: We studied a collection of 16 pediatric datasets (501 patients with OCD and 439 healthy control subjects), as well as 30 adult datasets (1777 patients and 1654 control subjects) from the OCD Working Group within the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) Consortium. Asymmetries of the volumes of subcortical structures, and of measures of regional cortical thickness and surface areas, were assessed based on T1-weighted magnetic resonance imaging scans, using harmonized image analysis and quality control protocols. We investigated possible alterations of brain asymmetry in patients with OCD. We also explored potential associations of asymmetry with specific aspects of the disorder and medication status.

RESULTS: In the pediatric datasets, the largest case-control differences were observed for volume asymmetry of the thalamus (more leftward; Cohen's $d = 0.19$) and the pallidum (less leftward; $d = -0.21$). Additional analyses suggested putative links between these asymmetry patterns and medication status, OCD severity, or anxiety and depression comorbidities. No significant case-control differences were found in the adult datasets.

CONCLUSIONS: The results suggest subtle changes of the average asymmetry of subcortical structures in pediatric OCD, which are not detectable in adults with the disorder. These findings may reflect altered neurodevelopmental processes in OCD.

Keywords: Brain asymmetry, Laterality, Mega-analysis, Obsessive-compulsive disorder, Pallidum, Thalamus

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Obsessive-compulsive disorder (OCD) is a psychiatric disorder with a lifetime prevalence of approximately 2% (1–4). OCD involves persistent, intrusive, and unwanted thoughts (obsessions) and repetitive behaviors that might be accompanied by mental acts (compulsions) (4). As a heterogeneous neuropsychiatric condition with a considerable heritability of roughly 40% (5), OCD has significant genetic and nongenetic determinants (4), but the pathophysiology of this complex disorder remains unclear.

Left–right asymmetry is an important aspect of human brain organization for multiple functions (6). For example, visuospatial processing and emotions that elicit withdrawal behaviors are usually right lateralized in healthy people (7–10), whereas language-related processes, hand motor dominance, and emotions that elicit approach behaviors tend to be left lateralized in the brain (11,12). Alterations of asymmetry have been reported in various psychiatric and neurocognitive conditions, including schizophrenia (13,14), autism (15), and dyslexia (16). Altered functional laterality has also been investigated in OCD (17,18), partly because of observations of psychometric deficits within the visuospatial domain (19–21), as well as altered emotional processing (22–25). For example, in a behavioral study, investigators found reduced functional asymmetry for spatial attention in patients with OCD, and reported that reversal of normal asymmetry was associated with more serious obsessions (20). Several studies found greater impairment in visuospatial memory compared with that in verbal memory in OCD, which is suggestive of right-sided dysfunction (17,18,26). Increased left–right asymmetry of electroencephalographic activity at rest, or reduced activity in the right hemisphere linked to approach and/or avoidance motivation, has also been reported in persons with OCD compared with activity in healthy control subjects (19,22). However, left-sided dysfunction has also been suggested in OCD, on the basis of neuropsychological data (23) and neuroimaging studies (27–29). Reduced right-ear advantage, which can indicate left-hemisphere dysfunction, was reported in OCD for certain tasks (23). In addition, hyperresponsiveness was observed in the left hemisphere based on event-related potentials (27,30). More recently, left-lateralized differences in functional connectivity of the amygdala were found in OCD versus control subjects, using task functional magnetic resonance imaging (31). Studies with animal models of OCD (32), and transcranial magnetic stimulation in patients with treatment-resistant OCD (33) have suggested that left-lateralized stimulation is more effective than right-lateralized stimulation. Therefore, overall, the literature suggests altered hemispheric functional balance in OCD but does not point consistently to one of the hemispheres as the primary site of disruption.

Importantly, any structural basis linked to altered functional laterality in OCD is still unclear. Two previous studies explored brain structural asymmetry in OCD as a specific outcome of interest, but both had small sample sizes. In one of these studies, with 16 patients with OCD, leftward asymmetry (i.e., left > right) of cortical thickness in the anterior cingulate region was found in patients with OCD and their siblings but not in matched control subjects, and investigators claimed that this finding presented a potential endophenotype linked to increased hereditary risk for OCD (34). In the other study, with 32 patients, significant differences of frontal white matter volume asymmetry were found in both medicated (n = 19) and nonmedicated (n = 13) patients with OCD, compared with frontal white matter in healthy control subjects (35). Unfortunately, small sample sizes tend to limit the reliability of findings in human neuroscience (36), and the extent of any association between OCD and structural brain asymmetry remains uncertain.

The OCD Working Group within the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) Consortium (37) recently achieved more highly powered analyses of brain changes in OCD, based on a sample size of >1500 individuals with OCD and a similar number of control subjects (38). They reported several regional case-control differences in cerebral cortical measures that involved only one hemisphere (38). However, these analyses did not examine whether effect sizes were significantly different on the left and right sides, and asymmetry was not quantitatively characterized. Unilateral patterns in this and other studies may arise from small but uniform bilateral effect sizes; the fact that statistical significance was achieved on one side but not on the other does not necessarily indicate a significant change in asymmetry. Furthermore, a post hoc statistical comparison of the left- and right-sided effect sizes as reported by the previous ENIGMA study (38) would not yield the same level of statistical power as can be provided by using the individual-level, paired left and right data to analyze asymmetry alterations in OCD. In addition, a previous ENIGMA study of subcortical volumes in OCD reported only combined left and right volumes (39).

Here, we used the latest data for both subcortical and cortical structures from the ENIGMA OCD Working Group, and we targeted hemispheric structural asymmetry across subcortical and cortical measures, as assessed by subject-specific asymmetry indices, AI = (Left − Right)/((Left + Right)/2) (40). The AI is a widely used approach in studies of brain asymmetry [e.g., Kurth *et al.* (41) and Leroy *et al.* (42)]. Our primary interest was to compare structural asymmetries between patients and healthy control subjects, but we also performed post hoc analyses to investigate possible associations of brain asymmetries with medication status, age at disease onset, disease duration, OCD severity, and presence of anxiety and depression comorbidities. As the recent studies from the ENIGMA OCD Working Group had indicated distinct alterations in pediatric and adult patients (38,39), and because asymmetries of both cortical and subcortical structures are also known to change subtly with age in the healthy population (40,43), we performed all analyses for the pediatric (<18 years of age) and adult (≥18 years of age) data separately [see also van den Heuvel *et al.* (44)].

METHODS AND MATERIALS

See Supplemental Methods and Materials in Supplement 1 for detailed methods.

Datasets

The datasets used in this study were provided by members of the OCD Working Group within the ENIGMA Consortium (37). There were 46 independent datasets from 16 countries: 16 pediatric datasets comprising 501 patients with OCD and 439

Table 1. Summary Information on the Case-Control Datasets Included in This Study

Group	Site[a]	Field Strength	Age, Years, Mean (SD)		Male, %		Control Subjects, *n*	Persons With OCD, *n*	Total Subjects, *n*
			Control Subjects	Persons With OCD	Control Subjects	Persons With OCD			
Pediatric									
	James	1.5T	16.63 (1.23)	16.3 (1.42)	58	54	12	13	25
	Lazaro	1.5T	14.63 (2.3)	14.61 (2.04)	47	58	32	31	63
	Buitelaar	1.5T	10.93 (1.04)	10.57 (1.41)	72	64	61	22	83
	Fitzgerald	3T	12.96 (2.73)	14.17 (2.59)	51	48	59	62	121
	Gruner	3T	14.19 (2.21)	14.33 (2.09)	52	57	23	23	46
	Arnold	3T	12.3 (2.19)	12.86 (2.35)	54	61	13	36	49
	Hoexter	3T	12 (2.42)	12.61 (2.45)	57	61	28	28	56
	Huyser	3T	13.32 (2.55)	13.59 (2.47)	36	37	25	27	52
	Stewart	3T	14.02 (3.48)	15.04 (2.68)	40	39	30	28	58
	Lazaro	3T	14.57 (2.1)	14.57 (2.04)	55	60	44	58	102
	Nurmi	3T	13.3 (2.49)	12.53 (2.84)	50	54	36	59	95
	Walitza	3T	14.64 (1.34)	15.68 (1.45)	50	81	20	16	36
	Reddy	3T	13.07 (2.06)	14.56 (1.98)	50	56	14	18	32
	Marsh	3T	9.14 (2.48)	12.12 (3.4)	57	52	14	25	39
	Hirano	3T	15.33 (1.03)	14 (2.18)	67	65	6	20	26
	Soreni	3T	11.09 (3.02)	13.09 (2.47)	50	37	22	35	57
Pediatric Samples Combined									
			13.06 (2.77)	13.67 (2.65)	53	54	439	501	940
Adult									
	Menchón	1.5T	33.06 (10.19)	34.83 (9.17)	45	50	66	117	183
	Cheng	1.5T	31.43 (7.96)	30.63 (10.21)	33	38	40	24	64
	KwonNMC	1.5T	24.05 (3.63)	24.76 (5.36)	56	76	104	45	149
	KwonSNU	1.5T	24.89 (5.35)	28.1 (6.71)	64	63	45	41	86
	Nakamae	1.5T	30.44 (7.9)	31.61 (9.15)	46	48	48	82	130
	Morgado	1.5T	27.58 (6.23)	27.69 (7.4)	38	47	53	59	112
	Mataix-Cols	1.5T	36.12 (11.26)	38.68 (10.9)	36	43	33	44	77
	Reddy	1.5T	27.22 (6.45)	27.45 (6.31)	74	59	46	44	90
	Hoexter	1.5T	27.62 (7.75)	31.46 (10.06)	35	44	37	50	87
	van den Heuvel	1.5T	31.57 (7.67)	33.54 (9.19)	39	30	49	54	103
	Beucke	1.5T	31.92 (9.5)	32.41 (9.74)	49	50	104	92	196
	Cheng	3T	26.19 (4.18)	32.89 (10.57)	28	55	95	56	151
	Nakamae	3T	29.57 (7.27)	32.82 (9.74)	45	35	42	34	76
	Brennan	3T	32.38 (12.14)	28.84 (9.99)	45	56	29	98	127
	van den Heuvel	3T	39.61 (11.37)	38.32 (10.07)	47	48	38	42	80
	Denys	3T	39.64 (10.32)	35.26 (9.17)	44	26	25	31	56
	Kwon	3T	26.26 (6.9)	26.7 (7.28)	61	62	89	90	179
	Benedetti	3T	33.98 (12.35)	35.02 (10.39)	73	71	62	66	128
	Hirano	3T	30.95 (8.36)	33.11 (7.82)	45	36	44	47	91
	Koch	3T	30.27 (9.04)	30.91 (9.55)	39	37	74	76	150
	Stein	3T	30.59 (10.76)	30.48 (10.63)	38	48	29	23	52
	Tolin	3T	48 (11.87)	32.11 (12.04)	22	67	32	27	59
	Simpson	3T	28.27 (8.04)	29.62 (7.98)	52	52	33	33	66
	Nakao	3T	39.34 (12.99)	36.6 (10.02)	39	42	41	81	122
	Spalletta	3T	36.52 (10.55)	36.67 (11.56)	59	67	128	84	212
	Stern	3T	28.17 (7.15)	27.87 (6.9)	44	33	18	15	33
	Wang	3T	26.24 (7.55)	29.47 (9.33)	54	55	37	53	90
	Nurmi	3T	30.76 (11.77)	33.31 (11.04)	56	51	25	49	74
	Walitza	3T	32.89 (9.21)	30.72 (7.76)	28	47	18	17	35

Table 1. Continued

Group	Site[a]	Field Strength	Age, Years, Mean (SD)		Male, %		Control Subjects, *n*	Persons With OCD, *n*	Total Subjects, *n*
			Control Subjects	Persons With OCD	Control Subjects	Persons With OCD			
	Reddy	3T	26.59 (4.88)	29.5 (6.74)	64	53	170	203	373
Adult Samples Combined									
			30.55 (9.73)	31.74 (9.66)	50	51	1654	1777	3431

NMC, National Medical Center; SNU, Seoul National University.
[a]Site indicates the representative author of each dataset.

healthy control subjects, and 30 adult datasets comprising 1777 patients with OCD and 1654 healthy control subjects (Table 1, Supplemental Figures S1 and S2 in Supplement 1, and Supplemental Table S1 in Supplement 2). All local institutional review boards permitted the use of measures extracted from their anonymized data. In addition, we leveraged publicly available summary statistics that describe the average form of brain regional asymmetries, based on our previous larger studies of healthy individuals (40,43).

Image Acquisition and Processing

Structural T1-weighted magnetic resonance imaging scans were acquired and processed locally at each collection site. Images were acquired at different field strengths (1.5T and 3T). All images were analyzed using one automated and validated pipeline, i.e., "recon-all" as implemented in FreeSurfer. For each participant, surface area and mean thickness were extracted for each of the 68 cortical regions (34 per hemisphere) in the Desikan-Killiany parcellation scheme (45), as well as total hemispheric surface area, and the average mean thickness over each hemisphere. In addition, volumes of eight subcortical regions of interest, including seven subcortical structures (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus), and the lateral ventricle volume were calculated.

Asymmetry Indices

The aim of this study was to investigate differences in subcortical and cortical asymmetry related to OCD. To this end, for each participant and for each subcortical or cortical measure, an AI was defined as $(L - R)/((L + R)/2)$, where L and R represent the corresponding left and right volume measures (from subcortical regions) or thickness and surface area measures (from cortical regions). This AI formula has been widely used in previous brain asymmetry studies (41,42,46), including our own (8,40,43).

Case-Control Analyses

Separately for the pediatric and adult data, and for each AI, we pooled data from all available individuals from each dataset, and we used a mega-analytical framework to investigate the case-control effects. Specifically, for each AI, we used a linear mixed-effect model (using *lme4* R package), with AI as the outcome variable and a binary indicator of diagnosis (0 = control subject, 1 = patient with OCD) as the predictor of interest. In each model, a binary variable for sex, and a continuous measure for age (in years at the time of scan) were included as confounding factors, and the categorical variable "dataset" as a random-effect term.

Separately for thickness and surface area, we additionally calculated an overall "typicality score" per participant, which indexed how much a given participant deviated from the population mean asymmetry profile when considered simultaneously across all 34 cortical regions. A lower typicality score indicates more deviation from the mean asymmetry profile in the population.

OCD Case-Only Analyses of Clinical Characteristics

For AIs that were potentially associated with OCD in the main analysis (see Results), we further investigated, within cases only, whether the AIs were associated with specific aspects of the disorder and medication status.

RESULTS

An overview of the datasets is provided in Table 1, Supplemental Figures S1 and S2 in Supplement 1, and Supplemental Table S1 in Supplement 2.

Pediatric Data

The results for both subcortical and cortical AIs in the pediatric data, including the effect size estimates for diagnosis on each AI, are presented in Figure 1 and Supplemental Tables S2 to S4 in Supplement 2.

The largest effects of diagnosis in pediatric cases were more leftward asymmetry of the thalamus ($t = 2.84$, $p = .0047$, $d = 0.19$) (Figures 1 and 2), and less leftward asymmetry of the pallidum volume ($t = -3.17$, $p = .0016$, $d = -0.21$) (Figures 1 and 2). These two findings were significant when controlling the false discovery rate at 0.05 (see Methods and Materials). Post hoc analyses showed that these case-control differences were mainly due to a left thalamus that was relatively larger in patients with OCD than in control subjects (left: $t = 4.08$, $p = 4.89 \times 10^{-5}$, $d = 0.27$; right: $t = 2.12$, $p = .034$, $d = 0.14$), and a left pallidum that was relatively smaller in patients with OCD than in control subjects (left: $t = -1.98$, $p = .048$, $d = -0.13$; right: $t < 1.0$, $p = .35$, $d = 0.062$) (see also Figure 2B for distribution and group differences of each unilateral volume measure). In addition, we confirmed that the effects remained when possible outliers were excluded in each AI per dataset (see Methods and Materials) (pediatric thalamus volume asymmetry: $t = 2.90$, $p = .0038$, $d = 0.19$; pediatric pallidum volume asymmetry: $t = -3.16$, $p = .0016$, $d = -0.21$).

In terms of cortical asymmetries in the pediatric data, no significant case-control differences in the global hemispheric AI for either cortical thickness or surface area were found (p values $> .40$). Regionally, only one AI showed a nominally

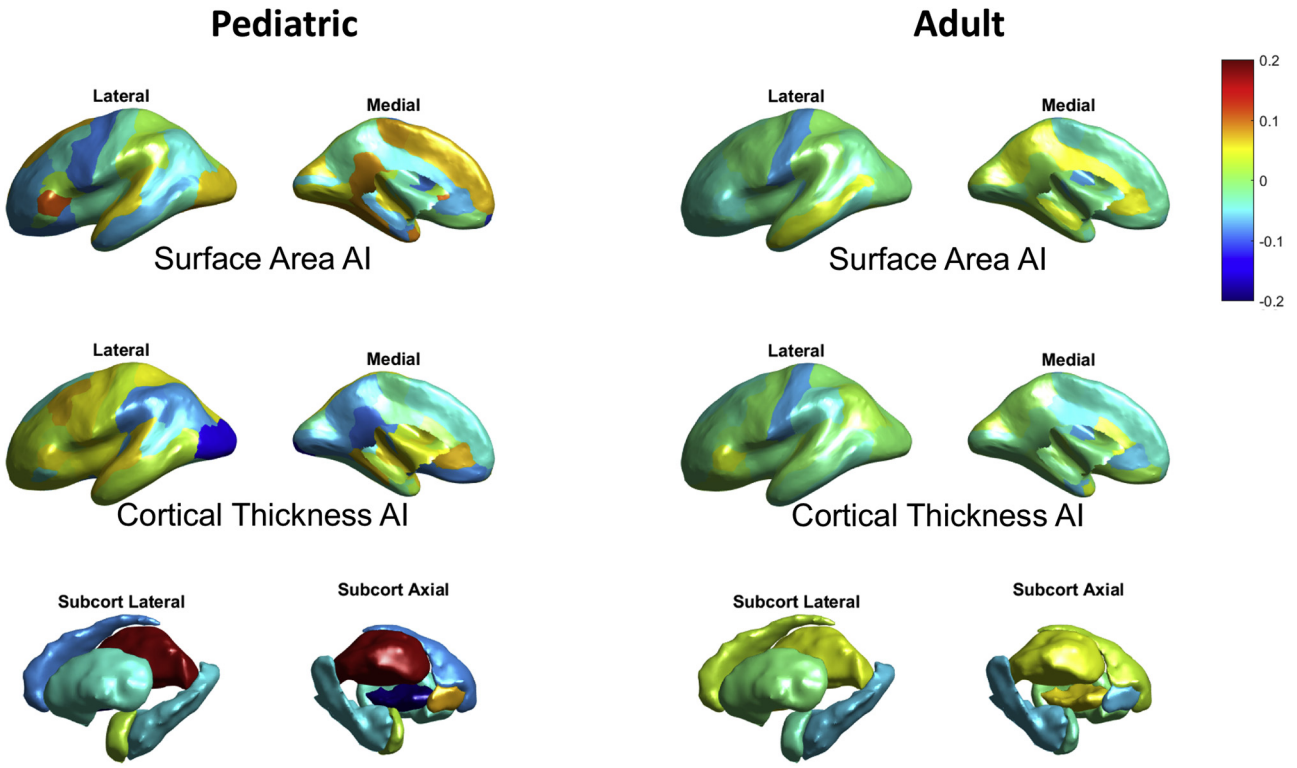

Figure 1. Effect size (Cohen's *d*) distributions for diagnosis on regional asymmetry indices (AIs) in the pediatric (left panel) and adult (right panel) data. Subcort, subcortical.

significant effect (i.e., prior to multiple testing correction) of diagnosis, which was for thickness asymmetry of the lateral occipital cortex (greater rightward asymmetry in patients with OCD; $t = -2.08$, $p = .038$, $d = -0.14$) (Figure 2). This finding did not survive multiple testing correction. No other AIs in case-control comparisons within the pediatric data showed significant effects (uncorrected p values $> .05$).

Within pediatric patients only, there were no differences of the thalamus or pallidum AIs between medicated and unmedicated participants (uncorrected p values $> .20$), nor with respect to current anxiety or depression comorbidity (p values $> .20$), or age at disease onset or disease duration (p values $> .05$). In terms of OCD symptoms, the pallidum AI showed significant association with two of the five major Yale-Brown Obsessive Compulsive Scale symptom components: hoarding ($t = -2.37$, $p = .0065$) and cleaning/contamination ($t = -2.29$, $p = .014$), such that cases with these symptoms had reduced leftward asymmetry of the pallidum compared with cases without these symptoms. No significant associations of symptom severity were observed with the thalamus AI among the pediatric cases (p values $> .10$).

When the main analysis was repeated with the inclusion of age-squared in the model, in case of substantial nonlinear effects of age on AIs, all of the Cohen's d values for the effects of diagnosis remained within 0.005 of their values in analysis without the inclusion of age-squared, and the same two AIs (thalamus volume AI, pallidum volume AI) remained significant after false discovery rate correction. None of the AIs showed significant scanner effects in the pediatric data (p values $> .05$), and the significant effects of diagnosis remained when scanner field strength was added to the main analysis models as a predictor variable (pediatric thalamus volume asymmetry: $t = 2.81$, $p = .0050$, $d = 0.19$; pediatric pallidum volume asymmetry: $t = -3.02$, $p = .0025$, $d = -0.20$).

We calculated per-participant typicality scores (see Methods and Materials) and compared the typicality scores between patients and control subjects. However, no significant differences were found in the pediatric data for either thickness or surface area asymmetries (p values $> .15$). This analysis might have been sensitive to multiregional disruptions of laterality that are not consistent in direction, as could conceivably arise from generally increased developmental instability.

Adult Data

The results for both subcortical and cortical AIs in the adult data, including the effect size estimates for diagnosis on each AI, are presented in Figure 1 and Supplemental Tables S5 to S7 in Supplement 2. All effects were subtle (Cohen's d between -0.086 and 0.066) and not as strong as those found in the pediatric data.

The largest effect in adults was a case-control difference in the AI of global hemispheric surface area ($t = -2.48$, $p = .013$, $d = -0.086$), indicating that adult OCD was associated with slightly more rightward overall asymmetry in surface area, compared with control subjects. However, this did not survive multiple testing correction when accounting for all regional surface area AI comparisons. Post hoc analyses showed that this difference was mainly due to relatively smaller surface area

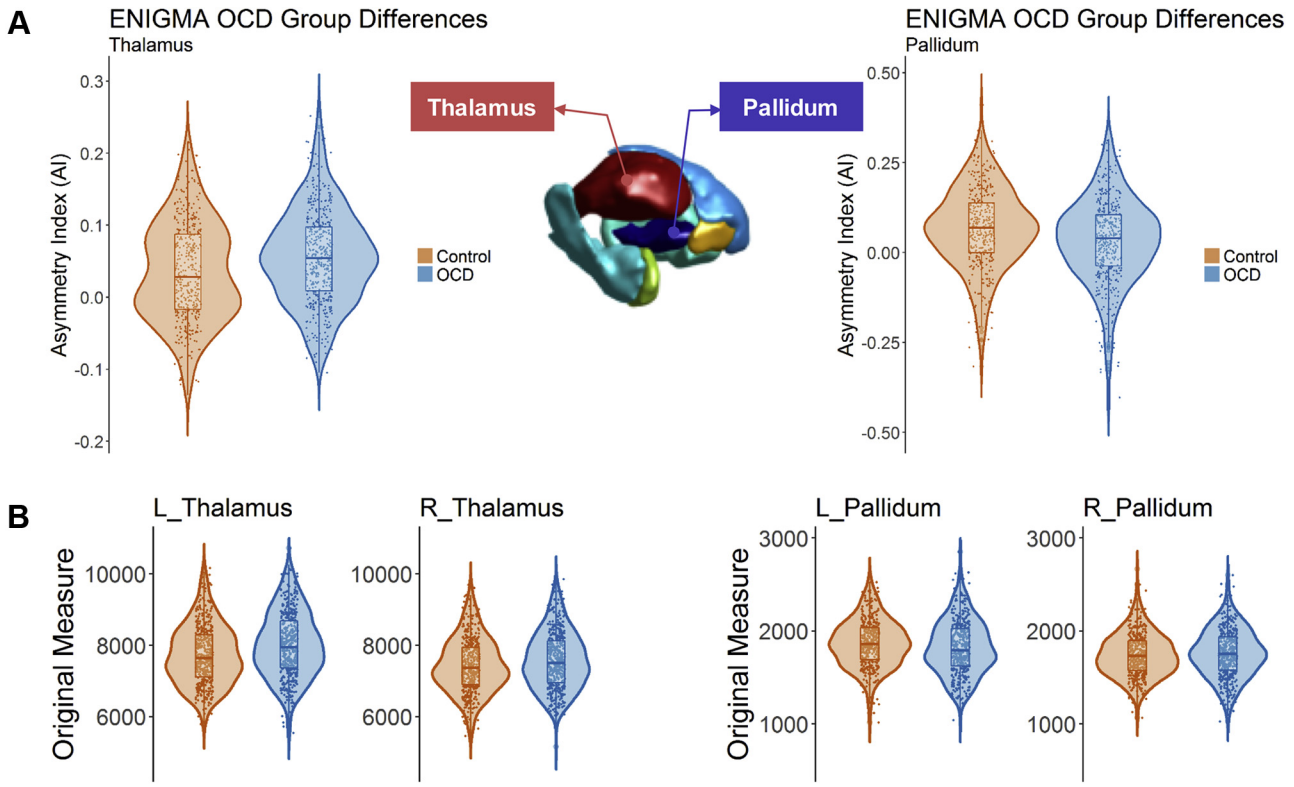

Figure 2. Subcortical structures showing altered volumetric asymmetry in pediatric patients with obsessive-compulsive disorder (OCD): the thalamus and the pallidum. The violin plots show the distributions and group differences of **(A)** the volume asymmetry and **(B)** the lateral volume measures (in mm^3) in each hemisphere for the thalamus and the pallidum. Note that the main analyses were based on linear mixed-effect modeling with "dataset" as a random-effect term, whereas data are plotted here without correction for the "dataset" variable, for display purposes only. AI, asymmetry index; ENIGMA, Enhancing Neuro Imaging Genetics through Meta Analysis; L, left; R, right.

in the left hemisphere (left: $t = -2.80$, $p = .0051$, $d = -0.098$; right: $t = -2.18$, $p = .029$, $d = -0.076$) in adult patients with OCD than in control subjects. The effect on this AI remained after excluding potential outliers (see Methods and Materials) ($t = -3.03$, $p = .0025$, $d = -0.10$). No significant case-control difference in the total average asymmetry of cortical thickness was found ($p = .35$). No significant difference was found in regional asymmetries after multiple testing correction (Supplemental Methods and Materials in Supplement 1).

Although the observed effect of diagnosis on the AI of global hemispheric surface area did not survive multiple testing correction, we were interested to explore associations of this AI with case-only variables, as it is a global rather than regional measure. Within the adult patients with OCD, there was a trend toward unmedicated cases showing a mean AI difference compared with medicated cases ($t = -1.77$, $p = .077$, $d = -0.086$; i.e., more rightward asymmetry in medicated cases). Adult cases with current depression showed a mean AI difference compared with those without ($t = -2.15$, $p = .032$, $d = -0.17$; i.e., more rightward asymmetry in cases with current depression), whereas no effect of current anxiety comorbidity was observed ($p = .48$). There was no correlation of this AI with the age at disease onset ($t < 1.0$, $p = .53$) or the disease duration ($t = -1.03$, $p = .30$). In terms of OCD severity measures, no significant association was found with either the severity in total score or the subcomponent variables (p values $> .10$).

Including age-squared or scanner field strength did not change the main results (Supplemental Methods and Materials in Supplement 1). In the adult data, typicality scores (see Methods and Materials) showed no case-control difference for either thickness or surface area asymmetry (p values $> .15$).

The effect sizes of the AI case-control differences in the pediatric and adult data were found to be uncorrelated across the 34 cortical regions, for either thickness AIs or surface area AIs (p values $> .40$).

The full set of results from this study is available both in the Supplemental Tables in Supplement 2 and online (https://conxz.github.io/AsymOCD/).

DISCUSSION

In this study, we aimed to map differences in brain asymmetry between patients with OCD and healthy control subjects by leveraging a collection of 16 pediatric datasets and 30 adult datasets collected via the ENIGMA Consortium. Using by far the largest sample size to address this issue to date, the results revealed a small number of asymmetry differences in patients with OCD. The largest effects were found in pediatric patients for the volume asymmetry of the thalamus and the pallidum. These effects both had Cohen's d values of around 0.2, which indicates their subtlety and suggests that altered structural brain asymmetry alone is unlikely to be a clinically

useful predictor of OCD. Nonetheless, these effect sizes were comparable with those reported by previous large-scale studies of disorder-related changes in brain structure, in which asymmetry was not studied, including studies of major depression (47,48), schizophrenia (49), posttraumatic stress disorder (50), and autism (51) as well as OCD (38,39). Given that the effect sizes in this study were estimated based on large sample sizes, relatively accurate estimations of the true effects were possible, whether they were statistically significant or not. As such, the effects are informative to share with the field.

Our finding of subtle changes in thalamus asymmetry in pediatric patients is broadly in accordance with previous disease models for OCD as regards the cortico-striatothalamocortical circuitry, which is involved in a wide range of cognitive, motivational, and emotional processes (44). Boedhoe *et al.* (39) observed a mean increase in bilateral thalamus volume (left plus right) in pediatric patients with OCD versus that in control subjects, while in this study, with a larger collection of 16 datasets (including 10 datasets used by Boedhoe *et al.*), we found that this OCD-related volume alteration was largely left lateralized and resulted in altered thalamus asymmetry. It is not clear what pathophysiological mechanisms might link altered thalamus asymmetry to OCD. Within individuals with OCD, we found no associations of thalamus asymmetry with medication status, age at a disease onset, disease duration, current anxiety and depression comorbidity, or disease symptoms, which might have given some insights into the observed differences. The thalamus is involved in diverse interactions among cortical, subcortical, and brainstem nuclei, and many of its functions are asymmetrical in normal participants (52). In addition, the thalamus is subdivided into cytoarchitectonically distinct nuclei with different functions (53). Future studies using higher resolution mapping of internal thalamus subsegment structure and function may therefore be informative in pediatric OCD.

For the pallidum, no total volume change (left plus right) was reported by Boedhoe *et al.* (39) in pediatric patients with OCD, while here, with a larger collection of 16 pediatric datasets (including 10 datasets used by Boedhoe *et al.*), we found an asymmetry difference of the pallidum that was largely driven by a significantly reduced left-sided volume in pediatric patients with OCD. Boedhoe *et al.* also reported that adult patients with OCD showed a larger pallidum (again, left plus right) than that of control subjects, driven by patients with a childhood onset of disease (39). We saw no significant effect on pallidum asymmetry in adult patients, in either the subgroup of early onset of disease or that of late onset of disease (Supplemental Methods and Materials in Supplement 1). This overall pattern of results suggests that disease chronicity, cumulative treatment effects, or late-adolescence volumetric changes in patients are linked to a bilateral increase in pallidum volume but that reduced left-sided volume in pediatric patients reflects a different, earlier developmental process. Moreover, pallidum asymmetry in the pediatric patients showed associations with symptom components hoarding and cleaning/contamination. Although recently hoarding disorder was suggested as a separate diagnostic entity (54), in the present data there was only one case with hoarding behavior in the absence of other symptoms. Thus, we do not consider this tentative effect on asymmetry to relate to hoarding disorder specifically.

The pallidum, linking with the striatum and the thalamus within the corticostriatothalamocortical circuitry (44), has roles in reward and motivation, as well as broader cognitive, affective, and sensorimotor processes (44,55). Further studies on specific functions of the (left) pallidum in compulsive symptoms, cleaning/contamination behaviors specifically, are needed. While it is not clear why lateralized changes in particular should be involved, in general terms our findings in pediatric cases help to characterize the brain structural changes in this disorder, and they suggest altered subcortical neurodevelopment affecting the corticostriatothalamocortical circuitry. Further research will be needed to clarify any potential functional relevance of asymmetrical alterations in particular.

In terms of cortical measures in the pediatric data, we found no significant case-control differences in the asymmetry of regional or global measures of cortical thickness or surface area. This result indicates that none of the cortical case-control differences reported by the previous large-scale ENIGMA study (38) are significantly lateralized, even when they might have been reported with respect to only one side. We also used a multivariable measure to describe the typicality of each participant's asymmetry pattern over all cortical regions with respect to a healthy and general population database (40). However, no case-control difference in this measure was found. Together, these analyses indicate that alterations of cerebrocortical anatomical asymmetry are not notable features of pediatric OCD.

In the adult data, there was no evidence for case-control differences of regional asymmetries for either subcortical or cortical measures. The strongest cortical effect in adults was at the total hemispheric level, whereby cases showed slightly more rightward asymmetry of total surface area, mainly due to having a relatively smaller surface area in the left hemisphere than that of control subjects. However, this very small effect, with Cohen's *d* of 0.086, was not significant in the context of multiple testing, so that further studies with even larger sample sizes will be needed to confirm or refute this result. The effect was more pronounced in cases with comorbid depression, although this observation also remains tentative in the context of multiple testing.

Consistent with previous findings of distinct alterations between pediatric and adult patients by the ENIGMA OCD Working Group (38,39), this study of structural asymmetry also showed different OCD-related effects between pediatric and adult data. There was also no correlation of case-control asymmetry differences between pediatric and adult data across the 34 cortical regions. Nonetheless, it is intriguing that the most notable effects in the pediatric and adult data all involved predominantly left-hemisphere alterations, a finding that might support previous models of left-hemisphere dysfunction in OCD, as has been suggested by some functional imaging and neuropsychological findings (see the Introduction) (23,27–29). However, it will be important for future functional imaging studies to avoid reporting lateralized dysfunction when only one of the two hemispheres shows significant case-control differences. A hemispheric difference

of significance does not necessarily indicate a significant difference of effects between hemispheres.

OCD is a heterogeneous neuropsychiatric condition with a heritability of roughly 40%, as has been observed using both twin- and/or family-based estimation and single nucleotide polymorphism–based estimation (5,56). A recent study showed that genetic variation across the genome, which affects risk for OCD, also includes variation that affects the volumes of the nucleus accumbens and putamen (57). The structural brain asymmetries that exhibited the strongest associations with OCD in this study have been shown to have significant heritability: 23% for the volume asymmetry of the thalamus, 15% for the volume asymmetry of the pallidum (43), and 17% for the total hemispheric asymmetry of cerebrocortical surface area (40). It may therefore be useful in future studies to assess the genetic correlation between these aspects of brain asymmetry and OCD, which might lead toward genome-wide association studies (58) to identify individual genetic loci that are involved in OCD-related asymmetry abnormalities.

This study has several limitations. First, the cross-sectional study design limits the interpretation of the results, particularly with respect to age-related changes. Further work using longitudinal studies and incorporating genetic and environmental variables may be useful to understand the mechanisms underlying the potential associations reported here. Second, while the region-based approach used in this study is feasible for large-scale, collaborative projects, it is necessarily limited in terms of spatial resolution, and this limitation might have contributed to some of the null results for regional cortical or subcortical regions. Investigation with more refined definition of regions [e.g., subregions of the thalamus (59)] or a vertex-wise approach combined with cross-hemispheric registration methods will be likely to be useful for future cortical asymmetry studies (60,61). Third, the symptoms of OCD are heterogeneous (4). Identifying potential subtypes of OCD could therefore provide further insights into the pathophysiology.

In summary, we mapped structural brain asymmetry in pediatric and adult OCD as compared with that of control subjects, using by far the largest sample size to date. Effects were small overall, and they were most pronounced in the thalamus and the pallidum in pediatric patients, a finding that also showed potential links with medication status, disorder severity, or anxiety and depression comorbidities. Our study adds to literature implicating the thalamus in the pathophysiology of pediatric OCD, and it additionally implicates the pallidum in pediatric cases.

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