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Brain Morphology Associated With Obsessive-Compulsive Symptoms in 2,551 Children From the General Population

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Objective: Obsessive-compulsive (OC) symptoms are common in the general population, but it is unclear whether subclinical OC symptoms and obsessive-compulsive disorder (OCD) are part of a neuroanatomical continuum. The goal of this study was to investigate the relation between OC symptoms and subcortical and cortical morphology in a population-based sample of children.

Method: The study included 2,551 participants, aged 9–12 years, from the population-based Generation R Study. OC symptoms were measured using the 7-item caregiver-rated Short Obsessive-Compulsive Disorder Screener (SOCS). Structural (3T) magnetic resonance imaging scans were processed using FreeSurfer to study the thalamus and other subcortical volumes, intracranial volume, vertexwise cortical thickness, and surface area. We used linear regression models to investigate the association between OC symptoms and brain morphology. Emulating case-control studies from the literature, we compared children scoring above the clinical cutoff of the SOCS (probable OCD cases, n = 164) with matched children without symptoms.

Results: Children with probable OCD had larger thalami compared with the control group (d 0.16, $p = .044$). Vertexwise analysis showed a positive association between OC symptoms and thickness of the right inferior parietal cortex, which disappeared after adjusting for total behavioral problems. SOCS scores correlated negatively with intracranial volume ($B = -2444$, $p = .038$).

Conclusion: Children with probable OCD showed thalamus alterations similar to those previously reported in unmedicated children with OCD. OC symptoms showed a stronger association with total intracranial volume than regional brain measures. Longitudinal studies are needed to further elucidate similarities and distinctions between neural correlates of subclinical and clinical OC symptoms.

Key words: FreeSurfer, MRI, OCD, neuroimaging, thalamus

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Obsessive-compulsive disorder (OCD) is characterized by repetitive anxiety- or distress-provoking thoughts (obsessions) and ritualistic behaviors (compulsions). It affects about 0.5%–1% of children and has a lifetime prevalence of 2.3%.[1,2] The disorder often starts in childhood and generally follows a chronic course.

It has been proposed that OCD results from dysfunctional cortico-striato-thalamo-cortical, frontolimbic, and frontoparietal circuits.[3,4] Previous multicenter brain morphology meta- and mega-analyses have reported structural differences of specific regions within these circuits.[5-8] The most recent meta- and mega-analyses performed by the ENIGMA-OCD consortium investigated adult and pediatric OCD separately.[7,8] Both adult and pediatric OCD was associated with thinner parietal cortices.[8] With regard to subcortical volume, unmedicated pediatric patients with OCD showed a larger volume of the thalamus, while adult patients with OCD showed larger pallidal (and normal thalamic) and smaller hippocampal volumes.[7] An earlier study found that the volume of the thalamus in children with OCD was larger at baseline, but decreased after 12 weeks of treatment with a selective serotonin reuptake inhibitor, and this normalization of volume was associated with a reduction in OCD symptoms.[9] This finding highlights the thalamus as a potential biomarker of clinical OCD in children.

Within the general population, obsessive-compulsive (OC) symptoms are distributed along a continuum, where a clinical diagnosis of OCD seems to represent the extreme

end of that spectrum. A population-based study found that 8% of children aged 11 reported having OC symptoms, and OC symptoms at that age was a strong predictor for developing OCD.[10] However, not all children who report OC symptoms will go on to develop OCD. In fact, ritualistic and compulsive-like behavior constitutes a part of normal development in young children.[11] It is currently unknown what factors determine which children with OC symptoms develop OCD and which children do not. Differences in neurodevelopment, under the influence of genetic and environmental factors, may underlie these distinct trajectories. As early detection and intervention in children with OCD is crucial, identifying children who are vulnerable and children who are resilient to developing OCD may greatly improve outcomes. Investigating neurobiological alterations associated with OC symptoms might provide brain markers to make such predictions. To this aim, we investigated the morphometric correlates of OC symptoms in the general population of school-aged children using both a dimensional and a case-control approach and whether these correlates align with previous findings of clinical OCD in children. Pediatric OCD is highly comorbid with anxiety and mood disorders as well as tic disorder, attention-deficit/hyperactivity disorder, and other externalizing disorders.[1,12] Therefore, it is essential to place any findings related to OC symptoms in the context of broader psychopathology and assess specificity.

A recent study examining the neural correlates of subclinical OC symptoms in 255 children (mean age of 9.7 years; range, 8–12.1 years) did not report a relation between brain morphology and overall OC symptoms.[13] It is plausible that such brain differences are subtle and require a substantial sample size. We present a larger study sample (N = 2,551) from the population-based Generation R Study to assess whether OC symptoms on a continuous scale are associated with changes in the volume of the thalamus and other subcortical regions, cortical thickness, cortical surface area, and intracranial volume (ICV). We also compared a group with probable OCD, scoring above the clinical cutoff, with a matched group without symptoms to emulate previous clinical morphology studies. Based on previous literature in pediatric OCD, we hypothesized that OC symptoms in the general pediatric population are associated with thinner parietal cortex and larger thalamus.

METHOD

Participants

Before any analyses, we preregistered our analysis plan on the Open Science Framework (https://osf.io/y6vs2/register/5771ca429ad5a1020de2872e). The children were participants of the Generation R Study, a prospective birth cohort that focuses on health- and mental health–related aspects of pediatric development.[14] As part of the cohort's magnetic resonance imaging (MRI) study, 3,992 children aged 9–12 years underwent MRI between March 2013 and November 2015.[15] Participants were excluded if they lacked available data on OC symptoms (n = 1,242) or in cases of unusable T1-weighted scans owing to failed reconstruction, artifacts from dental braces, incidental findings (n = 199), or poor quality of the cortical parcellation (n = 402) or subcortical segmentation (n = 0–308, region-dependent) (see Figure S1, available online, for flowchart). The final sample included 2,551 children for analysis of global brain measures and subcortical analysis, and 2,149 children were eligible for analysis of cortical morphology. The study was approved by the Medical Ethical Committee of the Erasmus Medical Centre in Rotterdam (The Netherlands) and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from the legal representatives of the children.

Short Obsessive-Compulsive Disorder Screener

OC symptoms were assessed with the Short Obsessive-Compulsive Disorder Screener (SOCS), rated by the primary caregiver.[16] The SOCS is a 7-item scale that measures OC symptoms on items including hand washing, checking, "just right" feeling, repetition, severity, and ability to stop behaviors. The clinical cutoff of 6 or higher has good specificity (0.84) and high sensitivity (0.94) for detecting OCD in the general pediatric population.[16] In case of one missing item, sum scores were calculated by multiplying the sum of the 6 items by 7/6 (= 1.17). SOCS scores with less than 6 items were excluded.

Covariates

Ethnicity was divided into 3 categories: Dutch, non-Dutch other Western (European, American Western, Asian Western, Oceania, and Indonesian), and non-Western (Moroccan, Surinamese and Turkish, Dutch Antilles, African, American non-Western, Asian non-Western, Cape Verdean). Maternal education level was defined as highest education level completed and divided into 3 categories: low (primary education or lower vocational education), middle (intermediate vocational education), and high (higher vocational education or university). Child behavioral problems were measured using the Child Behavioral Checklist (CBCL) version 6–18 years, reported by the primary caregiver.[17] The CBCL sum score was used to adjust for general behavioral problems. To avoid overcorrection, the items from the CBCL Obsessive-

Compulsive Scale were excluded (see Supplement 1.1, available online, for scale details).[18] Nonverbal IQ was assessed at age 5–8 years using the Snijders-Oomen Niet-verbale intelligentie Test-Revisie (SON-R 2.5-7).[19] Handedness was assessed using the Edinburgh Handedness Inventory.[20]

Image Acquisition and Processing

Structural MRI scans were obtained on a 3T Discovery MR750w scanner (GE Healthcare, Waukesha, Wisconsin). Preprocessing and subcortical segmentation was performed using FreeSurfer version 6.0 (see Supplement 1.2, available online, for further details).[21] Each image was visually inspected to assess the quality of cortical reconstructions and whether the subcortical segmentations followed proper boundaries (see Supplement 1.2, available online, for further details). The cortical surface reconstructions were used for whole-brain vertexwise analysis. The segmentation of 8 regions of interest occurred according to a standard atlas bundled with the software,[22] including 8 subcortical structures (bilateral thalamus, amygdala, caudate nucleus, hippocampus, pallidum, putamen, nucleus accumbens, and lateral ventricles). Total ICV was derived during the Talairach transformation.

Statistical Analyses

We performed a nonresponse analysis to compare nonverbal IQ and demographic characteristics of the sample investigated in this study with the sample that was excluded for lacking data on OC symptoms or imaging data, who participated in the previous wave of data collection (at the age of 6). We first tested our preregistered hypothesis about the thalamus, followed by exploratory analyses of the other subcortical structures, cortical morphology, and ICV. Analyses of regional subcortical and ICV were performed using R statistical software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). To investigate the relation between OC symptoms and cortical morphology, we performed vertexwise analyses of cortical thickness and surface area using a custom package developed within the department to perform multiple linear regression models at each cortical vertex (QDECR; https://qdecr.com/).

We performed linear regression analyses with weighted SOCS symptom sum scores as continuous predictors. Outcome variables included mean bilateral volume of the thalamus and the 7 other subcortical regions of interest, vertexwise cortical thickness, cortical surface area, and ICV. All regression models were hierarchically adjusted for age and sex (model 1), ethnicity and maternal education level (model 2), and total child behavior problems (model 3). Behavioral problems were measured using the parent-report CBCL sum score minus the items from the validated OCD subscale to avoid overcorrection.[17,23] Cortical surface area and subcortical analyses were adjusted for ICV to scale for head size. Additional sensitivity analyses included adjustment for nonverbal IQ measured at age 6 and handedness. We also fitted quadratic and cubic models to assess nonlinear relations. Additionally, we assessed interactions between sex and OC symptoms in the statistically significant models. In post hoc analyses, we fitted additional linear models to explore whether there was a disproportionate effect from the major brain regions that make up ICV, including volumes of subcortical gray, total gray matter, total white matter, cerebrospinal fluid, and cerebellum, unadjusted and adjusted for ICV.

To emulate a clinical case-control design, we identified the participants with probable OCD by selecting on OC symptoms above the clinical cutoff (SOCS score $\geq$6, n = 164, 6.4%) and symptom-free participants (SOCS = 0) as a control group, 1:1 nearest-neighbor matched on age ($\pm$ 6 months), sex, ethnicity, maternal education level, and handedness. We performed a paired t test for group comparison of thalamus volume and volume of other subcortical regions, cortical thickness, cortical surface area, and ICV. To adjust models for the remaining confounding factors, we residualized subcortical volumes and cortical surface area for ICV and CBCL and cortical thickness for CBCL only. We calculated d effect sizes for the regions showing a significant group difference and all subcortical regions. In post hoc analyses, we included an intermediate group with mild symptoms (SOCS score 2–4) analysis, and we explored volume difference between the group with probable OCD and this intermediate group as well as between the intermediate group and the control group without symptoms. One study recently demonstrated differences in the subcortical asymmetry between persons with and without OCD.[24] In a post hoc analysis we analyzed whether children with probable OCD showed more regional subcortical asymmetry than children in the control group, measured by the asymmetry index defined by (left − right)/[(left + right)/2].

Missing data of covariates were imputed using the mice package in R for multiple imputation.[25] After testing of our a priori hypothesis of the thalamus, we used 2-tailed false discovery rate (Benjamini-Hochberg) correction for the other 8 exploratory subcortical and ICV analyses. We corrected for multiple testing of the cortical surface–based analyses using Monte Carlo simulations and applying a cluster-forming threshold of $p = .001$.[26,27]

RESULTS

We included data from 2,551 children in the analysis of ICV. The number of subjects in subcortical analyses ranged from 2,243 to 2,535 (Table S1, available online), with sample size differences due to differences in segmentation quality. After exclusion of cases with suboptimal parcellation quality, the cortical analyses included 2,149 children. We studied 328 children in the case-control analyses (164 with SOCS score ≥6 and 164 with SOCS score = 0).

Sample Characteristics

Table 1 displays the demographic characteristics. Boys scored slightly lower than girls on the SOCS, but this difference was not significant (mean difference = −0.12, p = .18). We compared demographic characteristics of the current sample (N = 2,551) with the children who participated in the previous wave of data collection but did not participate during this wave or were excluded from our sample because of missing either MRI or SOCS data (n = 4,262). Children in the excluded sample were less likely from Dutch origin ($\chi^2 = 245.52$, df = 2, $p < .001$) and their mothers were more likely to have a lower education level ($\chi^2 = 238.02$, df = 2, $p < .001$) than children in the study. Excluded children had a lower nonverbal IQ at age 6 (mean difference = −5.36, $p < .001$) and had a higher total CBCL score (mean difference = 1.71, $p < .001$) than children included in the study.

Subcortical Volume

We found no significant linear association between SOCS score and the thalamus as well as the other subcortical volume of the 8 regions of interest. The results are summarized in Table S2 (available online). Next, we compared the subcortical structures of participants with probable OCD (SOCS score ≥6, n = 164) and participants in the matched control group (SOCS score = 0, n = 164). Children with probable OCD had larger thalamic volumes (d = 0.16, p = .047) than children in the control group when corrected for ICV (Table S3, available online). This effect remained after residualizing for the CBCL score (d = 0.16, p = .044) (Table 2). Figure 1 shows a bar plot of effect sizes of the case-control analysis for ICV and subcortical volumes combined. Regression estimates of all covariates for each region and level of adjustment are displayed in Table S4 (available online).

In post hoc analyses, we found no significant differences between children in the probable OCD group and a matched group with intermediate OC symptoms (d = 0.062, p = .43). Similarly, there were no differences between the group with children in the intermediate OC symptoms group and control group (d = −0.028, p = .72). We also found no differences in subcortical asymmetry, defined by (L − R)/[(L + R)/2], between the participants with probable OCD and the participants in the control group (Table S5, available online).

TABLE 1 Sample Characteristics

Characteristic	n	Descriptive value, % or mean ± SD
Maternal characteristics		
Maternal age at birth	2,551	31.81 ± 4.56
Educational level		
Primary	113	4.43%
Secondary	881	34.54%
Higher	1,409	55.23%
Missing	148	5.80%
Ethnicity		
Dutch	1,647	64.56%
Non-Dutch Western	315	12.35%
Non-Dutch non-Western	567	22.23%
Missing	22	0.86%
Family income		
Low	75	2.94%
Middle	568	22.27%
High	1,412	55.35%
Missing	496	19.44%
Maternal psychopathology (Brief Symptom Inventory)	2,055	11.94 ± 15.66
Child characteristics		
Age at MRI	2,551	10.09 ± 0.57
Boys	1,273	10.11 ± 0.59
Girls	1,278	10.06 ± 0.54
Sex		
Boys	1,273	49.90%
Girls	1,278	50.10%
Nonverbal IQ at age 6	2,254	104.12 ± 14.62
CBCL minus OCD	2,466	15.49 ± 13.55
SOCS score	2,551	1.75 ± 2.19

Note: CBCL = Child Behavior Checklist; MRI = magnetic resonance imaging; SOCS = Short Obsessive-Compulsive Disorder Screener.

Cortical Morphology

Whole-brain vertexwise analyses of cortical thickness (n = 2,149) showed that SOCS score was associated with increased cortical thickness of the right inferior parietal cortex (Table 3; Figure S2, available online) after adjusting for age, sex, maternal education level, and ethnicity (B = 0.0089, cluster-forming threshold p = .001). This effect disappeared after additional correction

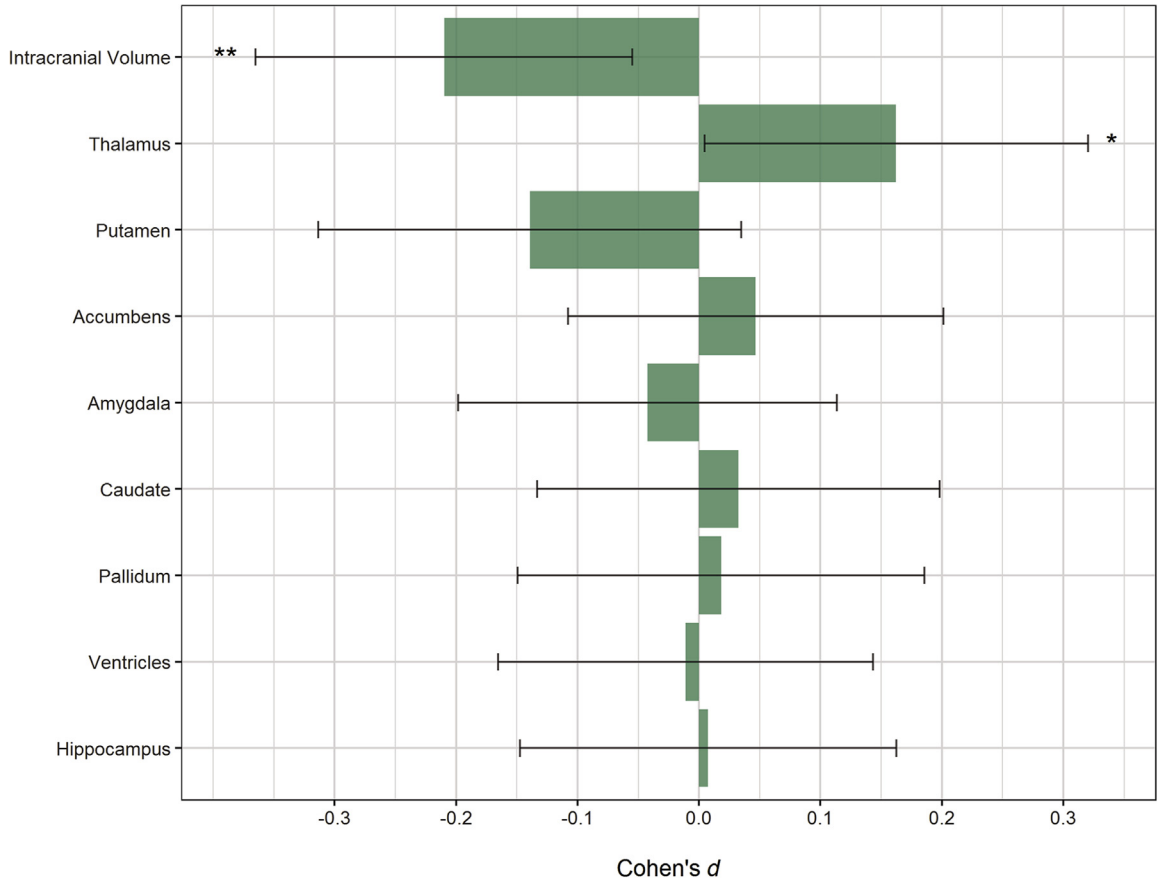
TABLE 2 Differences in Mean Subcortical Volume Between Probable Obsessive-Compulsive Disorder and Control Groups

	t	*df*	*p*	95% CI	Mean of differences	*d*
Thalamus	**2.03**	**156**	**.044**	**(2.65, 186.62)**	**94.64**	**0.16**
Putamen	−1.58	128	.12	(−216.74, 24.22)	−96.26	−0.14
NAcc	0.59	161	.55	(−12.213, 22.69)	5.24	0.05
Amygdala	−0.54	158	.59	(−43.92, 25.21)	−9.35	0.04
Caudate nucleus	0.38	140	.70	(−77.11, 114.29)	18.59	0.03
Pallidum	0.21	137	.83	(−34.11, 42.38)	4.13	0.02
Lateral ventricle	−0.14	161	.89	(−615.97, 533.78)	−41.10	−0.01
Hippocampus	0.10	160	.92	(−55.45, 61.12)	2.84	0.01

Note: Boldface type indicates significant results. Volume residualized for intracranial volume and the Child Behavior Checklist sum score minus the Obsessive-Compulsive Subscale items. NAcc = nucleus accumbens.

for total behavioral problems from the CBCL. There was no interaction between OC symptoms and sex. We did not find significant associations between SOCS score and cortical surface area when adjusting for ICV. We found no quadratic or cubic associations. The case-control analysis showed no significant differences between participants with probable OCD (SOCS score ≥6, n = 164) and participants in the control

FIGURE 1 Differences in Intracranial Volume and Mean Subcortical Volume Between Probable Obsessive-Compulsive Group and Controls



Note: Subcortical volumes are residualized for intracranial volume and Child Behavior Checklist sum score minus the Obsessive-Compulsive Subscale items. Intracranial volume is residualized only for Child Behavior Checklist sum score minus the Obsessive Compulsive Subscale items. Please note color figures are available online.
*p = .044; **p = .0080.

TABLE 3 Significant Cluster From Whole-Brain Cortical Thickness Analyses

Region	MNI (x, y, z)	CFT	*B*	Cluster size, mm^2
Right inferior parietal cortex	34.7, −52.7, 37.5	0.001	0.0089[a]	196.14

Note: CFT = cluster-forming threshold; MNI = Montreal Neurological Institute.
[a]*Adjusted for age, sex, maternal education level, and ethnicity.*

TABLE 4 Linear Association Between Obsessive-Compulsive Symptoms and Intracranial Volume

Model	*B*, mm^3	*p*[a]	95% CI
1	−7150.17	.0001	(−9302.61, −4997.72)
2	−3302.46	.004	(−5522.17, −1082.75)
3	−2577.68	.031	(−4903.19, −252.18)

Note: [a]*False discovery rate–adjusted* p = *.008. Model 1 is adjusted for age at scan and sex; model 2 is additionally adjusted for ethnicity and education of the mother; model 3 is additionally adjusted for behavior of the child measured by sum score of the Child Behavior Checklist minus the Obsessive-Compulsive Subscale items.*

group (SOCS score = 0, n = 164) in cortical thickness and surface area.

Intracranial Volume

In the whole sample (N = 2,551), we investigated the linear relation between OC symptoms, using SOCS score and ICV. We found a negative association between SOCS score and ICV adjusting for age and sex ($B = -7150$, false discovery rate–adjusted $p = .008$) (Table 4). The association remained significant after additionally adjusting for ethnicity, maternal education level, and total CBCL score, but the coefficient decreased markedly. Sensitivity analyses included further adjustment for nonverbal IQ at age 6 and handedness ($B = -2444$, $p = .038$). Considering that comorbid attentional problems may drive this effect, we also fitted a post hoc linear model specifically adjusting for the attention-deficit/hyperactivity disorder subscale of the CBCL.[28] The effect remained in the fully adjusted model ($B = -2{,}469$, $p = .031$). The subsequent paired group analysis of ICV between participants with probable OCD (SOCS score ≥6, n = 164) and children in the matched control group (SOCS score = 0, n = 164) showed that participants with probable OCD had lower ICV compared with the control group ($d = -0.22$, $p = .0080$) (Figure 1). We found no quadratic or cubic associations. Also, we found no interactions between OC symptoms and sex. We also fitted a model for each of the regional volumes that contribute to total ICV. No significant associations between SOCS score and subcortical gray, total gray matter, total white matter, cerebrospinal fluid, or cerebellum were identified in the fully adjusted model.

DISCUSSION

We investigated the relation between OC symptoms and brain morphology in 2,551 school-aged children from a population-based study. First, participants with probable OCD had a larger thalamus, as previously reported in unmedicated pediatric patients with OCD. Second, we found an association between OC symptoms and a thicker right inferior parietal cortex, which did not persist after adjusting for overall behavioral problems. Third, we found a significant negative linear relation between OC symptoms and ICV that remained after adjusting for possible confounding factors. This work forms an important step toward finding early markers of vulnerability to OCD.

The larger thalamus in participants with probable OCD fits with the recent ENIGMA-OCD meta-analysis findings in unmedicated children and with earlier work.[7,9,29] As such, this finding aligns with our a priori hypothesis based on previous literature, mentioned in our preregistered analysis plan (https://osf.io/y6vs2/register/5771ca429ad5a1020de2872e). As we did not find a linear association between OC symptoms and thalamic volume, this suggests that a larger thalamus is limited to only the participants with probable OCD. On one hand, it may be that this reflects a distinct neurobiology of mild ritualistic behaviors associated with normal development compared with actual OCD. Such a distinct phenotype is supported by the fact that we found no statistically significant intermediate group in between the participants in the case group and the control group in our case-control analysis. On the other hand, the idea of a neuroanatomical continuum cannot be fully dismissed because we found a negative linear association with ICV. It must be noted that it is premature to speculate on any neurodevelopmental trajectory of OCD from cross-sectional data.[11,30] To address this, it would be informative to see how longitudinal patterns of OC symptoms relate to brain morphology and thalamic volume in particular.

The effect size ($d = 0.16$) of the thalamic finding is modest. As has been illustrated in the ENIGMA-OCD publications,[7,8] clinical OCD studies require a substantial sample size to produce robust associations. This is even more the case in subclinical/population studies. The effect size of the observed thalamus differences was not as large as was found in the ENIGMA study (0.38 versus 0.16), but of similar magnitude as the cortical findings.[7,8] The difference

may partly arise from using a screening tool to identify children with probable OCD versus diagnosed OCD, which inherently tends to slightly overestimate the number of true cases, potentially diluting the association. Despite this, subtle yet reproducible findings can still inform us about pathophysiological processes. This has been shown in genomewide association studies in the context of Alzheimer disease[31] as well as structural imaging in schizophrenia.[32,33]

The thalamus is a vital hub within the cortico-striato-thalamo-cortical circuits and is implicated in the neurobiology of compulsivity, including the affective and ventral and dorsal cognitive circuits.[3,4,34] Inherent to its versatility, this structure is divided into many functionally distinct nuclei. To improve our neurobiological conceptualization of OCD, it will be useful to study the role of these specific thalamic nuclei in the disorder. Experimental work in monkeys demonstrated that overactivation of the ventral anterior and medial dorsal nuclei of the thalamus provokes compulsive-like behavior and anxiety-like states, indicating that these areas could play a prominent role in OCD.[35] In humans, shape analysis revealed surface expansion of the anterior and pulvinar thalamic nuclei in patients with OCD compared with participants in the control group.[36] Building on the present work, an opportunity lies in investigating whether individual thalamic nuclei drive the observed effects in thalamus volume in humans.

The association between OC symptoms and thicker right inferior parietal cortex is in stark contrast with our a priori hypothesis based on previous cortical morphology studies, where pediatric OCD was associated with a thinner inferior parietal cortex.[6,8] It must be noted that the cluster size and effect estimate are modest, and the association disappeared after adjusting for overall behavioral problems. Also, in our case-control analysis we did not observe this effect. Given these factors, the observed association may be spurious. Future waves of data collection will enable us to investigate whether this finding can be replicated. We did not find an association between OC symptoms and cortical surface area. Previous work has found lower surface area of frontal areas in pediatric OCD, but only when comparing medicated pediatric patients with OCD with participants in a control group.[8] As we were not able to account for medication use, we did not expect to replicate this finding in our sample.

Lower ICV has previously been described in pediatric OCD,[37] but, to our knowledge, not in association with OC symptoms measured in a community sample. Lower ICV was also seen in pediatric patients with attention-deficit/hyperactivity disorder.[38] In our sample, the association weakened but persisted after adjusting for comorbid attentional/hyperactivity problems, suggesting that in our sample it is not solely driven by these behaviors. Previous work in healthy children with similar ages showed that brain size correlates with intelligence, with performance IQ showing a stronger relation than verbal IQ with ICV.[39] Our models demonstrate that nonverbal IQ explains some of the variance in ICV, but an effect of OC symptoms remained even in the fully adjusted model.

Although the finding of thalamic volume aligned with ENIGMA-OCD, there were differences with regard to cortical thickness and ICV. As cortical development is strongly associated with developmental stage, discrepancies may partly be explained by difference in mean age between the ENIGMA samples (mean 13.8 years) and our sample (mean 10.1 years). Another explanation may be the use of different FreeSurfer versions (version 6.0 in our study, version 5.3 in ENIGMA). It has been shown that some volume measures may differ between versions.[40]

In this study, we used surface-based segmentation of MRI images, in accordance with the most recent meta-analyses.[7,8] Earlier meta-analyses using voxel-based morphometry reported more widespread cortical and subcortical abnormalities, including in the orbitofrontal cortex, anterior cingulate cortex, dorsomedial prefrontal cortex, pallidum, putamen, and thalamus.[5,41,42] It must be noted that these studies either combined adult and pediatric patients or used a relatively small separate pediatric sample, which hampers direct comparison. Also, as voxel-based morphometry measures gray matter volume voxel by voxel, it may be slightly more sensitive to local subcortical changes. In contrast, voxel-based morphometry is more prone to partial volume effects, leading to erroneous segmentation and possible overestimation of differences.[43,44] Considering these methodological differences, comparison with surface-based techniques seems most informative.

Our study has several limitations. The study participants are derived from the general population of a large city in The Netherlands. Even though our initial sample is a good representation of the city's demographics, our nonresponse analysis points out differences in ethnicity and socioeconomic status between the current and excluded sample, which may limit the generalizability of our findings. Nevertheless, we made first steps in bridging the gap between the neurobiology of OC symptoms in the general population and clinical OCD by using both a dimensional approach and a case-control approach. Another limitation is that we lacked complete data on OCD diagnoses, and therefore we selected children with probable OCD based on questionnaire data as cases for our case-control analysis. Also, we selected participants without symptoms as a control group, thereby excluding the middle group with mild

OC symptoms. However, this approach emulates many of the studies of OCD in the literature. We did not have complete information on either medication status or early streptococcal infections, so we could not account for these factors in the analyses. Additionally, we adjusted our models for nonverbal IQ that was measured at ages 6–8. Because our estimate of intelligence was not obtained at the same time as the neuroimaging, there may be residual confounding effects. Lastly, our study design is cross-sectional. As a result, we are unable to infer the directionality of the observed effects.

In future work, an opportunity lies in investigating longitudinal trajectories of brain morphology in relation to OC symptoms and its progression to OCD. Also, following the longitudinal course of OC symptoms may help identify vulnerable and resilient children and neural correlates associated with these phenotypes. The association between early environmental factors and OCD has been established in large-scale epidemiological studies.[45,46] It is of interest to study whether early environmental factors can explain OC symptom phenotypes in the general population and whether they have an intermediate role in brain development trajectories related to the development of OCD. Another important next step is to apply reliable thalamus subsegmentation methods to investigate whether changes in distinct nuclei are related to OC symptoms. The emergence of automated pipelines has enabled probabilistic segmentation of thalamic nuclei from T1 images.[47]

In conclusion, we conducted a large population-based neuroimaging study on the association between OC symptoms and brain morphology in school-aged children from the general population. In line with clinical pediatric OCD studies, we found that children with probable OCD have larger thalami compared with children without OC symptoms. We also demonstrated that OC symptoms are negatively associated with ICV. Lastly, OC symptoms were positively associated with thickness in the right inferior parietal cortex, but this association may have been spurious. Further research is needed to confirm our findings.

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